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A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management

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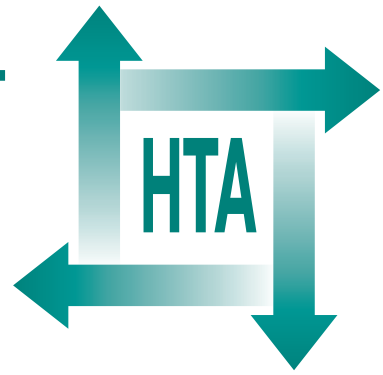

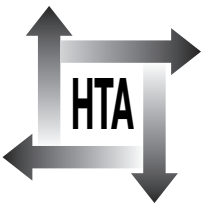

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 03/43/04. The contractual start date was in November 2004. The draft report began editorial review in July 2006 and was accepted for publication in July 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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Abstract

A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management

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Objectives: To review outcome measures and treatment costs in children with juvenile idiopathic arthritis (JIA) and low bone mineral density (BMD) and/or fragility fractures. To review evidence for effectiveness and safety of bisphosphonates and calcium and/or vitamin D in these children. To assess long-term bone health in adults with JIA.

Data sources: Major databases were searched up to July 2005 for effectiveness studies and up to January 2005 for costs.

Review methods: A structured search strategy was conducted. For the evaluation of long-term bone health, outcome data were derived from two cohorts of adult patients with JIA. As there were few published cost data, an ongoing UK longitudinal study (CAPS) provided background data on the cost of managing JIA.

Results: Sixteen studies (78 children with JIA) were included. At baseline, the children had BMD below the expected values for age- and sex-matched children; treatment with bisphosphonates increased BMD with mean percentage increases in spine BMD varying from 4.5 to 19.1%. None of the studies with control groups compared results between the intervention and control groups, they only compared each group with its own baseline. Overall, studies were heterogeneous in design, of variable quality and with no consistency in methods of assessing and reporting outcomes. Hence, data could not be combined or an effect size calculated. A further 43 papers were included in the safety review; side-effects were generally transient. Two studies assessed treatment with calcium and/or vitamin D; BMD was increased from 0.75 to 0.830 g/cm^2 after 6 months and BMD *Z*-score from –2.8 to –2.3 after 6 months and –2.4 after 1 year. There are relatively few long-term studies on the occurrence of low BMD and fragility fractures in children with JIA, with most studies only following children for 1 or 2 years. However, the long- and short-term data indicate that children with JIA have a lower BMD and more fractures than children without JIA. There are very few data on long-term bone health from adults who have JIA, but studies indicate that low BMD persists into adulthood, although adults in remission from JIA may attain the same BMD as healthy adults. From the available data, any predictors of low BMD and fractures in children and adults with JIA remain uncertain. No studies were found that discussed the costs of treating children with JIA and low BMD and/or fragility fractures. In CAPS, 297 of 457 children with JIA attended a 12-month follow-up visit. The mean annual total cost per child in the first year after diagnosis was £1649 (standard deviation £1093, range £401–6967). The highest cost component was appointments with paediatric rheumatologists. The study is continuing to accrue and follow up patients and further analyses will be undertaken as the study progresses.

Conclusions: BMD, adjusted for size, should be assessed as the primary outcome in studies of bone health in children with JIA. Quantitative computed tomography could be used where equipment is available as it offers the advantage of measuring volumetric density. Bisphosphonates are a promising treatment for osteoporosis in children with JIA, but the quality of the current evidence is poor. The accurate assessment of outcome is crucial. There are still uncertainties about the use of bisphosphonates in children, including whether the positive effects of treatment continue over time, the length of treatment and the maximal bone mass gain that can be achieved. Adults with JIA may have persistent low BMD compared with an otherwise healthy population together with an increased risk of fracture. There are no studies evaluating the costs of treating children with JIA and low BMD and/or fragility fractures. There are few data evaluating the costs of treating JIA in general. In the first 12 months after diagnosis, children with all JIA disease subtypes consume large, but highly variable, quantities of health service resources, the largest component being the consultant rheumatology appointments. Data from a larger cohort, over a longer period, are required to substantiate these results further. Further research is needed to assess more clearly the role and permit licensing of bisphosphonates for treatment of children, and in particular, longer-term studies.

Contents

Glossary and list of abbreviations

Glossary

Biochemical markers of bone turnover Indirect indices of skeletal metabolism which rely on the measurement, in serum or urine, of enzymes, matrix proteins and collagen degradation products that are released into the body fluids during bone modelling and remodelling.

Newcastle cohort Patients from the Medical School, Newcastle upon Tyne.

Patient-based outcome The assessment of health, illness and benefits of healthcare interventions from the patient's perspective.

Quantitative imaging techniques Non-invasive assessment of bone using measurements from imaging techniques.

Reference costs National average unit costs published by the Department of Health.

Standardised fracture ratios Ratio of the expected number of fractures to observed number of fractures.

Taplow cohort Patients from the Canadian Red Cross Hospital Taplow.

T-score Number of standard deviations from the young adult mean.

UK General Practice Research Database (GPRD) Computerised database of anonymised longitudinal medical records from primary care in the UK.

***Z*-score** Number of standard deviations from the mean for a child of the same age, race and sex.

List of abbreviations

aBMD	areal bone mineral density
ADSS	articular disease severity score
AIMS	Arthritis Impact Measurement Scales
ALP	alkaline phosphatase
ANA	antinuclear antibody
ARA	American Rheumatism Association
arc	Arthritis Research Campaign
ASBMR	American Society for Bone and Mineral Research
BA	bone area
BMAD	bone mineral apparent density
BMC	bone mineral content
BMD	bone mineral density
BNF	British National Formulary
BUA	broadband ultrasound attenuation
CAHP	Childhood Arthritis Health profile
CAPS	Childhood Arthritis Prospective Study

continued

List of abbreviations *continued*

CHAIMS	Childhood Arthritis Impact Measurement Scales
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Child Health Questionnaire
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
CTX	C-terminal cross-linked telopeptide of type I collagen
CV	coefficient of variation
DMARD	disease-modifying antirheumatic drug
DPA	dual-energy photon absorptiometry
DPD	deoxypyridinoline
DXA	dual-energy X-ray absorptiometry
DXR	digital X-ray radiogrammetry
ESP	European spine phantom
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GGHL	glucosylgalactosylhydroxylysine
GHL	galactosylhydroxylysine
GPRD	General Practice Research Database
HAQ	Health Assessment Questionnaire
HCHS	Hospital and Community Health Services
HLA	human leucocyte antigen
HRQoL	health-related quality of life
HYP	hydroxyproline
ICTP	C-terminal cross-linked telopeptide of type I collagen
ILAR	International League Against Rheumatism
JAFAR	Juvenile Arthritis Functional Assessment Report
JAFAS	Juvenile Arthritis Functional Assessment Scale
JAQQ	Juvenile Arthritis Quality of Life Questionnaire
JASI	Juvenile Arthritis Functional Status Index
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
MRI	magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
NTX	N-terminal cross-linked telopeptide of type I collagen
OC	osteocalcin
OI	osteogenesis imperfecta
PedsQL	Pediatric Quality of Life Inventory Scales
PICP	procollagen type I C-terminal propeptide
PINP	procollagen type I N-terminal propeptide
pQCT	peripheral quantitative computed tomography

continued

List of abbreviations *continued*

pQUS	peripheral quantitative ultrasound
PSS	personal social services
PSSRU	Personal Social Services Research Unit
PYD	pyridinoline
QALY	quality-adjusted life-year
QCT	quantitative computed tomography
QoMLQ	Quality of My Life Questionnaire
QUS	quantitative ultrasound
RCT	randomised controlled trial
RF	rheumatoid factor
SD	standard deviation
SF-36	Short Form with 36 Items
SLE	systemic lupus erythematosus
SOS	speed of sound
SPA	single-energy photon absorptiometry
SXA	single-energy X-ray absorptiometry
TNF	tumour necrosis factor
TRAP	tartrate-resistant acid phosphatase
vBMD	volumetric bone mineral density
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Low bone mineral density (BMD) and fragility fractures are serious complications of juvenile idiopathic arthritis (JIA), but evidence from strategies for prevention and treatment has not been evaluated. The original aim of this project was to undertake a cost-effectiveness analysis of the lifetime fracture risk of children with JIA. We reviewed methods of assessing bone health in children with JIA, including quantitative imaging techniques, biochemical markers of bone turnover and fractures, to assess the available evidence and to assess the strengths and limitations of each method. We then undertook a systematic review of (1) the evidence for effectiveness of bisphosphonates and calcium and/or vitamin D in children with JIA and (2) the costs of treating children with JIA and low BMD and/or fragility fractures. During this study, it became clear that the data are not available for a health technology assessment of interventions to prevent and manage osteoporosis in JIA that complies with these criteria. Key omissions are: the lack of comparative effectiveness data, the limitations of outcomes in that they do not assess all health effects on individuals and measurement of quality-adjusted life-years has not been carried out, the lack of prospective resource use and cost data in the appropriate patient group. Therefore, to produce some evidence as useful background for future research in this area, we estimated the lifetime risk of low BMD and fractures from two cohorts of adults with JIA and conducted a cost analysis of the management of JIA for 1 year from diagnosis.

Objectives

The objectives were as follows:

- to review outcome measures in children with JIA and low BMD and/or fragility fractures
- to review evidence for effectiveness and safety of bisphosphonates and calcium and/or vitamin D in these children
- to assess long-term bone health in adults with JIA
- to review costs of treating children with JIA and low BMD and/or fragility fractures
- to evaluate the cost of treating JIA.

Review of outcome measures

Low BMD in childhood JIA is a function of current growth and the morbidity caused by JIA; the combination of these factors complicates the assessment of bone health in these children. It is necessary to distinguish disease-related changes from natural growth and development in order to determine the effects of JIA and its treatment. The review question for this part of the report is as follows: in children with JIA, how effective are patient-based outcome measures, quantitative imaging techniques, biochemical markers of bone turnover and fractures for assessing bone health?

Methods

Electronic searches were undertaken (up to July 2006) together with checking of bibliographies of papers. Studies describing (1) patient-based outcome measures, (2) quantitative imaging measures: dual-energy photon absorptiometry (DXA), quantitative computed tomography (QCT), quantitative ultrasound (QUS) and digital X-ray radiogrammetry (DXR), (3) biochemical markers of bone turnover and (4) fractures, to assess bone health in children with JIA were included.

Results

Two studies evaluated the use of patient-based outcome measures in children with JIA and low BMD; one study found a correlation between BMD and Childhood Health Assessment Questionnaire score but the second found no correlation with Juvenile Arthritis Functional Assessment Report score. In the review of quantitative imaging techniques, DXA (25 studies) was sensitive to differences between different subtypes of JIA, disease severity and factors such as treatment with corticosteroids and could distinguish between children with JIA and healthy control children. However, DXA results in children must be interpreted with care because of technical issues. One study using QCT and one using peripheral QCT in JIA were identified and data were insufficient to assess the usefulness of this technique. However, QCT provides a true volumetric density but scanning equipment is harder to access and doses of radiation are relatively high. Seven studies used QUS and showed that ultrasound could distinguish between

children with JIA and healthy children and that there was correlation between ultrasound parameters and BMD from DXA. QUS is a promising technique that does not expose children to radiation, but there are limited data in children. Eighteen studies examined biochemical markers of bone turnover. In some studies, levels of osteocalcin, alkaline phosphatase, hydroxyproline, tartrate-resistant acid phosphatase, procollagen type I C-propeptide, C-terminal cross-linked telopeptide of type I collagen and deoxypyridinoline were changed in children with JIA compared with healthy children; in other studies, the levels were unchanged. Similarly, results from studies in children with different severities of disease were not consistent. Only two studies described the use of fractures as outcome measures. One study recorded an increase in spinal fractures in children with JIA who had started early treatment with corticosteroids compared with those who started treatment later. The second study noted four fractures during 18 months of follow-up.

Systematic review of effectiveness of bisphosphonate and calcium and/or vitamin D

We reviewed the safety and effectiveness of interventions for the prevention and/or treatment of low BMD and fragility fractures in children with JIA.

Methods

Electronic searches were undertaken (up to July 2005), together with checking of bibliographies of papers. Studies of bisphosphonates and calcium and/or vitamin D in children with JIA were included. Reports from children with osteogenesis imperfecta (OI) were also included in the review of safety.

Results

Because of the sparsity of data, we adopted a pragmatic approach and included all study designs, case series and case reports in the review of bisphosphonate treatment. Sixteen studies (78 JIA children) were included: one randomised controlled trial (RCT), three controlled cohort studies, 11 case series, and one case report. At baseline, children had BMD below the expected values for age- and sex-matched children; treatment with bisphosphonates increased BMD with mean percentage increases in spine BMD varying from 4.5 to 19.1%. None of the studies with control groups compared results between the intervention and control groups; they only compared each group with its own baseline. In the RCT, spine bone mineral apparent density increased significantly from baseline in the alendronate-treated group (0.266 to 0.307, $p = 0.013$), whereas there was little change in the placebo-treated group (0.255 to 0.276, $p = 0.156$). Overall, studies were heterogeneous in design, of variable quality and with no consistency in methods of assessing and reporting outcomes. Hence, data could not be combined or an effect size calculated. A further 43 papers were included in the safety review; side-effects were generally transient. Two studies assessed treatment with calcium and/or vitamin D; BMD was increased from 0.75 to 0.830 g/cm^2 after 6 months and BMD *Z*-score from –2.8 to –2.3 after 6 months and –2.4 after 1 year.

Evaluation of long-term bone health

The objective of this part of the study was to describe the long-term occurrence of fractures in adults with JIA and compare with that expected in the general population of healthy adults. Long-term outcome data were derived from two cohorts of adult patients with JIA.

Results

Large longitudinal studies using the General Practice Research Database provide age-related data on the occurrence of fragility fractures in adults and children. The relationship between low bone mass and increased risk of fractures in postmenopausal women is well recognised but there also appears to be an association between low BMD and fractures in children. There are relatively few long-term studies on the occurrence of low BMD and fragility fractures in children with JIA, with most studies only following children for 1 or 2 years. However, the long- and short-term data indicate that children with JIA have a lower BMD and more fractures than children without JIA. There are very few data on long-term bone health from adults who have JIA but studies indicate that low BMD persists into adulthood, although adults in remission from JIA may attain the same BMD as healthy adults. From the available data, any predictors of low BMD and fractures in children and adults with JIA remain uncertain.

Systematic review of costs

No studies discussed the costs of treating children with JIA and low BMD and/or fragility fractures.

Evaluation of costs of treating JIA

Because the published clinical effectiveness and cost data for the treatment of children with JIA and low BMD and/or fragility fractures are limited, it was not possible to undertake economic modelling. Therefore, as a starting point, the aim of this part of the study was to evaluate the overall cost of treating children with JIA. We analysed costs from an ongoing UK longitudinal study within the University of Manchester Arthritis Research Campaign (arc) Epidemiology Unit: Childhood Arthritis Prospective Study (CAPS). This study was not designed to study bone health specifically but the analysis provided background data on the cost of managing JIA.

Methods

Children with newly diagnosed inflammatory arthritis of one or more joints, which has persisted for at least 2 weeks, are recruited to CAPS. Data are collected at study entry, 6 months and 1 year: children undergo a rheumatological examination by the consultant and assessment by the nurse, and a comprehensive case notes review is undertaken. Health service resource use data (appointments with paediatric consultant rheumatologist, referrals to other healthcare professionals, drugs, laboratory tests and clinical imaging) were extracted, unit costs applied and the cost of management calculated.

Results

A total of 457 children with JIA have been recruited and 297 of these attended a 12-month follow-up visit. The mean annual total cost per child in the first year after diagnosis was £1649 (standard deviation £1093, range £401–6967). The highest cost component was appointments with paediatric rheumatologists. The study is continuing to accrue and follow up patients and further analyses will be undertaken as the study progresses.

Conclusions

Assessment of outcome measures relating to bone health in children with JIA

BMD, adjusted for size, should be assessed as the primary outcome in studies of bone health in children with JIA. QCT could be used where equipment is available as it offers the advantage of measuring volumetric density. Other outcome measures may also be useful but further data are needed to establish their role.

Systematic review of effectiveness of bisphosphonate and calcium and/or vitamin D

Bisphosphonates are a promising treatment for osteoporosis in children with JIA, but the quality of the current evidence is poor. Better studies are needed to assess more clearly their role and permit licensing of these agents for treatment of children. In particular, longer-term studies are needed to evaluate the effectiveness and safety of this treatment into adulthood. The accurate assessment of outcome is crucial.

There are still uncertainties about the use of bisphosphonates in children, including whether the positive effects of treatment continue over time, the length of treatment and the maximal bone mass gain that can be achieved. In particular, longer-term studies are needed to evaluate the effectiveness and safety of this treatment into adulthood.

Long-term bone health in JIA

Adults with JIA may have persistent low BMD compared with an otherwise healthy population together with an increased risk of fracture.

Systematic review of costs for managing children with JIA and low BMD or fragility fractures

There are no studies evaluating the costs of treating children with JIA and low BMD and/or fragility fractures. There are few data evaluating the costs of treating JIA in general.

Assessment of cost of treatment for JIA

In the first 12 months after diagnosis, children with all JIA disease subtypes consume large, but highly variable, quantities of health service resources. The largest component of health provider costs was consultant rheumatology appointments.

The right-skewed distribution of costs suggests that a few high cost outliers increased the mean costs for the group overall, and within individual disease subgroups. Data from a larger cohort, over a longer period, are required to substantiate these results further.

Implications for healthcare

All methods of assessing outcome have limitations; DXA is the current most practical measure but results in children must be interpreted with care. Fractures would be the ideal outcome measure but a study with this end-point would require large numbers of patients and long-term follow up.

However, fracture data could be routinely collected for local and other registers. Bisphosphonates seem to be effective in the management of children with JIA but the evidence is limited. Few children with JIA have been treated with bisphosphonates; the studies include case series and case reports and there are no true controlled studies, the studies are heterogeneic in design (different subtypes of JIA are included in different studies, children with other connective tissue disease also included, different bisphosphonates and varied doses and routes of administration are used and durations of treatment and follow-up times vary), together with poor assessment of outcome measures and varied methods of reporting results. There are still many unanswered questions about bisphosphonates' use, including the optimum dose and frequency of administration and length of treatment. The maximal BMD gain that can be achieved is not known. It is not clear whether the positive effects of treatment continue over time. There is limited evidence on the use of calcium and/or vitamin D. Assessment of outcome was poor in all studies. The problems of poor bone health persist into adulthood; adults with JIA have an increased numbers of fractures compared with expected values in otherwise healthy adults.

Recommendations for research

Areas for further research are as follows:

- The arc has initiated an RCT of bisphosphonates and 1-α-hydroxycholecalciferol (hydroxylated derivative of vitamin D) in children with JIA. This study should address some of the research issues raised in this report.
- Longer-term follow-up of studies with bisphosphonates and calcium and/or vitamin D is needed to determine the longer-term effect of treatment on both bone mass and fracture risk, and also safety.
- A cohort study of children with newly diagnosed JIA should examine the effects of disease and current management approaches on bone health in these children.
- Large prospective studies are needed to determine the predictors of bone mass and fractures in adults with JIA.
- Longitudinal studies of DXA should be conducted to consider whether bone mass measured by DXA predicts bone mass and fracture risk in adults.
- Most current evidence relates to the use of DXA for assessing bone health in children. Further evaluation of other quantitative imaging techniques is required.
- More studies are needed looking at the performance of biochemical markers in children with JIA. The effect of treatment on markers in children with JIA should be assessed.
- An HRQoL measure should be validated specifically for use in children with low trauma fractures.
- Future studies should examine costs of management of bone health in JIA in both the short and medium term. A cost-effectiveness or cost–utility evaluation could be incorporated. Future studies examining bone health in children should have an economic component.

Chapter 1

Background to juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is the most commonly diagnosed rheumatic disease in children.[1] It is defined as an arthritis which starts before the age of 16 years and persists for at least 6 weeks.[2,3] The major clinical manifestation is persistent joint swelling, which results from accumulation of synovial fluid and thickening of the synovial lining. From a national Diagnostic Register, the incidence of JIA has been estimated to be around 10 per 100,000 children per year in the UK.[4] The prevalence is probably around 40–160 per 1,000,000.[5] Thus approximately 10,000 children in the UK are affected.

JIA comprises a group of painful inflammatory conditions with variable presentation and course. Because of this heterogeneity, classification has been difficult. The International League against Rheumatism (ILAR) has classified JIA into eight categories:[2,3] systemic, oligoarthritis (persistent), oligoarthritis (extended), polyarthritis [rheumatoid factor (RF) negative], polyarthritis (RF positive), psoriatic arthritis, enthesitis-related arthritis and unclassifiable. Two older classification systems of arthritis in children use different terminology – the European League Against Rheumatism (EULAR) criteria for juvenile chronic arthritis (JCA) are used mainly in Europe[6] and the American Rheumatism Association (ARA) criteria for juvenile rheumatoid arthritis (JRA) are used mainly in North America.[7] The ILAR criteria are most precise. In this document, JIA is used throughout to describe the condition. All three classifications refer to children under the age of 16 years at the onset of arthritis. All the classifications are based on clinical expression of the disease and interpretation can vary. As a result, the comparison of clinical trials which use different classification systems can be difficult. In Europe, approximately 50% of children with JIA have oligoarthritis, 25% have polyarthritis and 10% have systemic disease.[4,8]

The causes of JIA also remain unclear, but there is evidence for an autoimmune origin from the familial predisposition to disease, human leucocyte antigen (HLA) associations, the presence of autoantibodies and persistent oligoclonally expanded T cell populations.[9] The environment may also have a role in some types of JIA; an infectious aetiology has been suggested; no definite pathogens have yet been identified but *Rubella*, *Chlamydia*, *Escherichia coli* and *Mycoplasma pneumoniae* have been implicated.[9]

Severe JIA results in joint damage, growth retardation, osteoporosis, psychosocial morbidity, reduced quality of life and educational or employment disadvantage. Although it was believed that up to 80% of children with JIA would achieve remission of disease, more recent studies have demonstrated that in most children active disease continues into adulthood with remission rates of only 40–60%.[10] The prognosis of JIA varies with subtype. The percentage of patients in clinical remission ranges from 33 to 80% for systemic arthritis, 0 to 15% for RF-positive polyarthritis, 23 to 46% for RF-negative polyarthritis, 12 to 35% for extended oligoarthritis and 43 to 73% for persistent oligoarthritis.[10] It is difficult to provide precise figures as different definitions of remission have been used and results across studies are inconsistent; a set of preliminary criteria for clinical remission has now been developed.

The aims of treatment in JIA are to relieve pain, reduce general and local inflammation, prevent disability, maintain locomotor function and sustain satisfactory growth and development. Treatment involves a combination of drugs depending on the type of JIA. Symptomatic treatment is often managed with oral non-asteroidal anti-inflammatory drugs (NSAIDs), which have anti-inflammatory and analgesic effects but do not modify the course of the disease. NSAIDs commonly used in JIA include naproxen, ibuprofen, ketoprofen, flurbiprofen, fenoprofen, indomethacin, sulindac, diclofenac and piroxicam. Methotrexate is the disease-modifying antirheumatic drug (DMARD) of choice in children and has established a good effectiveness and safety profile over almost 20 years of use in the clinic.[11] The major safety concern is liver toxicity, but the risk seems to be lower in children than in adults.[12] Gold salts, penicillamine, sulfasalazine and hydroxychloroquine may also be used. Studies suggest that ciclosporin is also

effective. Oral corticosteroids are effective and have been an integral part of the management of JIA, most frequently prednisone. However, there is now a tendency to avoid long-term use because of side-effects, including Cushingoid features, skin anomalies, ocular problems, immunosuppression and particularly growth failure and osteoporosis. 'Pulses' of high-dose parenteral corticosteroids have been used in systemic-onset JIA or severe polyarticular disease associated with systemic effects.[12] Corticosteroids may also be administered locally to the joints (intra-articular injections); triamcinolone is most effective.[12] Etanercept is an anti-TNF agent, which may be used in children unresponsive to or intolerant of methotrexate; although introduced into clinical practice relatively recently, safety data for ⩾4 years suggest that it is well tolerated.[13] In addition to drug therapy, physical therapies are an essential part of management to restore joint function. In the later stages of disease, surgical intervention may be necessary. In chronic diseases of childhood such as JIA, psychosocial and educational support form an integral part of management.

Low bone mineral density and fragility fractures in JIA

Low bone mineral density (BMD) and fragility fractures are well-recognised serious long-term complications of JIA and are associated with considerable morbidity.

Because peak bone mass is achieved in early- to mid-adult life, children with JIA who fail to achieve their optimum peak BMD are further at risk of premature osteoporosis in later life as their BMD declines. It is recognised that adult patients, both male and female, with a history of JIA have increased bone turnover and reduced bone BMD compared with healthy control subjects matched for age, sex, height and weight.[14] French and colleagues, found that a significant subset of adults with a history of JIA were osteopenic.[15] Known risk factors for osteoporosis in JIA include the inflammatory process,[16] nutrition,[17] growth impairment,[18] reduced physical activity[17] and treatment, especially corticosteroids.[19] Brik and colleagues found that children receiving long-term corticosteroid treatment had a significant decrease in BMD.[20] However, despite this association with severe disease and corticosteroid treatment, one study found that up to 30% of post-pubertal females with mild to moderate JIA who had never been treated with corticosteroids also had a low bone mineral content (BMC).[21] In a study using the UK General Practice Research Database (GPRD), there was a statistically significantly greater number of fractures in subjects with childhood-onset arthritis compared with healthy controls.[22] The long-term risks and predictors of low BMD and fracture in adults with childhood onset arthritis need to be defined further.

Assessment of bone health in children with JIA is complicated. BMC and BMD, which are the quantifiable parameters of bone strength *in vivo*, account for approximately 60% of the total bone strength or the resistance to fracture.[23] Dual-energy X-ray absorptiometry (DXA) is the most commonly used technique for the measurement of BMC and BMD in children and adults. DXA calculates density from the scanned area of bone and estimates BMD as g/cm^2 [areal bone mineral density (aBMD)]. In adults, aBMD measured by DXA predicts the risk of osteoporotic fractures in a similar way to blood pressure predicting the risk for stroke.[24] In postmenopausal Caucasian women, a working group of the World Health Organization (WHO) arbitrarily defined osteopenia as those with aBMD between more than 1 standard deviation (SD) but less than 2.5 SD and osteoporosis as aBMD of more than 2.5 SD below the mean for young adult women, defined as the '*T*-score'.[25] Those with *T*-score of more than –2.5 SD are defined as having osteoporosis. *Z*-scores, the number of SDs below the mean for a child of the same age, race and sex, can be calculated from reference data for children. The significance of BMD measurements in children is less clearly understood, for several reasons: first, because until recently, normative data on healthy children were not available, and second, since children, unlike adults, are still growing, increasing bone volume will erroneously result in an increase in BMD measurement although the unitary bone density may not actually have changed. Furthermore, it can be difficult to interpret BMD in individual children based on age alone as during growth there are very wide variations in height and weight. Finally, it is only recently that a definitive association between low BMD in children has been associated with subsequent fracture. A recent systematic review of the literature reported an association between low BMD and fractures, although all studies were retrospective.[26] As a result, there is no clear definition of osteopenia or osteoporosis in children. However, in girls with a previous forearm fracture, Goulding and colleagues observed that for every SD decrease in total body BMD, the risk of new fractures at any site doubled during the 4 years after initial fracture.[27] Thus, results from

this cohort follow-up study in children support the concept that low BMD is the major contributing factor to skeletal fragility.

The occurrence of low BMD can be reduced by ensuring good nutrition, encouraging physical exercise and supplementation with calcium and vitamin D. Although the benefit of bisphosphonates for the treatment of osteoporosis in adults is well established,[28] these agents have not been licensed for the treatment of children. There is much less information about the use of bisphosphonates in children and there are associated long-term safety concerns, particularly with regard to the growing skeleton.[29]

Finally, the costs and economic impact of osteoporosis and its treatment have not been investigated in JIA in either the short or long term.

Aims and objectives of this project

Low BMD and fragility fractures are a common and serious complication in children with JIA, with effects lasting into adulthood. The evidence relating to strategies for prevention and treatment of this condition in children, particularly with regard to long-term safety, has not been evaluated. There is also uncertainty about how best to assess the outcome of these strategies in clinical trials. We had planned a cost-effectiveness analysis of the prevention and management of lifetime fracture risk of children with JIA. During this study, it became clear that the data are not available for a health technology assessment of interventions to prevent and manage osteoporosis in JIA that complies with these criteria. Key omissions are as follows: the lack of comparative effectiveness data, the limitations of outcomes in that they do not assess all health effects on individuals and measurement of quality-adjusted life-years (QALYs) has not been carried out, the lack of prospective resource use and cost data in the appropriate patient group. Therefore, to produce some evidence as useful background for future research in this area, we estimated the lifetime risk of low BMD and fractures from two cohorts of adults with JIA and conducted a cost analysis of the management of JIA for one year from diagnosis.

Therefore, the aims of this project were as follows:

- to review outcome measures in children with JIA and low BMD and/or fragility fractures
- to review evidence for effectiveness of bisphosphonates and calcium and/or vitamin D in children with JIA
- to assess long-term bone health in two cohorts of adults with JIA
- to review costs of treating children with JIA and low BMD and/or fragility fractures
- to evaluate the cost of treating JIA from a longitudinal study in children with JIA.

Chapter 2

Assessment of outcome measures relating to bone health in children with JIA

Objectives

The review question for this part of the report is as follows: in children with JIA, how effective are patient-based outcome measures, quantitative imaging techniques, biochemical markers of bone turnover and fractures for assessing bone health?

The objectives were as follows:

- to evaluate the strengths and limitations of the different outcome measures for assessing bone health in children with JIA: patient-based outcome measures, quantitative imaging techniques, biochemical markers of bone turnover and fractures
- to make recommendations on the most appropriate outcome measures for future studies of JIA and bone health in children.

The outcomes proposed for assessing the outcome of management of bone health in children with JIA are health status, bone strength, blood or urinary biochemical markers of bone turnover and the incidence of fractures. Each outcome potentially assesses different aspects of bone health in these children. At present there are no recommendations as to the most appropriate outcome to use in clinical trials evaluating bone health in children with JIA. We wanted to investigate which would be the most appropriate measure for the ongoing monitoring of children and also whether surrogate measures (e.g. BMD, biochemical markers) can be used in place of fractures. Therefore, in order to assess the evidence for the use of these outcomes, studies in children with JIA were reviewed.

Patient-based outcome measures

Background

Patient-based outcome refers to the assessment of health, illness and benefits of healthcare interventions from the patient's perspective. The outcome measures address functional status and the broader concept of health-related quality of life (HRQoL), that is, how the disease and its symptoms affect the patient's overall health, emotional well-being and ability to perform daily activities. The effect of bone health could be incorporated into the general health status of children and be reflected in the assessment of patient-based outcome.

Instruments for determining patient-based outcome measures usually consist of questionnaires that are completed either by the patients themselves or by somebody on behalf of the patient. Fitzpatrick and colleagues reviewed the limitations and strengths of different instruments that can be used to determine patient-based outcome.[30] Disease-specific instruments provide the patient's perspective of a specific disease or health problem, such as the Arthritis Impact Measurement Scales. Site- or region-specific instruments assess heath problems in a specific part of the body, such as the Oxford Hip Score. Dimension-specific instruments assess one specific aspect of health status, such as the McGill Pain Questionnaire. In contrast, generic instruments capture a broad range of aspects of health status and the consequences of illness and are therefore relevant to a wide range of patient groups, such as the Short Form with 36 Items (SF-36). The purpose and content of the instruments vary and there are limitations and strengths to each of the particular instruments when used in a clinical trial.

Eiser and Morse undertook a systemic review of measures of quality of life in children with chronic disease.[31] A total of 137 papers describing 19 generic and 24 disease-specific measures were included, but the authors concluded that only three generic measures and two disease-specific measures fulfilled very basic psychometric criteria including reliability and validity. The authors drew attention to six problems associated with measuring HRQoL in children:

- confusion about the definition and measurement of HRQoL
- limited availability of disease-specific measures
- discrepancies between child and parent ratings
- limited availability of measures for self-completion by children

- lack of precision regarding the content of domains of HRQoL
- cultural appropriateness of measures for use in the UK.

Both JIA-specific and generic instruments have been used to assess patient-based outcomes in children with JIA (*Table 1*).[32,33] Instruments have either been developed to assess functional status and concentrate on the ability of patients to perform physical activities of daily life relevant to children with JIA such as dressing, walking and climbing stairs, or have been developed to measure the broader area of HRQoL in children with JIA. Instruments may be either disease-specific for JIA or generic. None of these currently available measures have been designed specifically to examine the effects of bone health in children with JIA, although it is likely that functioning of the child would be compromised by fractures.

The Childhood Health Assessment Questionnaire (CHAQ) is the most widely used instrument in paediatric rheumatology.[33] It is a disease-specific measure of functional status that comprises two indices, disability which assesses function in eight areas (dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities) and discomfort assessed from the presence of pain.[34] It is quickly and easily completed, valid, reliable and sensitive.[32,33] It can be completed by children >7 years and or parents. Lam and colleagues have developed revised versions of the CHAQ which they believe to be superior to previous versions as they were more sensitive and better at differentiating patients from controls.[35] The CHAQ has been adapted and validated for use in 32 counties worldwide.[36]

The CHAQ has been used in studies assessing the perception and effects of coping with pain in children with JIA.[37–39] A positive correlation was found between joint impairment and CHAQ score.[40] Takken and colleagues demonstrated a correlation between anaerobic performance and functional ability assessed with the CHAQ in children with JIA.[41] In two studies, grip strength and knee strength both correlated with the CHAQ.[42,43] Five cohort studies have used the CHAQ as part of the assessment of long-term outcome.[44–48] Most patients, even those with mild disease, experienced some degree of persistent disability and pain. A high disability index and poor well-being at baseline predicted reduced physical function after 3 years.[48] The CHAQ appears to be free of physical development bias, suggesting that it can be used in longitudinal studies.[34,49] The CHAQ had limited responsiveness in clinical trials assessing treatment with methotrexate[50–52] but reasonable responsiveness in a trial of etanercept treatment.[53] In a study of aquatic fitness training for children with JIA, there were improvements in CHAQ, although these were not statistically significantly different from a control group of children.[54]

Other instruments developed and tested for children with JIA have not yet been validated in longitudinal studies: the Juvenile Arthritis Functional Status Index (JASI),[55,56] the Juvenile Arthritis Functional Assessment Scale (JAFAS) and Report (JAFAR),[57,58] the Childhood Arthritis Impact Measurement Scales (CHAIMS)[59] and the Juvenile Arthritis Quality of Life Questionnaire (JAQQ).[60] CHAIMS applies selected components of the adult Arthritis Impact Measurement Scales (AIMS) to children with JIA and is the only

TABLE 1 *Instruments developed/used to assess patient-based outcome in children with JIA*

Measures of physical function
- Childhood Health Assessment Questionnaire (CHAQ)
- Childhood Arthritis Impact Measurement Scales (CHAIMS)
- Juvenile Arthritis Functional Status Index (JASI)
- Juvenile Arthritis Functional Assessment Scale (JAFAS) and Report (JAFAR)

Measures of health-related quality of life

Disease-specific:
- Juvenile Arthritis Quality of Life Questionnaire (JAQQ)
- Childhood Arthritis Health profile (CAHP)

Generic:
- Child Health Questionnaire (CHQ)
- Pediatric Quality of Life Inventory Scales (PedsQL)
- Quality of My Life Questionnaire (QoMLQ)

instrument to include a specific pain dimension. In one study, the pain scale was the most reliable measure in both children with active and inactive JIA.[59]

Of the generic instruments, the CHQ is most useful for assessment of health status in JIA. The CHQ is based on the adult SF-36 but also includes domains relevant to children and adolescents such as self-esteem and family functioning; overall it assesses 10 concepts including the child's physical functioning, bodily pain, changes in role and in social functioning because of physical, emotional or behavioural problems, general health, mental health, behaviour problems, self-esteem and the impact of the child's health on the parent's emotional well-being and the parent's personal time.[33] It can be completed by children >5 years old or parents. The CHQ has been adapted and validated for use in 32 countries worldwide[36] and has been validated for use in JIA.[61] Selvaag and colleagues observed that the CHQ discriminated between children with early JIA and controls and was sensitive to clinical changes.[62] In a 3-year cohort study, general health score and pain score from the CHQ were significantly worse in children with JIA compared with healthy controls.[48]

Two of the other generic instruments show reliability, validity and responsiveness in children with JIA but are in earlier stages of development: the Pediatric Quality of Life Inventory Scale (PedsQL)[63] and the Quality of My Life Questionnaire (QoMLQ).[64] New instruments are also being developed for use in children. The EQ-5D is a standardised instrument for use as a measure of health outcome in adults. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. It is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and in face-to-face interviews and takes only a few minutes to complete. A child-friendly version is being developed.[65] The European-funded DISABKIDS project is developing an instrument for assessing HRQoL. A pilot generic questionnaire for chronic conditions was tested in children with a range of chronic conditions including JIA.[66]

Review of patient-based outcome measures in children with JIA

Search strategy and inclusion of studies

A specific search strategy was developed in order to identify the papers describing the use of patient-based outcome measures in children with JIA and other connective tissue diseases (Appendix 1). Filters were used to identify studies in children with JIA and low BMD and/or fragility fractures. MEDLINE (on Ovid, searched from 1966) and EMBASE (on Elsevier, from 1974) were searched. The results of electronic searches were downloaded, checked for duplicates against previously downloaded references and stored using Reference Manager software. The final list of titles and abstracts was assessed and full publications were obtained where articles were thought to be potentially relevant. Bibliographies of papers were checked for further potentially relevant papers. The main electronic searches were conducted in January 2006. To be included in the review, studies had to describe the use of patient-based outcome measures in children (<18 years) with JIA or other connective tissue diseases and low BMD and/or fragility fractures. Studies had to be published in full.

Results

Two studies were included. One study used the JAFAR and the articular disease severity score (ADSS) to determine disease severity in children with JIA.[67] There was no correlation between BMD assessed using DXA and JAFAR score. In the second study, Mul and colleagues found a significant correlation between CHAQ score and lumbar spine BMD SD in a study of factors influencing BMD in children with rheumatic diseases.[68]

Summary

At present there is virtually no information on the use of patient-based outcome measures in children with JIA and low BMD and/or fragility fractures. Hence the usefulness of the approach cannot be determined from these data. Of the instruments available, the disease-specific CHAQ and the generic CHQ instruments seem to be most widely used in JIA and are associated with the most evidence. New instruments are being developed and may be applicable to JIA; the adult EQ-5D is being adapted for children and will include a question on pain.

Quantitative imaging techniques

Background

Bone strength depends on the mass of the bone and on the diameter, shape and microarchitecture of the bone. Skeletal growth and bone turnover are high in infancy; this slows and then stabilises towards puberty. At puberty there is a rapid increase in growth and peak BMD is usually

achieved in the second or third decade.[69] Thus, BMD is dependent on age and pubertal status in both boys and girls. Boys have a larger and stronger (but not denser) skeleton than girls. BMD is also dependent on the ethnic background of the child. All these factors must be taken into account when assessing bone status in children. An ideal bone health measure would be able to distinguish between changes in bone status resulting from the expected growth of children taking into account age, sex, pubertal status, ethnic background and those changes resulting from disease and treatment. The three most commonly used quantitative imaging techniques for assessing bone health and strength are DXA, peripheral quantitative computed tomography (pQCT) and quantitative ultrasound (QUS). Digital X-ray radiogrammetry (DXR) is a fourth, but less commonly used, option. All these four methods are described in the next sections.

Dual-energy X-ray absorptiometry

Principles of DXA

Single-energy photon absorptiometry (SPA) was one of the earliest techniques to become available for assessment of BMD.[70,71] A beam of radiation (commonly from an iodine-125 source) is passed through the limb and the difference in numbers of photons between the incoming and outgoing beam (attenuation) is determined; the higher the BMC, the greater is the attenuation. BMC is then calculated by comparing the results with the scan of a reference standard. Depending on the machine, scanning takes place at a single place or covers a rectilinear scanning pattern to cover a larger area of bone. However, single-energy densitometry has important limitations. The measurement site must be immersed in water in order to cancel the effect of the overlying soft tissues so that only the attenuation effect of bone is measured. Therefore, only peripheral bones such as the calcaneus and forearm can be measured and it is not possible to make measures in the hip or total body. Using a dual-energy radiation source eliminates the influence of soft tissue and a water bath is not needed to correct for soft tissue attenuation. Any skeletal site can be measured including the whole body and regions such as the lumbar spine, hip, calcaneus and distal radius. Dual-energy photon absorptiometry (DPA) used an isotope source of photons, principally gadolinium-153. Because SPA and DPA used radionuclides as photon sources, these methods had limitations; the radionuclides decayed and had to be replaced regularly and had a low photon flux, which caused scanning time to be long and spatial resolution to be poor.

Single-energy X-ray absorptiometry (SXA) and DXA use an X-ray system as the photon source and have superseded SPA/DPA. As with SPA, scanning with SXA requires the limb to be placed in a water bath. In adults, DXA is currently the gold standard for the measurement of bone density. The fundamental principle of DXA is to measure the transmission of X-rays through the body at high and low energies. The attenuation of these X-ray beams is dependent on the thickness, composition and density of the soft tissue and bone in the scan path: the low-energy photons penetrate only the soft tissue surrounding the bone whereas the high-energy photons penetrate both the soft tissue and the bone. The attenuation values are converted into a pixel by pixel measurement of aBMD by reference to a bone equivalent calibration phantom. Software algorithms detect the bone edges and bone area (cm^2) is calculated by summing the pixels within the bone edges. The reported value of the aBMD (g/cm^2) is the mean bone density over all the pixels within the bone area, and the bone mineral content (g) is calculated by multiplying the mean aBMD by bone area.

DXA clinical measurements are generally made at the lumbar spine (L1–L4) and the proximal femur (femoral neck, total hip, Ward's area and trochanter). It is not clear in children how reliably the measurement of one region reflects those of other regions or of the whole body measurement. For example, measurement of the lumbar spine may, or may not, be predictive of whole body measurement and/or hip measurement. Henderson found a significant correlation between lumbar spine and proximal femur *Z*-scores in 339 children.[72] However, the difference was often substantial for individual patients and increased as BMD deviated further from normal. In contrast, Shore and colleagues found no correlation between lumbar spine and forearm DXA results in children.[73] A study in 236 healthy adolescent girls found correlations between BMC and BMD at various sites including lumbar spine, femoral neck, trochanter, Ward's triangle and distal radius.[74] Hernandez-Prado and colleagues found significant correlations between BMD measured at peripheral sites (distal forearm and calcaneus) using a portable densitometer with DXA technology and central measurement (total body excluding head, proximal femur and lumbar spine) using DXA in 219 females aged 9–22 years.[75]

Strengths of DXA

DXA is the most widely used imaging technique of those reviewed in this chapter. The advantages of DXA are that it is precise and reproducible and

doses of radiation are relatively low (*Table 2*). Precision is a measure of the repeatability of a measurement and is normally expressed by the coefficient of variation (CV), which is calculated as the SD of repeated measurement divided by the mean. CV = (SD/mean)/100. Precision is machine and site specific. Although older DXA machines use pencil beam systems with a single detector, which take 15 minutes to complete a scan, most modern DXA machines use fan beam technology utilising a fan-beam X-ray source and multiple detectors and take only 1–5 minutes to scan. DXA instruments are also widely available.

DXA may be applied to the whole body or skeletal regions of interest, for example, the spine, proximal femur and radius.

In adults, BMD predicts the risk of osteoporotic fractures with the risk of fracture doubling for each 1 SD decrease in BMD.[24] A systematic review of studies investigating the association between bone density and fractures in children found an association of low BMD evaluated with DXA with increased fracture risk in five of eight studies.[26]

Limitations and precautions with DXA

Cortical and trabecular bone cannot be differentiated

Although DXA measures the average BMC at a specific skeletal area, it does not allow separate assessment of cortical and trabecular bone. The skeleton consists of dense cortical and spongy trabecular (cancellous) bone and the proportions differ across different skeletal sites. Trabecular bone predominates in the vertebrae and proximal femur whereas the midshaft of long bones consists entirely of cortical bone. Cortical and trabecular bones do not respond to diseases, drugs, mechanical loading or hormonal influences in the same way.[69]

Specific software needed for edge detection in children

During DXA scanning, the edges of the bone are detected using a software algorithm and the two-dimensional projected bone area is calculated. Edge detection algorithms that are designed for use in adults may not be able to detect the bone edges as accurately in children with low mineralisation of bones. Low-density software designed for use in children is available but the results cannot be compared with those based on adult software. Inaccuracies in DXA may also arise from unknown composition of soft tissues adjacent to the bone being analysed. Corrections are based on the assumption of a homogeneous distribution of tissue around the bone. This is not a problem if weight and body size remain constant but may be a problem for longitudinal measurements in children.

Appropriate reference data must be used in children

As with all scanning techniques, it is important to know what results would be expected in normal children before DXA scans from children with disease can be assessed. Adult BMD values are often expressed as *T*-scores: *T*-scores are calculated from the SD of the results compared with a reference normal population. In postmenopausal Caucasian women, a working group of the WHO arbitrarily defined osteopenia as those with aBMD between more than 1 SD but less than 2.5 SD and osteoporosis as aBMD of more than 2.5 SD below the mean for young adult women.[25] Those with *T*-scores of more than –2.5 SD are defined as having osteoporosis. However, T-scores are totally inappropriate for assessing children's data, but *Z*-scores, the number of SDs below the mean for a child of the same age, race and sex, can be calculated from reference data for children. The use of an appropriate reference is crucial for the interpretation of DXA scans and a major problem for using DXA is the shortage of appropriate reference data for use in children. As discussed in the following section on studies with DXA in normal children, there may be differences in BMD between girls and boys. There may also be differences in BMD between different ethnic groups. Therefore, the use of reference data could lead to erroneous BMD values if the reference

TABLE 2 *Precision, dose and time for scanning*[76]

Site	Radiation dose (μSv)	Precision (CV, %)	Time needed for scan (minutes)
Lumbar spine	0.2–5	2–3	1–5[b]
Total body	0.1–5	1–2	3–10[b]
Proximal femur	0.15–5.4[a]	0.5–5	1–5[a]

[a] The quoted radiation does not include the Lunar expert (now obsolete).
[b] For procedure, not scan acquisition time, which is 10–30 seconds.

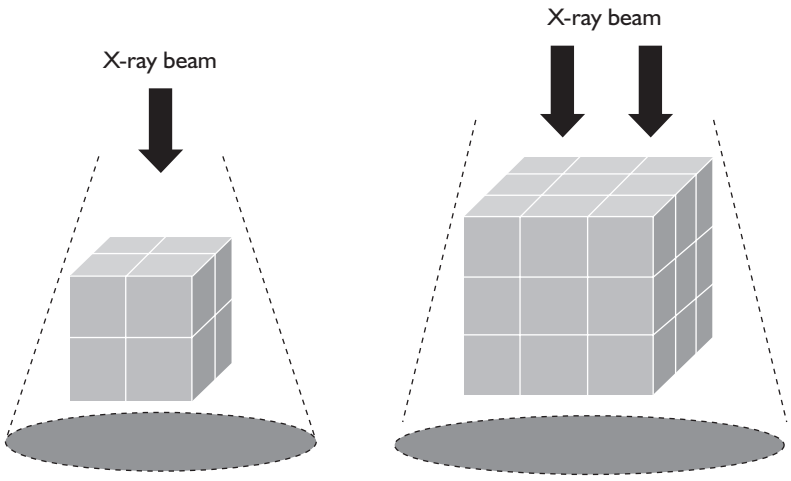
data were collected from children with a different balance of sexes and ethnic groups.[77–79] Ideally, the most appropriate reference database would be based on the sex and ethnicity of children being studied. Reference values reflecting the local population are preferable to manufacturers' and published reference values, but these are difficult and expensive to collect. Also, the use of different reference databases makes it difficult to compare results from different studies of DXA scanning. In general, large reference databases are preferable because any outliers will be less likely to affect the reference values collected. Ideally, reference databases should be provided by the manufacturer of each instrument; manufacturers are recognising the need for reference data in children and are developing such databases. A paediatric BMD reference database is being developed in the USA by Hologic.[80]

Results must be size-adjusted

The major drawback to using DXA in both children and, to a lesser extent, adults is that it is a projectional technique and its measurements are based on the two-dimensional projection of a three-dimensional structure. DXA provides the measurement of total amount of BMC (g) contained within the scanned skeletal region. The thickness of bone cannot be measured and therefore DXA provides only an approximation of the size of the bone. Only the two-dimensional bone area (BA) is available and BMD is estimated as the ratio of BMC to BA, that is, aBMD (g/cm^2). DXA is strongly influenced by bone size; bone density measured by DXA increases progressively in healthy children as they grow. Children may have low BMC or BMD either because they have small bones and/or because they have less mineral than expected for their size. It is important to distinguish between these two factors in terms of underlying pathology and need for treatment.[81] aBMD probably underestimates BMD in small children and overestimates BMD in larger children (*Figure 1*).

This size dependence may present problems in longitudinal studies of children, as DXA values will reflect both changes in skeletal size and BMD related to growth disease or its treatment. However, adjustments can be made to allow for size of bones using one of three possible methods.

- Bone mineral apparent density (BMAD) can be calculated by dividing BMC by the three-dimensional bone volume derived from its two-dimensional projected BA (Katzman, Carter



Mineral weight (g)	16	54
Volume (cm^3)	8	27
Projected area (cm^2)	4	9
Volumetric BMD (g/cm^3)	2	2
Areal BMD (g/cm^2)	4	6

FIGURE 1 *Size dependence of DXA. Each bone has exactly the same volumetric density; however, because DXA BMD does not take the depth of bone into account, the smaller bone has an apparently lower aBMD than the larger one. Reproduced by permission of the National Osteoporosis Society from* A practical guide to bone densitometry in children. *London: National Osteoporosis Society; 2004.*

and Kroger methods).[82–84] The BMAD of the lumbar spine is estimated by modelling it as a cube[83] or cylinder in order to obtain an estimate of volume.[84]
- Size-adjusted BMC can be estimated using a regression or multivariate statistical model to adjust BMC for confounders such as projected BA, overall body weight and height and Tanner stages of sexual development (Prentice method).[85,86] However, body height and weight may not completely control for all relevant differences in size and shape of the skeletal region of interest.
- A three-step approach aims to determine the following: (1) is the child's height appropriate for age; (2) is the bone size (area) appropriate for height; and (3) is the BMC appropriate for bone area (Molgaard method)[87]? These three steps correspond to three different causes of reduced BMD: short bones, narrow bones and light bones. Using these three steps, *Z*-scores are calculated for the following: BMC for age, height for age, BA for height and BMC for BA. These values are then compared with the relevant reference data obtained from healthy children.

Fewtrell and colleagues compared DXA scans in healthy children and children attending hospital (medical conditions not stated).[88] Five measures of BMC or BMD were derived, all adjusted for age and sex: aBMD, BMAD ($BMC/BA^{1.5}$), BMCh ($BMC/height^3$), BMCa (BMC adjusted for BA), and BMCt (BMC adjusted for BA and height). Results for size-corrected BMD were similar and classified significantly fewer patients as abnormal compared with aBMD. The additional adjustment for height did not improve on adjusting for BA alone. Thus, BMAD, BMCh or BMCa appear to be reasonable measurements for interpretation of DXA in children.

General quality control measures for DXA

Whether scanning children or adults, general quality control procedures are needed to ensure robustness of results. Scans should be performed in a specialist unit by staff skilled in the technique. Calibration phantoms provided by the manufacturer should be used. Follow-up DXA measurements must be made on the same machine and preferably by the same operator as the original measurement. Data should be analysed using the same software. The UK National Osteoporosis Society and the British Paediatric and Adolescent Bone Group have published recommendations on the use of densitometry in children.[76]

The comparison of patient data from different machines has been complicated because there is no universally accepted cross-calibration procedure or standard. The European spine phantom (ESP) has been developed with support from the European Union under its organisation Committee d'Actions Concertés–Biomedical Engineering (COMAC–BME).[89] Genant and colleagues cross-calibrated standard phantoms from manufacturers, the ESP and the ESP prototype to allow comparison of different DXA systems.[90]

Practicalities of performing DXA scans in children

Different age groups of children require different approaches when performing DXA scans. Babies may be scanned while sleeping but toddlers may require light sedation. From age 3 years upwards, children may cooperate when they are given an explanation of what is happening and a reward for staying still. Teenagers should be able to stay still.

DXA data from healthy children

Data in healthy children for DXA have been collected in many studies and 20 of the largest studies are summarised in Appendix 2.[91–113] Twelve of these studies are used as sources of reference data in healthy children.[92–97,101,105,107,109,110] A further paediatric BMD reference database[104] is being developed in the USA; data have only been published in abstract form to date.[80]

The DXA measurements demonstrated that BMC and BMD increased with higher age and pubertal status. The differences in BMD were greatest at puberty correlating with the growth spurt. In most studies there were no significant differences in BMD between boys and girls but girls reached peak BMD earlier than boys; in both sexes 80–90% of peak values were achieved by late adolescence. BMD differed between girls and boys. BMC and BMD of upper limbs were greater in boys than girls whereas the BMC and BMD of the pelvis were greater in girls than boys.[94] Lu and colleagues found a higher total body BMD in boys compared with girls.[114] Boot and colleagues noted that girls had higher spine BMD and BMAD but there was no difference in total body BMD.[98] Four studies noted a higher BMD in black compared with white girls and boys.[102–104,109] In the study by Boot and colleagues, ethnicity was not associated with BMD or BMAD in boys; Asian girls had a lower total body BMD than Caucasian girls but the BMD and BMAD of black children did not differ from other children.[98]

In clinical trials, DXA was able to detect differences in bone health after interventions

intended to improve the accrual of BMD. Fulkerson and colleagues reviewed the use of DXA in studies of interventions with physical activity programmes such as jumping exercises or with calcium-enriched diets or calcium supplementation in healthy children.[115] In 13 out of 14 studies, physical activity significantly increased BA, BMC and/or BMD. In 9 out of 10 studies, increased calcium intake significantly increased BA, BMC, aBMD and BMAD.

Peripheral quantitative computed tomography

Principles of QCT

The use of computed tomography (CT) to obtain bone density measurements is referred to as quantitative computed tomography (QCT) in order to differentiate it from imaging CT. QCT can be performed on most commercial CT systems for measurement of spine BMD with the addition of a bone mineral standard for calibration of the CT measurement and appropriate software. A single-energy low-dose scanning technique is used to reduce the radiation exposure to below that of a normal CT examination,[116,117] approximately 55 μSv in the spine, which is equivalent to two or three chest radiographs. Three or four lumbar vertebral bodies are measured using an 8–10-mm slice through the centre of each vertebra. The scan can consist of a single CT slice or a range consisting of multiple slices. Calibration is achieved by simultaneous scanning of a bone mineral reference calibration. From the CT images, the average attenuation of the vertebral body trabecular bone is determined in addition to that of the calibration standard. The known density of the standard allows the CT Hounsfield units to be converted into mg/cm^3 of bone mineral equivalents. QCT can uniquely provide separate measures of cortical and trabecular bone and, as most bone remodelling units are found on trabecular bone, it has high sensitivity for early changes in BMD.[116]

Specialised QCT systems, pQCT, have been introduced for measuring peripheral skeletal sites, particularly the forearm. These also provide measures of trabecular, cortical and integral (trabecular plus cortical) bone. Compared with axial QCT systems, dedicated pQCT systems are less expensive. In addition, they use lower levels of ionising radiation and measurements are easier to perform. Solid hydroxyapatite phantoms are generally used and in longitudinal studies the same phantom and scanner should be used.

Strengths of QCT

QCT is the only non-invasive three-dimensional BMD measurement available and it provides a volumetric density (mg/cm^3) as opposed to an areal density as reported with DXA.[116] Although QCT delivers a larger dose of radiation compared with DXA and radiogrammetry, the dose is lower than that used for imaging and less than for other commonly used imaging radiographic diagnostic tests and not greater than other 'everyday' radiation exposure, for example a round-trip transatlantic flight (100 μSv)[116] (*Table 3*). A further advantage over DXA is that pQCT can estimate bone size and shape.

Limitations and precautions with QCT

A major problem with QCT is that its use is limited to radiological facilities with the equipment and scanner time with competing pressures for use. The equipment is expensive, maintenance is costly and considerable technological expertise is required for proper execution. pQCT is less expensive than QCT.[116] The levels of ionising radiation are low compared with axial QCT, measurements are easier to perform and relatively scarce CT time is freed for other clinical patients. In adults, there is high precision and good correlation with axial BMD measurement.[116] However, very small children may find it difficult to keep their arms still. Precision, dose and time for scanning for pQCT are summarised in *Table 3*.

TABLE 3 *Precision, dose and time for scanning (includes positioning of patient and scanning)*[76]

Site	Radiation dose (μSv)	Precision (CV, %)	Time needed for scan (minutes)
Axial QCT			
Spine	30–60	0.8–1.5	10–15
Peripheral QCT			
Radius	<1.5–4 per scan	0.8–1.5	10
Tibia	<1.5–4 per scan	3.6–7.7 (3–5 years old)	
		1.3–1.8 (12 years old)	10
Femur	<1.5–4 per scan	1.2–4	10

The relationship between BMD as determined using QCT and the risk of fracture in children is unclear. Clark and colleagues systematically reviewed studies investigating the association between bone density and fractures in children and only one of two studies found an association between low BMD and fractures.[26]

General quality control measures for QCT

As for all measurement techniques, quality control measures are needed for QCT. In particular, as CT instruments are designed for imaging and not quantitative assessment, the stability of the system should be monitored frequently.[118]

QCT data from healthy children

QCT has been used to assess bone density in the lumbar spine of healthy children[119,120] (Appendix 3), but this site is little used because it involves exposing the abdomen to ionising radiation. Data using pQCT in healthy children are summarised in Appendix 3.[106,121–126] In a cohort study, Loro and colleagues examined whether pQCT could identify children predisposed to low peak BMD and osteoporosis in later life.[126] Forty healthy white children were followed for 3 years. Measurements of the cross-sectional dimensions of the femora and lumbar vertebral bodies and of the density of trabecular bone at the beginning of puberty, accounted for 62–92% of the variation at sexual maturity.

Quantitative ultrasound

Principles of QUS

Ultrasound has been used as an imaging technique for many years and has been adapted to allow measurement of bone health. Measurements from QUS are based on the loss of energy of the ultrasound beam (attenuation) as it passes through bone. Two primary measurements are obtained from the site being measured when using QUS: speed of sound (SOS) and broadband ultrasound attenuation (BUA). SOS (m/s) represents the time taken for an ultrasound pulse to travel a given distance through a bone. BUA is reflected in the reduced amplitude of the ultrasound wave because of scattering and absorption as it passes through bone. BUA (Db MHz^{-1}) is measured by calculating the slope of the change in attenuation over the frequency range of 0.2–0.6 MHz.[118] BUA and SOS are defined in different ways by different QUS devices.

The ultrasound scanning technique consists of two transducers, a transmitter and a receiver that are placed on opposite sides of the bone of interest. Most ultrasound scanners transmit the ultrasound wave through the bone with the receiver measuring the attenuated wave at the other side of the bone, most commonly the calcaneus. These scanners have fixed emitting/receiving transducers; some systems provide an image of the calcaneus and the position of the region of interest. However, a more recently developed device (Omnisense) is based on just one probe being used, the ultrasonic wave travelling along the cortical bone, and this reflected wave being measured; this technique is called ultrasound critical angle reflectometry. No information on bone structure is provided.

Ultrasound can only be applied to the peripheral skeleton and sites for measurement include the calcaneus, phalanges, radius, patella and tibia. The most commonly measured site is the calcaneus, which is rich in metabolically active trabecular bone and is weight bearing with little surrounding soft tissue. Axial sites cannot be measured because of the large amount of soft tissue and muscle that overlie these sites which attenuate the ultrasonic beam.[76]

The calcaneus is also the most usual site for QUS measurement in children. There are two approaches to calcaneal QUS; the first uses a water bath in which the foot must be placed. However, these are designed for adults and do not accommodate the smaller feet of children.[118] In addition, it is difficult for children to keep their feet immobile and reproducible foot positioning is difficult, if not impossible.[118] Calcaneal dry systems have been developed. These use gel as a form of coupling; transducers are manually positioned over the calcaneus in direct contact with the patient's skin. Dry systems have also been developed for the fingers and tibia. The Omnisense can measure QUS parameters at any skeletal site including spine, radius, phalanx and calcaneus.

Strengths of QUS

QUS offers several advantages over other methods of measuring bone density, including the lack of exposure to ionising radiation, cost, speed and ease of use. Also, the equipment is compact and portable and can be used in a community rather than a hospital or clinic setting.[116]

Limitations and precautions with QUS

QUS has only modest precision compared with DXA and QCT. This may be explained in part by the effect of soft tissue, acoustic coupling and repositioning errors affecting the site being measured. The complex bone structure of the

TABLE 4 *Precision, dose and time for scanning*[76]

Site	Radiation dose (μSv)	Precision (CV, %)	Time needed for scan (minutes)
Calcaneus	Not applicable		5
Phalanges	Not applicable	BUA 1.6–5	<5
Radius	Not applicable	0.5–1.2	5–10
Tibia	Not applicable		

calcaneus and its lack of homogeneity may result in variable transmission times. In addition, foot positioning may be an important source of error especially in children using equipment designed for adults. *Table 4* lists precision, dose and time for scanning with QUS.

QUS results are temperature dependent and can be adversely affected by inadequate coupling with gel between transducer and skin, poor positioning of hand-held transducers, variations in foot size and shape and the presence of subcutaneous oedema in the site of measurement.[76]

It is not clear what is being measured by QUS.[116] Ultrasound values depend on structural parameters which are not fully understood and limit its interpretation, for example, the number, thickness and mineral content of the trabeculae and their three-dimensional arrangement influence measurements.[127] QUS measurements may be correlated more with bone size than with changes in the amount, density or geometry of bone, that is, recorded changes may be related to skeletal growth.

QUS parameters can predict hip, wrist or other fractures in post-menopausal women and men[128–130] but little information is available for children. In a systematic review of studies investigating the association between bone density and fractures in children, the two studies using QUS found an association between low bone mass and fractures, thus suggesting that QUS measurements may be able to predict fracture occurrence.[26]

General quality control measures for QUS

The main concern with QUS is that the large number of scanners available make it difficult to compare results from different machines and there is no universally accepted calibration phantom. Several QUS scanners previously available are now no longer manufactured.

QUS data from healthy children

Twenty-two studies evaluated calcaneal QUS in healthy children (Appendix 4).[125,131–151] In 3299 children, BUA increased with age in both girls and boys but there was no correlation between SOS and age, height or weight.[137] Van den Bergh and colleagues found that BUA increased significantly with age in both girls and boys and SOS increased with age in girls but not in boys.[138] Micklesfield and colleagues examined QUS in three different ethnic groups of children; BUA and SOS were lower in the white girls even after adjusting for height and Tanner stage.[141] Sawyer and colleagues found that age, weight, height, and hours of weight-bearing physical activity were all significantly associated with BUA and SOS.[136] However, after controlling for age and weight, hours of weight-bearing physical activity showed little or no additional effect on these parameters. Daly and colleagues observed that gymnasts had a significantly greater SOS in calcaneus (and also in radius and phalanx) than non-gymnasts, but there were no differences in BUA.[149] Calcaneal SOS and BUA were significantly correlated with total body BMD from DXA,[132,135] but in two studies, calcaneal QUS could not distinguish children with low spinal BMD as determined by DXA.[134,152]

Three studies have assessed tibial QUS.[142–144] There was a significant correlation between tibial QUS and lumbar spine and total body BMD from DXA.[143] QUS in the patella has also been evaluated. In a longitudinal study, QUS values increased throughout the study, peaking earlier in girls than boys and the maximum bone density occurred at ages corresponding with those expected from DXA measurements.[151] In two other studies, apparent velocity of ultrasound was positively correlated with age and pubertal stage[145] and negatively correlated with activity.[146]

Digital X-ray radiogrammetry

Principles of DXR

Radiogrammetry is the quantitative measurement of the thickness of bone, measured from a radiograph of the non-dominant hand; the approach is based on that of Barnett and Nordin, who demonstrated age-related bone loss in women.[153] Measurements made in the second metacarpal of the hand assess total width and cortical thickness; the results are expressed as a

cortical index.[116] Garn established a large database of normal data from adults.[154] Studies in adults have shown a relationship between cortical index and BMD, but this has not been validated for children.[116] Meema and colleagues found that radiogrammetry discriminated between fracture and non-fracture cases in adult women.[155–157] Initially, radiogrammetry had to be performed manually with callipers and a ruler and was simple and inexpensive but impractical for large studies. It has recently been automated; this approach is referred to as DXR (Sectra Pronosco devices).[116]

Strengths of DXR

DXR has several advantages over the other available techniques. It is easy to use, X-ray equipment is widely available, the effective radiation dose is low and the method is less sensitive to motion artefacts and soft tissue thickness compared with DXA.[116] In addition, DXR has the advantage of using simple radiographs of the hand, which are common practice for bone ageing in children suspected of decreased bone maturation; thus children will not be exposed to additional radiation.[116] The automated technique has the advantages of low cost and ease of use.[116]

Limitations and precautions with DXR

Using DXR, BMD is measured in two dimensions only. DXR measures the peripheral skeleton only, although studies in adults have indicated that the hand is a good indicator of BMD at other skeletal sites.[116] However, there are no data on the relationship between bone strength as determined by DXR and the risk of fracture. Studies are needed to confirm the applicability of the automated system in children.[116]

DXR data from healthy children

Malich and colleagues were able to use the DXR in children from the age of 6 years and observed BMD increases with increasing age; girls aged 11–12 years also had higher BMD compared with boys of the same age corresponding to the start of puberty.[158]

Review of quantitative imaging techniques in JIA

Search strategy and inclusion of studies

A specific search strategy was developed in order to identify the papers describing the use of different quantitative imaging techniques (DXA, QCT, QUS, DXR) to assess bone health in children with JIA and other connective tissue diseases (Appendix 5). A range of terms had to be used, including terms for the various expressions of outcome and also the terms for the method of measurement. A filter was used to identify studies in children, using appropriate terms such as babies, infants, children and adolescents. MEDLINE (on Ovid, searched from 1966) and EMBASE (on Ovid, from 1980) were searched. The results of electronic searches were downloaded, checked for duplicates against previously downloaded references and stored using Reference Manager software. The final list of titles and abstracts was assessed and full publications were obtained where articles were thought to be potentially relevant. Bibliographies of papers were checked for further potentially relevant papers. The main electronic searches were conducted in March and April 2005.

To be included in the review, studies had to describe the use of different methods (DXA, QCT, QUS, DXR) to assess bone health in children (aged <18 years) with JIA. All study designs were included but excluding case series and case reports. Studies had to be published in full.

Forty-nine papers were identified through the searching process and 16 papers were excluded from the review (Appendix 6). Therefore, 33 papers were included in the review: 25 studies used DXA, two used QCT or pQCT, five used QUS and one used DXR. Studies which assessed bone health after treatment with bisphosphonates were included in the review of effectiveness (Chapter 3).

Results: dual-energy X-ray absorptiometry

A total of 25 studies evaluated the use of DXA to measure BMD in children with JIA and other connective tissue diseases: 13 cross-sectional studies,[17,21,68,73,103,159–166] five case–control studies,[20,67,167–169] six cohort studies[19,170–174] and children from a clinical trial of growth hormone[175] (Appendix 7).

As in healthy children, BMD of children with JIA and connective tissue diseases increased with age and pubertal stage. Thirteen studies compared BMD in children with JIA and other connective tissue diseases with BMD of healthy control children.[17,20,21,67,103,159,160,164,167–170,174] DXA consistently identified that children with JIA and other connective tissue diseases had lower BMD than healthy controls at sites including the total body, lumbar spine and femoral neck. For example, BMD was significantly lower in JIA children compared with healthy controls (mean 0.533 g/cm^2 versus 0.636 g/cm^2, $p < 0.001$).[67] These areal BMD data might be affected by

growth impairment in JIA. In contrast, in a 24-month cohort study, Lien and colleagues[174] found no difference in BMC (corrected for size using the method of Kroger and colleagues[84]) at baseline but healthy children had significantly greater gains than children with rheumatic disease in total body BMC (difference 35 g, $p = 0.035$) and distal radius BMC (0.08 g, $p < 0.001$).[174] BMC was low or very low (Z-score <–2) in 24% of children with JIA and 12% of healthy children.

In 12 studies, the effect of disease status on DXA measurements was determined. Active disease, including high erythrocyte sedimentation rate (ESR), increased physical function limitation and higher joint count severity, was associated with lower BMD than quiescent disease in five studies.[17,159,167,171,173] A further study found no relationship between disease activity and BMD.[166] Increasing duration of disease and/or young age at onset of disease were associated with lower BMD.[67,160,162] In children with arthritis, acquisition of bone was also affected by disease subtype. Pereira and colleagues noted that BMD loss occurred in polyarticular, pauciarticular and systemic subtypes but was highest in children with polyarticular disease.[160] In a second study, total body BMC was lower in children with polyarticular disease compared with those with oligoarticular disease.[164] At baseline, Kotaniemi and colleagues recorded a significantly decreased lumbar spinal and femoral neck BMD in children with polyarticular JIA compared with healthy controls, but was only significantly decreased at the femoral neck in children with oligoarticular disease.[170] During follow-up, children with polyarticular JIA acquired less bone at the femoral neck than healthy children but there was no difference in spinal bone acquisition. In children with oligoarticular JIA, the acquisition of bone at the femoral neck was similar to controls but aBMD was increased at the spine, which may be caused by rapid increases in volumetric bone mineral density (vBMD).[170] Henderson and colleagues found that of three different clinical indices of articular inflammation (swollen joints, involved joints which were defined as joints with swelling, pain on motion, tenderness or limitation of motion, and articular severity score) only the number of involved joints was significantly lower in children with JIA who had normal BMC compared with those with low BMC.[21] There were no significant differences between groups with normal and low BMC for age at disease onset, JIA course subtype, disease activity, disease duration, ESR, number of swollen joints, articular severity score, JAFAR score or the number of years between disease onset and menarche.

In eight of 11 studies in which treatment with corticosteroids was assessed, corticosteroids were generally associated with reduced BMD, particularly at the lumbar spine.[17,20,67,160,166,167,170,171] Alsufyani and colleagues found that children with low BMD tended to have received higher doses of corticosteroids compared with those who have normal BMD.[166] Celiker and colleagues noted that BMD was significantly reduced in corticosteroid-treated children compared with controls; BMD was also reduced in non-corticosteroid-treated children, but the difference was not significant.[67] Kotaniemi and colleagues found a correlation between BMD and dose but not duration of corticosteroid treatment.[167] Three studies found no effect of corticosteroid treatment on BMD.[19,21,68] Treatment with methotrexate did not appear to affect acquisition of bone mass.[21,171] Four years of treatment with growth hormone increased BMAD in children with JIA.[175]

Eight studies corrected BMD for size[17,21,68,163,167,170,174,175] using the methods of Kroger and colleagues,[84,176] Molgaard and colleagues[87] or Carter and colleagues.[83]

Eleven studies determined values for precision of DXA in children with JIA or connective tissue diseases (*Table 5*). Depending on the site of measurement, *in vivo* values of 0.7–3.8% were obtained.

Results: peripheral quantitative computerised tomography

Two studies assessing the use of QCT or pQCT in children with JIA or connective tissue disease were included (Appendix 8): one cross-sectional study and one case–control study.[177,178] One study was published in German and was translated.[178] Fredericks and colleagues performed CT scans of the lumbar spine in 132 children aged 3–15 years with various disorders associated with osteopenia, including six with collagen disease.[177] Thirty-seven control children underwent CT scans for other reasons. Children with idiopathic osteoporosis, osteogenesis imperfecta (OI) and some with prolonged corticosteroid therapy had low values for total BMC compared with the controls.[177] In a study using pQCT of the radius, Lettgen and colleagues compared 27 children with active rheumatic disease with age- and sex-matched controls.[178] Children with disease had lower total and trabecular BMD than the controls but there was no significant difference in cortical BMD.

TABLE 5 *Precision: studies of DXA in children with JIA or connective tissue disease (only values determined by investigators or their institution reported)*

Study	Site	Precision (CV, %)	Dose of radiation (μSv)
Kotaniemi *et al.*, 1993[167]	Lumbar spine, femoral neck	Hospital 1: spine 1%, femoral neck 1.8% Hospital 2: spine 0.9%, femoral neck 1.5%	Not stated
Henderson *et al.*, 1997[159]	Skull, arms, hips, legs, thoracic and lumbar spine, pelvis	Total body 0.9% for 5–10 years	Not stated
Kotaniemi *et al.*, 1998[170]	Lumbar spine, femoral neck	Spine 1.4%, femoral neck 3.8%	Not stated
Bianchi *et al.*, 1999[171]	Total body, lumbar spine	Spine <1%, total body <1.3%	40
Kotaniemi *et al.*, 1999[17]	Lumbar spine, femoral neck	Spine 1.4, femoral neck 3.8%	Not stated
Henderson *et al.*, 2000[21]	Total body, lumbar spine	Total body 0.7%, spine 1.2%	Not stated
Falcini *et al.*, 2000[172]	Lumbar spine	*In vitro*, 0.4%	Not stated
Perez *et al.*, 2000[19]	Total body	>1.5%	Not stated
Lien *et al.*, 2003[164]	Total body, lumbar spine, hip, forearm	0.98–0.99%	Not stated
Fielding *et al.*, 2003[163]	Total hip, femoral neck, lumbar spine, whole body	<1% all sites	Not stated
Lilleby *et al.*, 2005[169]	Femoral neck, lumbar spine, total body, distal one-third radius	*In vitro*, 0.5%; *in vivo*, spine 1.6%, femoral neck 2%	Not stated

TABLE 6 *Precision: studies of QCT in children with JIA or connective tissue disease (only values determined by investigators or their institution reported)*

Study	Site	Precision (CV, %)	Dose/scan time
Fredericks *et al.*, 1990[177]	Lumbar spine		2 s
Lettgen *et al.*, 1996[178]	Radius	Phantom 0.21%, *in vivo* 0.75%	0.1 Gy

There were no differences in bone density between children with and without systemic disease and between corticosteroid-treated children and those not receiving corticosteroid treatment.

One study determined values for precision of pQCT in children with JIA or connective tissue diseases; the *in vivo* value for CV was 0.75% for the radius (*Table 6*).

Results: quantitative ultrasound

Seven studies evaluated the use of QUS in children with JIA or other connective tissue diseases: four cross-sectional studies[152,162,163,179,180] and three case–control studies[165,172,180] (Appendix 9).

Five studies have compared the bone density parameters obtained from ultrasound with those from DXA. A study using the paediatric contact ultrasound bone analyser in children with JIA, systemic lupus erythematosus (SLE), or juvenile dermatomyositis demonstrated a good correlation between calcaneal BUA and lumbar spine BMD from DXA; in 53 children, spine BMD from DXA measurements and calcaneal BUA were lower than in healthy controls.[172] Njeh and colleagues[162] noted a good correlation between ultrasound measurements (using the Soundscan 2000) in the tibia and BMD in the spine and total body in Caucasian children with JIA. Hartman and colleagues[165] noted a good correlation between lumbar spine DXA and radial, but not tibial, ultrasound parameters (Omnisense 7000S ultrasound bone sonometer device) in Caucasian children with JIA and other rheumatic diseases. Fielding and colleagues found only a weak correlation between calcaneal ultrasound results (Lunar Achilles Plus ultrasonometer) and spinal BMD (assessed with DXA) in 42 children (67% Caucasian, 19% Asian-American 12% Hispanic and 2% African-American) with chronic disease and/or fragility fractures.[163] Sensitivity/specificity

TABLE 7 *Precision: studies of QUS in children with JIA or connective tissue disease (only values determined by investigators or their institution reported)*

Study	Site	Precision (CV, %)
Jaworski *et al*., 1995[180]	Calcaneus	SOS 0.2, BUA 1.5, stiffness 1.8
Falcini *et al*., 2000[172]	Calcaneus	*In vitro* BUA 1.8, *in vivo* BUA 3.7
Fielding *et al*., 2003[163]	Calcaneus	BUA 0.3, SOS 1.8
Baroncelli *et al*., 2003[179]	Phalanges	*In vivo* intra-observer and inter-observer 0.55 and 0.91, respectively

analyses indicated 80% concordance between children identified by calcaneal ultrasound and spinal DXA BMD as having osteopenia. Baroncelli and colleagues assessed fractures bone quality in children with a range of bone and mineral disorders including JIA using QUS of the phalanges of the hand (DBM Sonic 1200).[179] Amplitude-dependent SOS cortical area to total area ratio, lumbar BMD area and lumbar BMD volume (assessed with DXA) were significantly reduced in these children compared with reference values. These measurements were also significantly lower for children with fractures compared with those without fractures. Jaworski and colleagues found a good correlation between calcaneal SOS, BUA and stiffness (a mathematical combination of BUA and SOS) using the Achilles ultrasound densitometer and BMD measured for total body, spine and heel, and found that these measurements were significantly lower in children with osteopenia compared with healthy children.[180]

Four studies determined values for precision of QUS in children with JIA or connective tissue diseases (*Table 7*). Three studies obtained precision (CV) at the calcaneus: *in vivo* BUA 0.3–3.7% and SOS 0.2–1.8%. One study obtained values for the phalanges.

Results: digital radiogrammetry

One study in both healthy children and children with inflammatory bowel disease and JCA was included.[181] There were statistically significant differences in BMD between healthy boys and girls for ages 11, 12, 16, 17 and 18 years and also differences in BMD between the sequential Tanner stages. Girls with JIA had a statistically significantly lower *Z*-score than matched controls ($p = 0.001$); boys had a lower *Z*-score but this was not significant ($p = 0.361$). Girls with a history of forearm fractures also had a significantly lower BMD than controls ($p = 0.018$).

Summary

Most data were available for DXA. In addition to assessment in healthy children where DXA showed increases in BMD with increased age, largely because of increased size, and also differences between the sexes and pubertal stages, DXA has been widely used in studies of children with JIA and connective tissue disease and was shown to be sensitive to differences between different subtypes of disease, disease severity and factors such as treatment with corticosteroids. DXA facilities are readily available and easy to use, although they have limitations when interpreting the results in children. However, the studies were heterogeneous in design and analysis. The studies were of cross-sectional, case–control, cohort design and included children with a range of different diseases in addition to JIA, the definitions of JIA were unclear, different subtypes and severities of disease were included and children were receiving different treatments. BMD was assessed at different sites and only some studies adjusted the results for body size. QCT offers advantages over DXA in that it provides a true volumetric density and so is not size dependent, but scanning presents problems in that it is more difficult to access and doses of ionising radiation are relatively high. At present, there have been few studies in children with JIA. QUS is a promising technique which does not expose children to ionising radiation, but data are limited and interpretation of the results in children with JIA is unclear. Finally, there are few data using DXR.

Biochemical markers of bone turnover

Background

Biochemical markers of bone turnover are indirect indices of skeletal metabolism. They rely on the measurement, in serum or urine, of enzymes, matrix proteins and collagen degradation products that are released into the body fluids during bone modelling and remodelling. Markers of bone formation are the products of osteoblasts. Type I collagen is produced during proliferation of osteoblast precursor cells; the expression of

alkaline phosphatase (ALP) starts after cell proliferation has stopped and declines as matrix mineralisation starts.[182] Bone resorption includes dissolution of calcium salts and subsequent enzymatic breakdown of the organic matrix, which is mainly composed of type I collagen.[182] Breakdown of collagen fibres results in a mixture of peptides and free amino acids. Although these markers are classed as being indicative of bone formation or resorption, these processes are coupled and therefore whenever bone turnover is increased, both processes are accelerated and markers of both phases are increased.[183] A range of biochemical markers of bone formation and resorption have been investigated and the next section discusses those most widely used in clinical trials and in routine clinical practice and their applicability to measurement of bone status in children.

Biochemical markers of bone turnover used in children

The commonly used biochemical markers of bone turnover for adults are listed in *Table 8*. These markers are predominantly used only in a research setting, although they may sometimes be used in clinical practice to monitor response to treatment. This section summarises the use of bone markers in healthy children.

Markers of formation

Human ALP constitutes a system of enzymes that hydrolyse a phosphoric ester acid bond from organic and inorganic substrates.[183] Skeletal ALP is released into the circulation from osteoblast membranes;[184] about 80% of total ALP in children is derived from bone (bone-specific ALP).[185] Other sources of ALP, in addition to bone, include the liver, kidney and intestine. Serum total ALP has been widely used as a marker of bone formation but it lacks sensitivity and specificity.[184] In children, bone-specific ALP levels increase until mid-puberty to 2–3 times adult levels, then decrease in late puberty, with adult levels being achieved earlier in girls than boys.[186–189]

Osteocalcin (OC), also referred to as bone Gla-protein, is a non-collagenous protein present almost exclusively in bone and dentin;[183] its precise function remains unknown.[184] OC is predominantly synthesised by mature osteoblasts and is mainly incorporated into the bone matrix, but 10–25% is released into the circulation.[183] Neonates have OC levels of 20–40 ng/ml, which then decline slightly in infancy.[183] During adolescence, levels increase with a peak at about 12 years in girls and 14 years in boys (coinciding with the growth spurt), and then decreasing to adult levels.[186,188,190–192]

Collagen is the predominant protein in bone, comprising about 90% of the organic bone matrix, of which 91% is type I collagen.[182] During the extracellular processing of type 1 collagen, the amino (N)-terminal and carboxy (C)-terminal extension peptides are removed by enzymes; procollagen type I C-terminal propeptide (PICP) and procollagen type I N-terminal propeptide (PINP) then circulate in blood. In adults, PICP is more sensitive than PINP in detecting deviations from normal in patients with metabolic bone diseases.[183] Studies report that PICP levels were highest in infants and then fell by 2–4 years old, and then decreased further towards adult levels in late puberty.[189,191,193–196] Zanze and colleagues observed that PICP levels were lower in 24- than 10-month-old children.[197] PINP has been less studied than PICP in children. However, PINP levels were also highest in infancy, with levels decreasing with age; prepubertal levels were four to five times higher than adult levels, and they decreased towards adult levels in late puberty.[198]

Markers of resorption

Hydroxyproline (HYP) has been the most widely used marker of bone resorption in adults and children for more than 30 years.[182] It is a product of the post-translational hydroxylation of proline in the procollagen chain.[186] Because half of human collagen is found in bone where its turnover is probably faster than in soft tissues, excretion of HYP in urine is regarded as a marker of bone resorption.[184] However, HYP is not specific for bone as it is found in collagen in other

TABLE 8 *Biochemical markers of bone turnover*

Formation

Serum

- Osteocalcin (OC)
- Total and bone-specific alkaline phosphatase (ALP)
- Procollagen type I C- and N-propeptides (PICP, PINP)

Resorption

Plasma/serum

- Tartrate-resistant acid phosphatase (TRAP)
- C-terminal cross-linked telopeptide of type I collagen (ICTP)

Urine

- Pyridinoline (PYD) and deoxypyridinoline (DPD)
- C-terminal (CTX) and N-terminal (NTX) cross-linked telopeptides of type I collagen
- Hydroxyproline (HYP)
- Galactosylhydroxylysine (GHL)

tissues; also, levels can be raised, for example by dietary protein.[186] HYP levels are high and exceed adult levels, by about five times in infancy and puberty; levels decline after puberty.[183,186] Weaver and colleagues found highly significant correlations between bone resorption measured by calcium kinetics and serum levels and urine creatinine ratios of HYP.[199]

Hydroxylysine is the result of hydroxylation of lysine in the procollagen chain forming two glycosides: galactosylhydroxylysine (GHL) and glucosylgalactosylhydroxylysine (GGHL).[186] GHL is a prevalent product of bone collagen whereas GGLH is more specific of skin collagen.[183] Few data are available on the use of hydroxylysine in children. In children, GHL excretion is higher than in adults. Rauch and colleagues found that excretion was 3–5 times higher in subjects aged 4–16 years compared with adults; the highest values were in the youngest children and the lowest results in the oldest age group.[200,201] Levels correlated with growth velocity and other urinary markers of bone resorption.[200]

Acid phosphatase is a lysosomal enzyme that is present primarily in bone osteoclasts, prostate, platelets, erythrocytes and spleen.[184] Only the bone acid phosphatase [tartrate-resistant acid phosphatase (TRAP)] is resistant to L-(+)-tartrate. TRAP is probably required for normal mineralisation of developing bone and for the resorption of adult bone. However, lack of specificity of TRAP for osteoclasts, its instability in frozen samples and the presence of enzyme inhibitors in serum are potential drawbacks.[186] Few studies have examined TRAP in children. In girls aged 11–16 years, TRAP levels were maximal in mid-puberty then decreased to adult levels during late puberty.[193]

Pyridinoline (PYD), also known as hydroxylysylpyridinoline, and deoxypyridinoline (DPD), also known as lysylpyridinoline, are generated from hydroxylysine and lysine during post-translational modification of collagen and form two major cross-links in the collagen molecule.[186] PYD and DPD are released during matrix resorption and are excreted in the urine. Urine levels of DPD show less variance than PYD in urine and DPD is a more specific bone resorption marker.[185] In children younger than 18 months, PYD concentrations were significantly greater than adult concentrations; levels declined from 1 to 18 months of age.[202] Similarly, Zanze and colleagues observed that both DPD and PYD levels were lower in 24- than 10-month-old children.[197] Husain and colleagues observed a decrease in PYD and DPD with increasing age up to 10 years, with a wide range of values between individuals.[203] Prepubertal levels of PYD and DPD were 4–6-times higher than in adults and they decreased towards adult levels in mid- to late-puberty.[187,193,198,204–206] Conti and colleagues noted that the highest levels of DPD occurred at Tanner stage II–III (mid-puberty) in girls and at stage IV–V (mid-late-puberty) in boys.[207] Two studies noted high variability in PYD and DPD levels in individual children, indicating that single measurements of DPD and PYD may not adequately reflect bone resorption rates in children.[204,208]

The N-terminal cross-linked (NTX) and C-terminal cross-linked telopeptides of type I collagen (CTX, ICTP) are PYD- and DPD-containing peptides located at the N- and C-intermolecular sites of the collagen fibrils.[185] Mora and colleagues observed that NTX levels decreased from 4 years old with a peak of excretion at puberty.[198] However, Zanze and colleagues observed that NTX levels were lower in 24- than 10-month-old children.[197] Bollen and Eyre noted that NTX excretion was highest during the first year of life, with minor increases around age 5–8 years for girls and 6–9 years for boys and a peak around age 11–12 years for girls and 12–13 years for boys.[209] There were highly significant correlations between bone resorption measured by calcium kinetics and fasting serum levels and urine creatinine ratios of biochemical markers.[199] The highest ICTP levels were in infants younger than 1 year and then were lower between the ages of 2 and 14 years.[191] ICTP levels were maximal in mid-puberty then decreased to adult levels during late puberty.[193,195] These findings were confirmed by Crofton and colleagues, who measured ICTP in children from birth to 19 years old to develop reference data.[210] They observed that the highest concentrations of ICTP occurred during the first month of life, with slightly lower concentrations at 1 year of age and then a marked decrease but then no significant changes until age 9 years. In boys, there were then progressive increases peaking at 14–17 years before decreasing again at 17–19 years. In girls, ICTP increased progressively from 1–9 years to 9–11 years, peaking at 11–13 years before decreasing at 13–15 years and further at 15–19 years. For neonates, infants and children aged 1–9 years, there were no differences in ICTP between males and females but girls aged 12–13 years had higher ICTP levels than boys and girls aged 14–15, 15–16

and 16–17 years all had lower concentrations than boys.[210]

Strengths of using bone markers in children

In adults, it has been suggested that markers of bone turnover may be sensitive to treatment effects before densitometry techniques can pick up early changes in BMD.[211] Bone markers may be useful as an adjunct to BMD measurements in postmenopausal women in whom they may predict osteoporosis and fracture risk as they respond rapidly to therapeutic interventions before changes in BMD are detected.[212] However, there are few data in children. However, Mora and colleagues noted a significant inverse correlation between bone-specific ALP and osteocalcin with femoral BMD (measured using QCT).[187] Previous growth velocity and bone mass accretion were correlated with PICP levels in infants aged less than 18 months but were not associated with future growth.[202] PICP is also positively correlated with bone mineral accrual.[186] DPD and PYD correlated with apparent vertebral density but not material density of the femur.[187]

Limitations and precautions with using bone markers

Although the role of bone markers is being evaluated in children, good markers in children are still to be determined. Schoenau and Rauch reviewed the biochemical markers of bone turnover that are used in children and provided reference ranges for the different markers in healthy children (total and bone-specific ALP, OC, HYP, PICP, DPD, ICTP, CTX, NTX).[182] The values were obtained from published studies or from the manufacturers of the assay equipment and materials. The reference ranges were wide for all markers. In addition, the intra-person variation in bone markers was high and the variation of markers in urine was greater than those in serum. Therefore, a single measurement of bone markers may be of limited value.[185]

Biochemical markers cannot distinguish whether changes in remodelling rates are the result of focal bone disease or reflect systemic conditions.[183] Circulating markers can also be influenced by factors other than bone turnover.[183] Liver uptake and metabolism, renal excretion trapping in the bone tissue or uptake by osteoblasts may significantly affect results.[183]

There are also practical problems associated with determining levels of markers in children. Urine assays are less invasive than blood assays but are hard to collect in children. There are practical problems associated with measuring urinary excretion of markers in children and adolescents. It may be difficult to obtain a 24-hour urine collection. Early morning specimens may be taken but results may be affected because of the circadian rhythms with some bone markers.[186] For example, levels of PYD and DPD are measured using a 24-hour urine sample; 2-hour samples are also possible but yield higher values than 24-hour samples because bone resorption occurs more rapidly during the night than the day.[183] The excretion of hydroxyproline during a 24-hour urine sample is highly dependent on dietary collagen and patients must follow a collagen-free diet for at least 2 days before urine collection.[183] Alternatively, a 2-hour sample may be taken and corrected for creatinine after an overnight fast.[183]

Review of biochemical markers of bone turnover as outcome measures in children with JIA

Search strategy and inclusion of studies

A specific search strategy was developed in order to identify the papers describing the use of biochemical markers of bone turnover to determine bone health in children with JIA or other connective tissue disease (Appendix 10). MEDLINE (on Ovid, searched from 1966) and EMBASE (on Ovid, from 1980) were searched. The results of electronic searches were downloaded, checked for duplicates against previously downloaded references and stored using Reference Manager software. The final list of titles and abstracts was assessed and full publications were obtained where articles were thought to be potentially relevant. Bibliographies of papers were checked for further potentially relevant papers. The main electronic searches were conducted in June 2005. Included in the review were studies, published in full, describing the use of biochemical markers of bone turnover in children and adolescents (aged <18 years) with JIA and other connective tissue diseases. All study designs were included but excluding case series and case reports.

Twenty-nine papers were identified through the searching process. Eleven papers were excluded (Appendix 11) and, therefore, 18 papers were included in the review. Studies which assessed biochemical markers of bone turnover after treatment with bisphosphonates were included in the review of effectiveness (Chapter 3).

Results

Of the 18 papers included in the review, there was one clinical trial,[213] four cross-sectional

studies,[21,161,164,214] seven case–control studies[20,168,169,215–218] and three cohort studies;[174,219,220] three studies included children with JIA who had received growth hormone for retarded growth[18,175,221] (Appendix 12). Nine studies compared children with JIA with healthy control children.[20,168,169,174,214–219] Three studies compared children with JIA and low BMD with children with JIA and normal BMD.[21,161,164] Five studies examined the effects of treatment with corticosteroids on bone markers.[20,168,213,217,218]

Differences between JIA and healthy children and children with JIA

In cross-sectional studies, studies noted different effects of JIA on bone markers. Periera and colleagues noted age- and sex-dependent differences in OC and bone-specific ALP and HYP:creatinine and DPD:creatinine ratios between children with JIA and healthy controls.[218] All markers were reduced in older healthy children (girls aged >12 years and boys >14 years) compared with younger children. Girls aged ⩽12 years and boys ⩽14 years with JIA had lower levels of the OC and bone-specific ALP compared with healthy children of the same age. Girls aged ⩾13 years had increased HYP:creatinine and DPD:creatinine compared with healthy children of the same age. Two studies also found that OC, bone-specific ALP and TRAP were reduced in children with JIA.[168,216] In contrast, three studies noted no differences in OC between children with JIA and healthy children.[20,214,217] Falcini and colleagues[217] also found no differences in total ALP, PICP and ICTP and Pepmueller and colleagues[168] found no differences in PICP and urinary DPD:creatinine ratio between the groups. Two studies found no differences in OC, ALP or HYP between children with JIA and healthy children at baseline or 1-year follow-up[215,219] or 2-year follow-up.[174] However, of these studies serum, OC was normal at baseline but decreased during follow-up in JIA patients in one study[219] and PICP and DPD were higher in JIA children at baseline than controls but lower at follow-up in a second study.[174]

Differences between severities of disease

Four studies compared markers of bone turnover between children with different subtypes or severities of JIA. Reed and colleagues compared bone markers in children with active and inactive JIA; at baseline more children with active disease had reduced OC compared with children with inactive disease.[220] At 2–6 months follow-up, there were no significant changes in OC levels but OC levels increased in children whose disease remitted. In a second study, OC, PICP and ICTP levels were significantly lower in children with active disease compared with children with inactive disease and also in children with polyarticular and systemic disease compared with children with pauciarticular disease.[217] However, two studies noted no differences between different subtypes of JIA (pauciarticular, polyarticular and systemic) in ALP, OC and HYP.[215,219]

Three studies compared children with JIA and reduced BMC with children with JIA and normal BMC. Henderson and colleagues noted that children with low BMC had higher levels of OC and ICTP compared with children with low BMC[21] but Lien and colleagues observed no differences between the groups for bone-specific ALP, OC, ICTP and urinary DPD.[164] Chlebna-Sokol and colleagues reported no difference in bone-specific ALP and total ALP but an increased HYP excretion in children with osteoporosis compared with those who were not osteoporotic.[161]

Four studies examined the effects of treatment of JIA on bone markers. Pepmueller and colleagues found low levels of OC, bone-specific ALP and TRAP, similar levels of PICP and similar urinary deoxypyridinoline:creatinine and urinary calcium:creatinine ratios in children with JIA compared with healthy controls, and these results remained unchanged when corticosteroid-treated children were excluded from the analysis.[168] Similarly, Falcini and colleagues found no difference in levels of bone markers between corticosteroid-treated children or NSAID-treated children or children treated with both NSAIDs and methotrexate.[217] Pereira and colleagues found that OC levels were increased in corticosteroid-treated children compared with non-treated children but there were no significant differences for bone-specific ALP, HYP or DPD.[218] In contrast, Reeve and colleagues found no relationship between changes in markers of bone turnover and changes in BMD in 31 children with JIA during treatment with prednisone or deflazacort.[213]

In two studies of treatment of growth-impaired children with JIA, OC levels were low at baseline but increased during treatment with growth hormone.[18,221] Touati and colleagues noted that OC levels returned to pre-treatment levels when treatment was stopped.[221] Bechtold and colleagues found that levels of ALP were low at baseline.[175] ALP levels rose during treatment with growth hormone[175,221] and continued to be raised 1 year after stopping treatment.[221] PICP, HYP, PYD and DPD levels increased and

returned to pretreatment levels after treatment was stopped.[175,221,222]

Summary

Few studies specifically examined the issue of identifying the risk of low BMD and/or fragility fractures. Studies evaluated the effects of JIA on biochemical markers of bone turnover but the results were not consistent; neither were the effects of JIA treatment consistent. The study designs were heterogeneous, including children with a range of different diseases and assessing a range of different markers using different analysis methods. Hence from these data, the role of these markers as an outcome measure is still unclear.

Fractures in children with JIA

Background

The occurrence of fractures is well recognised in children with JIA and would be the outcome of real interest in any studies of bone health in children with JIA. This section reviews the use of fractures as an outcome measure.

Review of fractures as an outcome measure in children with JIA

Search strategy and inclusion of studies

A specific search strategy was developed in order to identify the papers describing fractures as an outcome measure in children with JIA or connective tissue disease (Appendix 13). MEDLINE (on Ovid, searched from 1966) and EMBASE (on Ovid, from 1980) were searched. The results of electronic searches were downloaded, checked for duplicates against previously downloaded references and stored using Reference Manager software. The final list of titles and abstracts was assessed and full publications were obtained where articles were thought to be potentially relevant. Bibliographies of papers were checked for further potentially relevant papers. The main electronic searches were conducted in June 2005. Included in the review were studies, published in full, of the incidence of fractures in children and adolescents (aged <18 years) with JIA and other connective tissue diseases. All study designs were included but excluding case series and case reports.

Six papers were identified. Four papers were excluded (Appendix 14) and therefore two papers were included in the review. Studies which assessed biochemical markers of bone turnover after treatment with bisphosphonates were included in the review of effectiveness (Chapter 3).

Results

The two papers are summarised in Appendix 15. Varonos and colleagues compared children with JIA and spinal fractures with children with JIA and no spinal fractures.[223] Children with spinal crush fractures had started treatment with corticosteroids at an earlier stage of disease. Elsasser and colleagues followed 63 children for 18 months.[224] Nine children had at least one crush fracture at baseline and four experienced further fractures during 18 months follow-up. Five children without fractures at baseline experienced a fracture during follow-up.

Summary

Only two studies have examined the fractures as an outcome of JIA. There were no direct comparisons with healthy children but the data suggest that the risk of fractures was increased in children with JIA. These studies were relatively short-term studies. Studies looking at longer-term occurrence of fractures in children and adults with JIA are discussed in Chapter 4.

Discussion

This part of the study reviewed the data available for four approaches to assess outcome in studies of bone health in children with JIA and low BMD and/or fragility fractures: health status, bone strength, blood or urinary biochemical markers of bone turnover and the incidence of fractures. There are virtually no data on the use of patient-based outcomes in these children. From the available data on JIA generally, the CHAQ is the most widely used instrument and is sensitive to differences in disease severity between children and can also detect changes during treatment, but it has not been designed to assess the effects of bone health on quality of life. Assessment of health status may not be useful in clinical trials of bisphosphonates as the main benefits of bisphosphonates are likely to be long term in reducing fractures and therefore the patient may not experience any current increased well-being as a result of treatment. It is also possible that any side-effects of bisphosphonates could reduce the patient's HRQoL. However, these instruments may have a role in longer-term studies. Griebsch and colleagues reviewed 54 published cost–utility analyses of interventions in child and adolescent health.[225] Most studies did not follow guidelines for the most appropriate choice of utility instrument; this may have been attributable to poor practice or may have been an attempt to make the research more rigorous. The instruments

were developed for use in adults and use in children is complicated by the effects of growth and the cognitive ability of young children to understand the process.

There are extensive data on the use of DXA to assess BMD in healthy children and children with JIA. DXA is precise and is sensitive to differences between ages, sex, pubertal stages and race. DXA showed differences in BMD between children with and without JIA and, in children with JIA, detected differences in BMD between active and inactive disease, between different subtypes of disease and between corticosteroid- and non-corticosteroid-treated children. Although the equipment is not portable, DXA is widely available and the dose of radiation is low. There are potential technical and practical issues in scanning children but approaches are available to overcome these problems. The major disadvantage is that DXA does not provide a vBMD and the results must be adjusted for body size of child size otherwise they may not clarify whether there should be a diagnosis of low BMD or whether the child is just small for their age. Issues to be clarified include which is the best body site for measurement and a clinically meaningful change in BMD in these children, both for the short term and for the longer-term implications in adults, needs to be defined. In clinical studies, details of the method of BMD assessment using DXA should be specified. Further data are needed in children with JIA. In contrast, QCT and pQCT estimate a true vBMD and can also distinguish between trabecular and cortical bone. Although there are more limited data in children compared with DXA, QCT and pQCT measurements are sensitive to differences between different ages, sex and pubertal stages of healthy children. There are only two studies in children with JIA but QCT and pQCT were able to distinguish between healthy children and children with JIA. QCT equipment and staff are more difficult to access than DXA. The dose of axial radiation is higher with QCT than DXA but is reduced when using pQCT, which involves less radiation than DXA; levels are still acceptable for occasional scans. QUS has the advantages over DXA and QCT that it is portable and does not use radiation. There are several studies in healthy children but the measurements were taken at a number of different skeletal sites. The studies show that QUS parameters reflect differences in age, pubertal stage and race, but the findings are not consistent across studies. A major limitation is that it is not clear what is being measured by QUS; there is a correlation between SOS/BUA and BMD measured with DXA in some but not all studies. Thus the clinical utility of QUS in children is yet to be determined. The precision of QUS in the calcaneus tends to be less good than that of DXA or QCT and the sites of measurement are predominantly composed of cortical bone with slow turnover (tibia, phalanx, distal radius).[76] It should only be used to complement other bone densitometry techniques.[76] There are few data on using DXR in children with JIA.

Biochemical markers of bone turnover could be a useful outcome to measure; in adults they show changes before changes in BMD are apparent.[211] However, there are a number of problems currently limiting their applicability in studies of children. The levels of bone markers vary with age and pubertal status and diurnal variation causes problems with measurement. The available reference ranges in children are wide. It is possible that any changes as a result of disease or treatment may not be detected in some children. At present, biochemical markers of bone turnover are mainly used in research studies and are of limited value in most clinical practice. Several studies examined bone markers in children with JIA, but the results were not consistent and it is unclear which are the best markers for use in future studies. Future clinical studies could recruit smaller numbers of subjects and have shorter follow-up, but no information is yet available. Biochemical markers of bone turnover are difficult to assess in children because of differing ages and the effects of puberty and growth. It is not certain whether they are sensitive or specific enough to provide information for individual patients. There is little information on expected levels of markers in children with JIA and poor bone status compared with healthy children. It is not clear which would be the best marker or markers to use as an indicator of outcome.

The occurrence of fractures is well recognised in children with JIA and would be the end-point of real interest, but few studies have used fractures as an outcome measure. BMD and biochemical markers of bone turnover are surrogate endpoints but there are few data on the relationship between them and fractures in children. However, because of the relatively low incidence of fractures in both the general population and children with JIA, a study using fractures as an end-point would require large numbers of patients and long-term follow-up. Therefore, fractures may be a more appropriate outcome for large-scale long-term epidemiology studies.

Limitations of study

There are several limitations to this section of the project which examined outcome measures in children with JIA and low BMD and/or fragility fractures. Several of these were caused by the lack of evidence from the small numbers of heterogeneous studies. There are virtually no data on the use of patient-based outcomes in children with JIA and low BMD and/or fragility fractures, so little could be determined about their usefulness for the assessment of outcome in studies of bone health in JIA. It is hard to determine from the studies reviewed whether biochemical markers of bone turnover are useful as an outcome measure. In addition, there are no clear definitions for osteopenia and osteoporosis in children. Unlike adults, no prospective studies have identified a fracture threshold in children for any given *Z*-score.

Conclusions

- Currently available evidence indicates that BMD, adjusted for size, should be assessed as the primary outcome in studies of bone health in children with JIA.
- QCT could be used where equipment is available as it offers the advantage of measuring volumetric density.
- Other outcome measures may also be useful but further data are needed to establish their role.

Chapter 3

Systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D

Objectives

The question being addressed in this part of the report is as follows: in children with JIA who are at risk of low BMD and/or fracture, how beneficial or harmful are bisphosphonates or calcium and/or vitamin D in increasing BMD or reducing the incidence of fracture?

The objectives were as follows:

- to evaluate the effectiveness of bisphosphonates and calcium and/or vitamin D for the prevention or treatment of low BMD and/or fragility fractures in children with JIA
- to evaluate the safety of bisphosphonates and calcium and/or vitamin D in children with JIA.

Methods

Data sources and search strategy

MEDLINE (on Ovid, searched from 1966 to July 2005) and EMBASE (on Ovid, 1980 to July 2005) were searched, as were the Cochrane Library (on Update Software, including the Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Databases of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database and Health Technology Assessment Database) and ISI Web of Science Conference Proceedings (from 1990 to July 2005). Current Controlled Trials was also searched (http://www.controlled-trials.com).

The search strategies included terms for all interventions of interest: bisphosphonates used in the management of osteoporosis, calcium, vitamin D (both generic and trade names; see Appendix 16); the search strategies are listed in Appendix 17. Terms for low BMD, osteoporosis and fractures were included. The initial search included terms for JIA but some papers describing children with JIA were not indexed for the condition, for example, where the condition was only detailed in a table and not in the text. Therefore, this filter was removed and only the terms for osteoporosis were used; this approach would also identify studies of other childhood rheumatic diseases such as SLE, dermatomyositis, connective tissue disorders and idiopathic juvenile osteoporosis. Terms for OI were included as it was known that bisphosphonates had been studied most in this condition and studies in this condition would provide useful safety data. A filter was used to identify studies in children using appropriate terms such as babies, infants, children and adolescents. A filter for study type was not used as it was known before searching started that there were few if any randomised controlled trials (RCTs) and all types of studies were required.

The results of electronic searches were downloaded, checked for duplicates against previously downloaded references and stored using Reference Manager software. The final list of titles and abstracts was assessed and full publications were obtained where articles were thought to be potentially relevant. Bibliographies of included studies and review papers were checked for potentially relevant studies. These were checked against the list of studies assessed for inclusion and new potentially relevant studies collected.

The main electronic searches were run in November and December 2004. Attendance at the International Conference on Children's Bone Health in May 2005 resulted in the identification of two additional recently published relevant studies.

Inclusion of studies

Studies identified in the search were included in the review if they met the following criteria.

Effectiveness

- Population: children (aged <18 years) with JIA and low BMD and/or fragility fractures.
- Interventions: bisphosphonates administered orally or by infusion, calcium and/or vitamin D.
- Outcome: any outcome(s) indicative of low BMD and/or fragility fractures were included; the most commonly used outcomes were densitometric measurement, radiographic, markers of bone turnover and fracture incidence.

- Design: as it was expected that few, if any, RCTs of interventions in JIA and low BMD and/or fragility fractures had been conducted, it was planned to include all types of studies in the review, including controlled and uncontrolled cohort studies, case series and case reports.

Safety

- Population: children with JIA and low BMD and/or fragility fractures and children with OI.
- Interventions: bisphosphonates administered orally or by infusion, calcium and/or vitamin D.
- Outcome: adverse events and safety.
- Design: all types of studies, including controlled and uncontrolled cohort studies, case series and case reports.

Inclusion decisions were made by one reviewer (JT). Both abstracts and full papers were included.

Data extraction and quality assessment

From preliminary searches, it was expected that few RCTs would be identified and that all study types would be included in the review, including observational studies, case series and case reports. As a result, data extraction and quality assessment forms were developed for use in this review that would be suitable for all types of studies. Deeks and colleagues reviewed non-randomised intervention studies and concluded that although instruments existed for evaluating observational studies, they lacked important domains.[226] Similarly, a review of case series methodology identified no satisfactory instrument for assessing the quality of such studies.[227] Therefore, tables for data extraction and quality assessment were developed for use in this review that would be suitable for all types of studies. Issues of bias relevant to a range of study types were addressed (selection, performance, attrition, and detection biases).[228]

The data extraction and quality of the included studies (not masked to study authors) were assessed by a first reviewer (JT) then checked by a second (DA). Differences between the reviewer's results were resolved by discussion.

Quantitative data analysis (meta-analysis) was not undertaken because of wide variations between studies in terms of subjects, ages, disease type and method and type of outcome assessment. In addition, there was no consistency between studies in reporting of outcome measures, with some studies reporting BMC or BMD that were not adjusted for size and a few studies reporting BMAD or vBMD. Values were reported as individual or mean values, as raw values before or after treatment, as change in raw values or a percentage change. Some studies only reported *Z*-scores. Studies evaluated a range of different biochemical markers of bone turnover. Fracture occurrence was reported in only five studies and clear figures were not provided. Hence pooling of data would not be meaningful and effect sizes could not be calculated. Although four studies included an intervention group of children treated with bisphosphonates and a control group of children receiving standard treatment, none of these studies compared directly the results of intervention and control groups; the results were only compared with the group's own baseline. Therefore, findings were summarised using tables and narrative synthesis.

Results: effectiveness

Identification and exclusion of studies

For the review of effectiveness of bisphosphonates, calcium and/or vitamin D in JIA and other childhood rheumatic diseases, 96 papers were identified through the searching process (*Figure 2*). Thirty-five papers were excluded from the review (Appendix 18). Eighteen papers discussed the use of bisphosphonates (16 papers) or calcium and/or vitamin D (2 papers) in children with JIA or other rheumatic diseases. The other 43 papers evaluated these treatments in OI and were included in the safety review.

Bisphosphonates: included studies

Sixteen papers discussed the use of bisphosphonates in children with JIA or other connective tissue diseases (*Table 9*).

Two studies were only published as conference abstracts.[236,237] One study was only available as an abstract from EMBASE as the full paper could not be obtained;[241] as many data as possible were taken from the abstract. One paper was published in Polish but the abstract and tables were in English and information could be extracted.[242]

Bisphosphonates: characteristics of children

A total of 78 children with JIA could be identified in the 16 effectiveness studies (Appendix 19). A further five children had corticosteroid-induced low BMD and may have included JIA children. However, the children in the study of Bianchi and colleagues[231] were also included in the study of Cimaz and colleagues.[234] Three studies included no children with JIA but only other rheumatic diseases,[237,238,244] and the exact diagnosis of

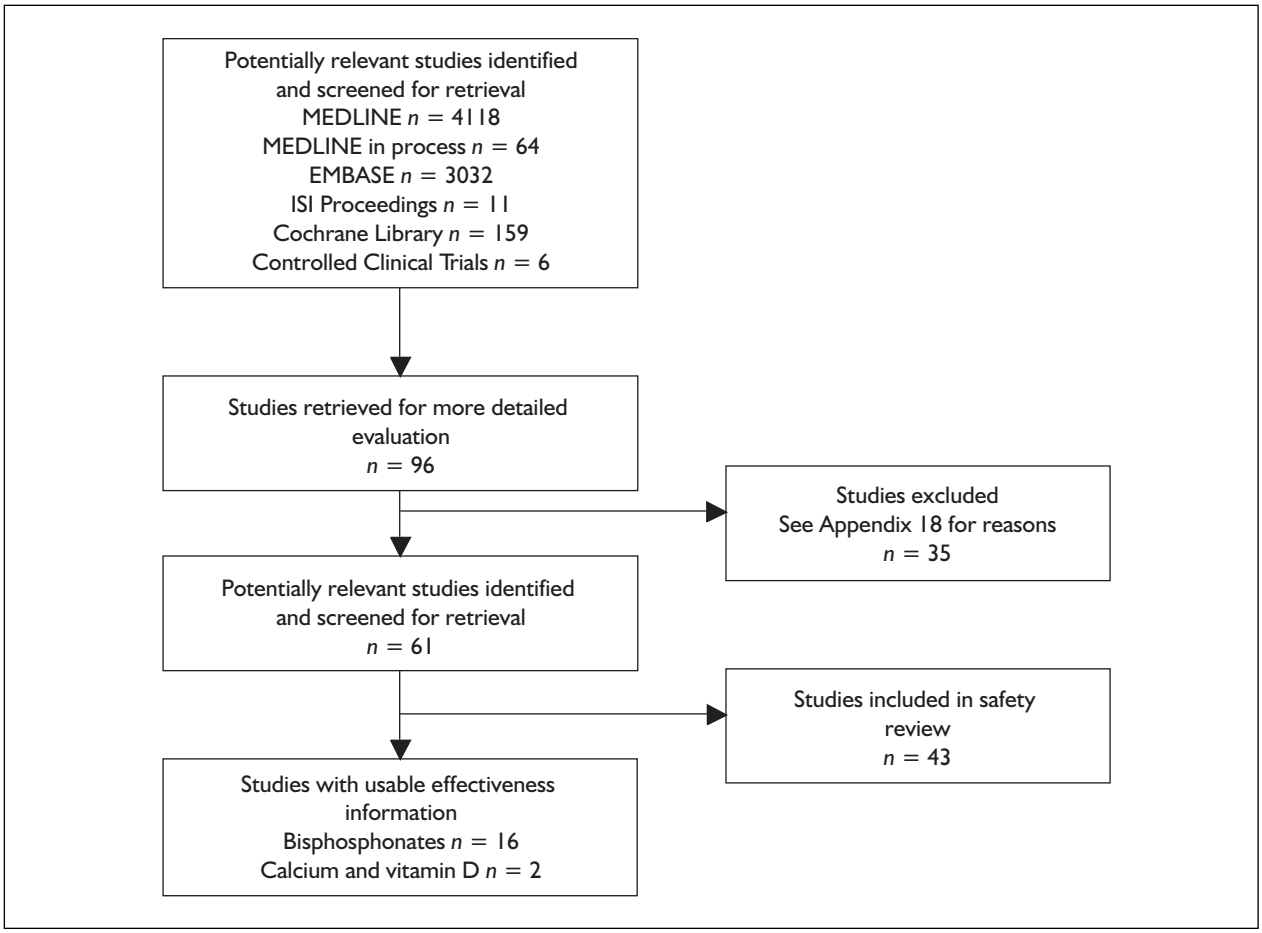


FIGURE 2 *Progress through the stages of review of effectiveness*

children was unclear in two studies.[241,242] The remaining studies included a mixture of children with JIA, other rheumatic diseases and OI.

Studies recruited children between 4 and 18 years old. One study included children and young adults up to 25 years old.[236] Most studies included more female than male children. Three studies recruited more male than female children[241–243] and two studies did not state the sex distribution.[232,240] Three studies recorded the pubertal stage of children.[231,234,239]

Two studies recruited children at risk of low BMD and fractures because of disease and long-term corticosteroid treatment.[229,236] The remaining studies recruited children who already had problems; four of these studies required a history of fragility fractures.[230,231,234,235]

Children in the studies had low BMD at baseline with BMD *Z*-scores below the expected values for age and sex-matched children. For example, in the study by Bianchi and colleagues, baseline spine *Z*-scores were –1.6 to –5.3,[231] in the study by Noguera and colleagues, –1.87 to –4.73,[233] and in the study by Gandrud and colleagues, –2.6 to –4.46.[235]

Bisphosphonates: interventions

Sixteen studies evaluated bisphosphonates (Appendix 19): alendronate (seven studies),[229,231,234,237,238,241,243] pamidronate (five studies),[230,233,235,240,244] alendronate and pamidronate (one study),[239] clodronate (one study)[232] and etidronate (one study);[236] the bisphosphonates used could not be determined in one study.[242] Five of the bisphosphonate studies evaluated intravenous administration[230,235,236,238,240] and nine evaluated oral administration,[229,231,232,234,236,237,241,243,244] one study used a combination of intravenous and oral administration[239] and the method of administration could not be determined in one study.[242] The studies used a range of different doses and cycle lengths.

Doses of intravenous bisphosphonates varied. For intravenous pamidronate, Noguera and colleagues[233] used a dose of 2–4 mg/kg every

TABLE 9 *Summary of studies with bisphosphonates in JIA/connective tissue disease and osteoporosis*

Study	Design	Patients	Intervention
Rudge *et al.*, 2005[229]	RCT	22 children. Treated: JIA (2), SLE (6), autoimmune haemolytic anaemia (1), inflammatory bowel disease (1), renal transplantation (1). Control: JIA (5), dermatomyositis (4), inflammatory bowel disease (1), cystic fibrosis (1)	Alendronate
Acott *et al.*, 2005[230]	Cohort, controlled	17 children: JRA (1), dermatomyositis (6), polychondritis (1), post-renal transplant (2), rapidly progressive glomerulonephritis (5), nephrotic syndrome (2). 17 controls matched for age, sex, disease, corticosteroid treatment	Pamidronate
Bianchi *et al.*, 2000[231]	Cohort, controlled	38 children: systemic JIA (7), polyarticular JIA (9), SLE (11), dermatomyositis (6), Bechet's syndrome (2), Wegener's granulomatosis (1), undefined connective tissue disease (2)	Alendronate
Lepore *et al.*, 1991[232]	Cohort, controlled	13 children with JIA: 7 treated, 6 controls	Clodronate
Noguera *et al.*, 2003[233]	Case series	10 children: JIA (8), SLE (1), dermatomyositis (1)	Pamidronate
Cimaz *et al.*, 2002[234]	Case series	45 children: SLE (14) dermatomyositis (7), systemic JIA (8), polyarticular JIA (10), other (6)	Alendronate
Gandrud *et al.*, 2003[235]	Case series	11 children: corticosteroid-induced osteoporosis (4), JIA (1), OI (6)	Pamidronate
Gattinara *et al.*, 2000[236]	Case series	25 children with rheumatic disease and long-term corticosteroid treatment: systemic JCA (7), polyarticular JIA (11), pauciarticular JCA (4), SLE (3)	Etidronate
Bardare *et al.*, 2000[237]	Case series	6 children with corticosteroid-induced osteoporosis: SLE (5), dermatomyositis (1)	Alendronate
Falcini *et al.*, 1996[238]	Case series	4 children: post-streptococcal (1), polyarteritis (1), lupus-like syndrome (1), juvenile dermatomyositis (1)	Alendronate
Brumsen *et al.*, 1997[239]	Case series	12 children: JIA (1), idiopathic juvenile osteoporosis (1), idiopathic osteoporosis (5), OI (4), mitochondrial myopathy (1)	Pamidronate
Shaw *et al.*, 2000[240]	Case series	5 children: JIA (1), Cushing's syndrome (1), OI (1), liver transplant (1), idiopathic juvenile osteoporosis (1)	Pamidronate
Bayer *et al.*, 2002[241]	Case series	9 children: corticosteroid-induced osteoporosis (3) OI type Ia, Ib, IV (6)	Alendronate
Chlebna-Sokol *et al.*, 2003[242]	Case series	45 children: secondary osteoporosis (13/15) or osteopenia (2/15), primary osteoporosis (16/30) or osteopenia (2/30)	Bisphosphonates (5)
Fernandes *et al.*, 2004[243]	Case series	2 children: SLE (1), JIA (1)	Alendronate
Oliveri *et al.*, 1996[244]	Case report	1 child (dermatomyositis)	Pamidronate

6 months, Gandrud and colleagues[235] a dose of 1 mg/kg every 3 months, and Acott and colleagues[230] a dose of 1 mg/kg every 2 months; Shaw and colleagues[240] administered a 3-monthly cycle with a total yearly dose of 0.5–12 mg/kg. Brumsen and colleagues[239] used a dose of 7.5 mg daily intravenously for 18 days followed by oral administration. Intravenous alendronate was administered at a dose of 3.25 mg/day for three consecutive days with a second course after 3 months.[238] Studies using oral alendronate administered doses of 5 or 10 mg daily.[231,234,237,241,243] Rudge and colleagues administered alendronate 1–2 mg/kg weekly.[229] Oral clodronate was administered at a dose of 1200 mg daily,[232] oral pamidronate at a dose of 4 mg daily,[244] and oral etidronate at a dose of 150–300 mg daily for 15 days followed by calcium citrate for 75 days, then the cycle was repeated.[236]

In nine studies, all children continued with their usual corticosteroid treatment,[229–231,234–238,245] and in seven studies it was not clear whether children were receiving corticosteroids.[232,239–244] In the bisphosphonate studies, eight studies reported on the calcium and vitamin D status of the children. Eight studies ensured that calcium and/or vitamin D intakes were adequate; if found to be inadequate dietary intake was increased or supplements administered during the study.[229,231,234,236,238,241,242,244] Acott and colleagues administered calcium and vitamin D supplements to all children.[230] Gattinara and colleagues administered oral calcium citrate for 75 days after oral etidronate.[236] One study did not permit any treatments interfering with calcium metabolism.[233] Six studies did not report any details about calcium and vitamin D status.[232,235,237,239,240,243]

Bisphosphonates: follow-up

Follow-up in these studies was generally for 1–2 years; two studies followed children for up to 6 years.[233,239]

Bisphosphonates: outcomes assessed

The outcome measures included bone densitometry, biochemical markers of bone turnover and the occurrence of fractures (Appendices 19 and 20). All 16 studies assessed bone densitometry and eight studies also assessed markers of bone turnover.[229–231,233–235,239,244] Five studies assessed occurrence of fractures as an outcome measure.[229,230,235,237,240] Other outcome measures included pain and disability (four studies).[233,235,238,239]

Thirteen studies assessed bone densitometry using DXA,[229–231,233–238,240,242–244] one study used both DPA and DXA,[239] and one study used CT scanning.[232] The method of measurement could not be ascertained in one study.[241] Densitometry was performed and reported for the spine in nine studies,[230–234,236–238,240] for the spine and whole body in four studies,[235,241,242,244] for the spine and femoral shaft in one study[229] and for the spine and femoral neck in one study.[239] The site of measurement was not clear in one study but could have involved the whole body.[243] For bone densitometry results, five studies reported BMD only,[232,236–238,242] five studies reported BMD *Z*-score[230,233,240,241,243] and six studies reported both BMD and BMD *Z*-score.[229,231,234,235,239,244]

Bisphosphonates: study quality

Potential sources of bias in the studies and discussions of their internal and external validity are summarised in Appendices 21 and 22.

There was one RCT,[173] three studies were cohort studies with control groups,[230–232] 11 studies were case series[233–243] and one of these studies[234] was an update of the controlled study conducted by Bianchi and colleagues;[231] one paper described a case report.[244] Although four studies included an intervention group of children treated with bisphosphonates and a control group of children receiving standard treatment,[229–232] none of these studies compared directly the results of intervention and control groups; the results were only compared with the group's own baseline.

The studies were generally small. The RCT recruited a total of 22 children: 11 children each for the intervention and control groups. One controlled cohort study recruited 38 children,[231] one recruited 13 children[232] and one recruited 17 children.[230] The case series recruited between two and 45 children.

There are limited data on the types of children included in the studies. Five studies reported specific inclusion criteria requiring children to have osteoporosis (low BMD and/or fractures)[235] or to have been receiving long-term corticosteroid treatment[229] or long-term corticosteroid treatment and have osteoporosis.[231,233,234] Six further studies did not report inclusion criteria but appeared to recruit children who had osteoporosis with or without corticosteroid treatment.[230,236–238,240,244] Brumsen and colleagues included children who were not receiving treatment with corticosteroids.[239] Four studies did not report any information on recruitment of children; hence there is no information on the types of children included in these studies.[232,241–243] Most studies included a mixture of children with JIA and other connective tissue diseases. The case report described one child with dermatomyositis.[244] Only one study reported that they used a standard definition of JIA.[231] The other studies did not discuss how they defined arthritis in children. Therefore, it is not clear how the JIA children differ within and between studies. Overall, it is hard to determine how these results relate to the population of JIA children in general.

A range of doses of intravenous and oral bisphosphonates were used in the studies but, even though bisphosphonates are not licensed for use in children, none of the authors explained their choice of drug, route of administration, dose or duration of treatment. It is not clear whether choices were based on any expected differences in effectiveness by the investigator or on availability and convenience of administering a particular

drug; the preference of the child and family for oral or intravenous administration may also have been taken into account. Therefore, it is uncertain whether the drugs, routes and doses used in the studies are appropriate for use in the wider population of JIA children. In UK clinical practice, bisphosphonate doses are generally based on those used by Glorieux and colleagues,[246–250] which were derived from adult dose equivalence (Mughal MZ, St Mary's Hospital for Women and Children, Manchester: personal communication, 2006).

A potential source of bias in the studies with bisphosphonates is whether children received concomitant treatment with calcium and/or vitamin D or not, as this may affect outcome. Ten studies ensured that the children had an adequate calcium and/or vitamin D status through dietary measures or supplementation.[229–231,234,236,238,241–244] One study did not permit any treatments affecting calcium metabolism.[233] Five studies did not report calcium and/or vitamin D status.[232,235,237,239,240]

Another potential source of bias is whether children continued receiving corticosteroid treatment during the study, as for many children the osteoporosis may have been induced by corticosteroid treatment. In eight studies, all children continued with their usual corticosteroid treatment.[229–231,234–238] In eight studies it was not clear whether children were receiving corticosteroids or not.[232,233,239–244]

The studies recruited children aged between 4 and 18 years old. Growth and bone development are affected by pubertal stage. Three studies recorded the pubertal stage of children,[231,234,239] although they did not take account of this in the analysis of outcome.

Acott and colleagues compared corticosteroid-treated children who had experienced fractures with corticosteroid-treated children who had not experienced fractures and had greater BMD.[230] Similarly, the control group of children recruited by Bianchi and colleagues had less severe disease which did not require corticosteroid therapy and had not experienced fragility fractures.[231]

The methods of assessment of outcome were a major weakness in most of the studies. All the studies included changes in BMD as an outcome. Brumsen and colleagues used DPA when first studying children, then later changed to DXA.[239] Bianchi and colleagues[231] described the methodology of BMD assessment using DXA in most detail and the methodology used by Cimaz and colleagues[234] in the follow-up study is assumed to be similar. A standard protocol for measurement was used, each child was always scanned using the same machine, a quality control procedure was instituted, results were adjusted to account for children and *Z*-scores were calculated using local reference data. In other studies, detailed methodology was not reported but all seemed to be deficient in at least one of these areas. It is possible that some studies did not account for scanning children and the results may be unreliable.

Lepore and colleagues measured density using CT scanning and thus obtained a true vBMD value.[232] Bianchi and colleagues[231] and Cimaz and colleagues[234] adjusted aBMD for body surface area. Gandrud and colleagues[235] and Rudge and colleagues[229] reported BMAD in addition to aBMD. All other studies reported aBMD, which makes it difficult to compare results between studies. In addition, values were reported as individual or mean values, as raw values before or after treatment, as change in raw values or a percentage change. Some studies only reported *Z*-scores.

Ten studies evaluated the effect of treatment on biochemical markers of bone turnover. Different markers were assessed. It is known that levels of these markers are affected by growth in children regardless of osteoporosis. None of the studies discussed the effects of growth and so the implications of any changes in level are uncertain.

BMD and markers of bone turnover are surrogates for occurrence of fractures; reducing the incidence of fractures is the long-term aim of treatment. Although the studies were short term, three studies did note a reduction in the incidence of fractures during treatment with bisphosphonates.[231,235,240] Only four studies examined any subjective outcomes including pain and quality of life.[233,235,238,239]

Four studies with bisphosphonates included control groups. In the RCT, the children in the intervention group had been receiving corticosteroid treatment for longer and were shorter in height than the control group.[229] There was also a difference in the distribution of disease types between the two groups. In the case–control study, the two groups were well matched for age, sex, disease and corticosteroid treatment, but it is not clear whether the severities of disease were taken into account.[230] Bianchi and colleagues

included control children who had less severe disease than the treatment group who did not require treatment with corticosteroids; therefore, the two groups were not similar and it is hard to draw conclusions from any comparisons of outcomes.[231] Lepore and colleagues did not report inclusion criteria for either the treatment group or the control group, so again it cannot be determined whether the groups were equivalent.[232] None of the studies with control groups compared results between the intervention and control groups; they only compared each group with its own baseline.

Bisphosphonates: effectiveness

In all studies, treatment with bisphosphonates increased BMD compared with baseline: the mean increase in spine BMD from baseline ranged from 4.5 to 19.1% (Appendix 20). The greatest increase was in a single case report which observed an increase in spine BMD of 70% after 2 years of treatment.[244]

In the RCT of Rudge and colleagues, BMAD increased significantly from baseline in the alendronate-treated group ($p = 0.013$) whereas there was little change in the placebo group.[229] In the alendronate group, children with the lowest initial aBMD score had the greatest increment in BMAD with treatment. The BMC of the femoral shaft increased by a mean of 3% in the placebo group and 4.4% in the alendronate group. In children treated with alendronate, Bianchi and colleagues recorded a statistically significant mean increase in BMD (adjusted for body surface area) after 1 year compared with baseline of 14.9±19.8% ($p<0.002$); the increase was smaller and non-significant for untreated children (2.6±6.5%).[231] In the study by Acott and colleagues, treatment with pamidronate resulted in significantly increased spine aBMD *Z*-scores compared with baseline.[230] The control children had higher baseline *Z*-scores compared with the treated children and the *Z*-scores decreased during the study. Lepore and colleagues recorded an 8% increase in aBMD of children treated with clodronate for 1 year compared with a 7% decrease in untreated children.[232] As previously, mentioned, these studies did not directly compare the bisphosphonate-treated children with untreated children but only compared each group with their own baseline.

In the study by Gandrud and colleagues, spinal aBMD and BMAD increased from baseline by a mean of 20.1 ± 16.9 and 15.1 ± 18.1% per year, respectively. Increases in BMD were also recorded at other skeletal sites. There were mean annual increases in whole-body aBMD of 5.6 ± 3.8%, femoral neck of 13.6 ± 11.0% and hip of 17.1 ± 17.1%.[235] Oliveri and colleagues recorded an increase in pelvic aBMD of 65% in one child.[244] Rudge and colleagues observed an increase in femoral shaft BMC during treatment with alendronate.[229]

Nine studies with bisphosphonates[229–231,233–235,239,242,244] evaluated the effect of treatment on biochemical markers of bone turnover (Appendix 20). Bianchi and colleagues and Cimaz and colleagues observed statistically significant decreases in ALP and NTX after treatment with alendronate.[231,234] Cimaz and colleagues also reported decreases in PYD and OC.[234] Rudge and colleagues observed a significant decrease in the N-terminal telopeptide/creatinine ratio in alendronate-treated children but not in children receiving placebo.[229] Chlebna-Sokol and colleagues noted a decrease in ICTP during treatment with bisphosphonates; OC levels fell in two children but increased in three children, and dypyridinoline:creatinine and pyridinoline:creatinine ratios fell in most children.[242] Five studies with bisphosphonates noted no significant changes in the levels of markers of bone turnover.[230,233,235,239,240]

Five studies reported the incidence of fractures before and after treatment (Appendix 20).[229–231,235,240] Before entering the study of Rudge and colleagues, three children had sustained fractures but during the study only one child in the control group sustained a fracture.[229] In the study by Acott and colleagues, 17 children had experienced fracture before entry including lower thoracic vertebral collapse (15 children), rib fractures (one child), pathological appendicular fracture (one child) and thoracic vertebral fracture with rib fracture (one child).[230] One of these children had a recurrence of a thoracic compression fracture 1 year after discontinuation of pamidronate. Ten children in the study by Gandrud and colleagues had experienced 38 fractures in the year before treatment; 12 of these fractures had been in children with corticosteroid-induced osteoporosis.[235] Only two fractures occurred in the first year of treatment with pamidronate and neither of these was in children with corticosteroid-induced osteoporosis. Bianchi and colleagues reported that no new fractures occurred during treatment with alendronate.[231] However, they did not report the incidence of fractures before treatment. In the study by Shaw and colleagues three out of four children had fractures in both the lumbar and thoracic spine at

baseline; there were no further vertebral fractures during the study.[240]

Improvements in subjective outcomes were also noted during bisphosphonate treatment (Appendix 20). In one study, children experienced a progressive reduction in chronic bone pain and disability;[233] in a second study, children also experienced reduced bone pain and increased strength.[235] In a third study, back pain resolved in all children, and standing with a corset became possible.[238] In a fourth study, all children (except two) who were immobilised were able to walk within a few weeks after starting therapy.[239]

Calcium and/or vitamin D: included studies

Two papers discussed the use of calcium and/or vitamin D in children with JIA or other rheumatic diseases (*Table 10*).

One study evaluated vitamin D[251] and one evaluated calcium and vitamin D[245] as interventions (Appendices 21 and 22); 21 children were treated with calcium and/or vitamin D.

Calcium and/or vitamin D: characteristics of children

Twenty-three girls and boys were included in the two studies. The inclusion criteria for one study included long-term corticosteroid treatment.[245] In one study, all children continued with their usual corticosteroid treatment,[245] and in one study seven children continued with their corticosteroid treatment.[251]

Calcium and/or vitamin D: follow-up

Reed and colleagues followed children for 1 year.[251] Warady and colleagues followed children for 6 months only.[245]

Calcium and/or vitamin D: outcomes assessed

Both studies assessed bone densitometry (using SPA and/or DPA) and markers of bone turnover.[245,251] Densitometry was performed and reported for the forearm and spine in one study[245] and for the forearm only in the other.[251] For bone densitometry results, one study reported BMD only[245] and the other reported BMD *Z*-score.[251]

Calcium and/or vitamin D: study quality

Potential sources of bias in the studies and discussions of their internal and external validity are summarised in Appendices 21 and 22. None of the studies were RCTs. One study was a cohort study with control group[245] and the other was a case series.[251]

Both studies were small (10–13 children). There are limited data on the types of children included in the studies. The two studies reported specific inclusion criteria requiring children to have osteoporosis (low BMD and/or fractures)[251] or to have been receiving long-term corticosteroid treatment and have osteoporosis.[245] Studies included a mixture of children with JIA and other connective tissue diseases. One study reported that they used a standard definition of JIA[251] but the other study did not supply any information. Therefore, it is not clear how the JIA children differ between these studies.

Another potential source of bias is whether children continued receiving corticosteroid treatment during the study, as for many children the osteoporosis had been induced by corticosteroid treatment. In one study, all children continued with their usual corticosteroid treatment[245] and in the other seven children continued with their corticosteroid treatment.[251]

The studies recruited children aged between 4 and 18 years. Growth and bone development are affected by pubertal stage. Neither of studies accounts for pubertal stage in the analysis of outcome.

The methods of assessment of outcome were a major weakness in the studies. The two studies included changes in BMD as an outcome but used SPA or DPA to measure BMD;[245,251] these technologies have now been superseded. The studies evaluated the effect of treatment on markers of bone turnover. Different markers were assessed. It is known that levels of these markers

TABLE 10 *Summary of studies with calcium and/or vitamin D in JIA and osteoporosis*

Study	Design	Patients	Intervention
Warady *et al.*, 1994[245]	Cohort, controlled	10 children: systemic JRA (4), polyarticular JRA (2), SLE (2), mixed connective tissue disease (2)	Calcium and vitamin D
Reed *et al.*, 1991[251]	Case series	13 children with polyarticular JIA	Vitamin D

are affected by growth in children regardless of osteoporosis. None of the studies discussed the effects of growth, so the implications of any changes in level are uncertain. Neither study assessed the incidence of fractures during treatment or examined any subjective outcomes.

Children in the calcium and vitamin D crossover design study acted as their own control and therefore it would be expected that results from treatment and control could be compared.[245] However, it is uncertain whether there was an adequate washout period between the treatment periods. Neither investigators nor children were blinded to treatment in this study.

Calcium and/or vitamin D: effectiveness

Children in the studies had low BMD at baseline with BMD *Z*-scores below the expected values for age and sex-matched children. Treatment with calcium and/or vitamin D resulted in increased BMD (Appendix 20). The mean BMD for spine at baseline was 0.75 ± 0.05 g/cm^2, after supplementation with calcium and vitamin D this increased to 0.830.00 g/cm^2 (11% increase) and, after supplements were withdrawn, this decreased to 0.80 ± 0.05 g/cm^2.[245] The BMD *Z*-score for spine increased after vitamin D supplementation from -2.8 ± 0.5 at baseline to -2.3 ± 0.5 after 6 months and -2.4 ± 0.4 after 1 year.[251]

Results in relation to effect of treatment on markers of bone turnover are presented in Appendix 20. In one study, there were no significant changes in levels of markers, although ALP levels were increased in seven children.[245] In the other, there was a statistically significant increase in OC levels during treatment with vitamin D from low baseline levels.[251]

Results: safety

Included papers

The 18 papers identified in the effectiveness review were also included in the safety review (*Figure 3*). A further 43 papers evaluated bisphosphonates in OI (*Figure 3*). Two of these papers may have included small numbers of children with JIA but only evaluated safety and therefore these papers

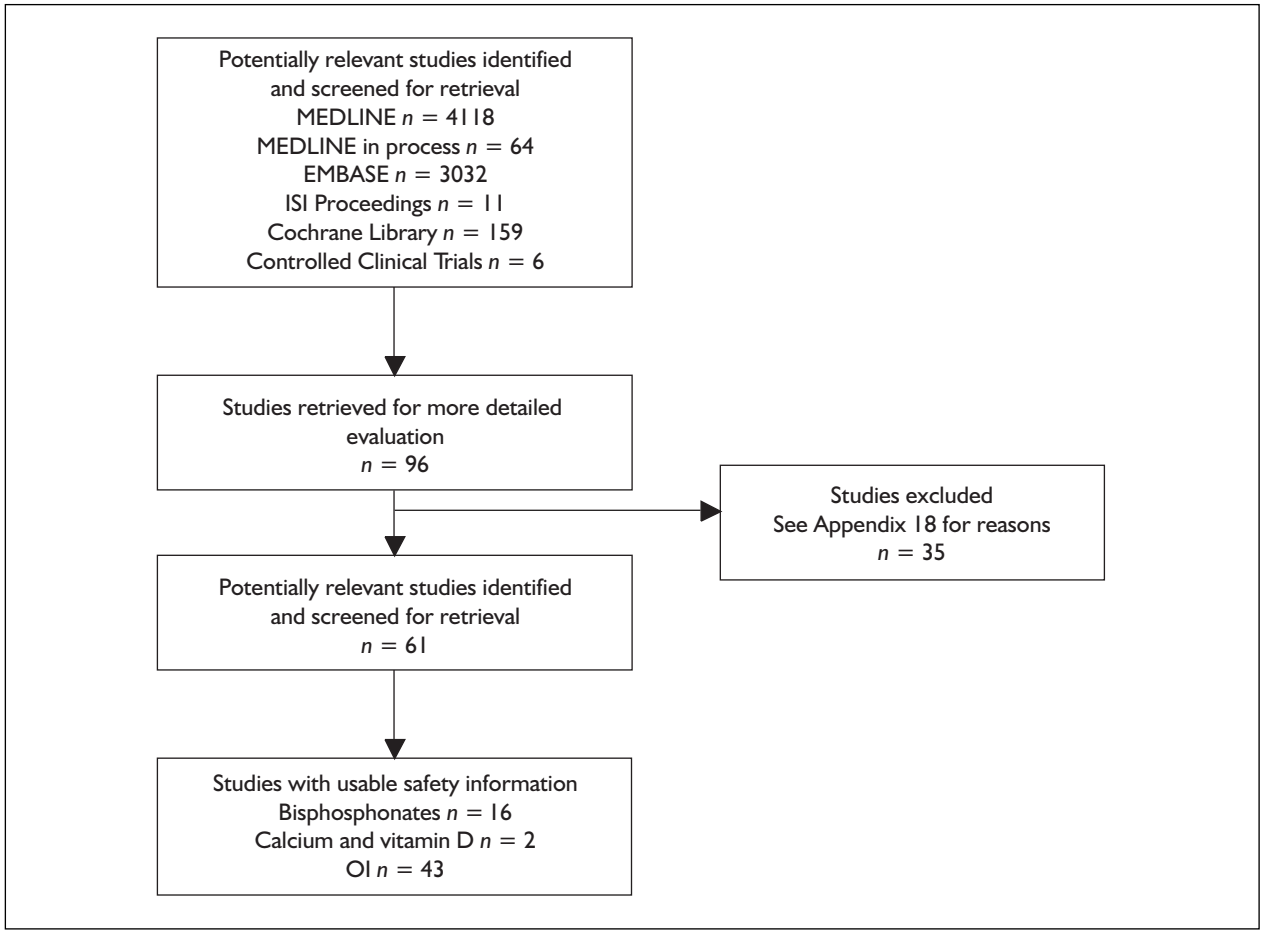


FIGURE 3 *Progress through the stage of the review of safety*

were included in the safety review.[252,253] No papers evaluated calcium and/or vitamin D in OI. One paper was published in Croatian but the abstract and tables were in English and information could be extracted.[254] One paper was published in French but was understandable and no adverse effects were reported.[255]

Juvenile idiopathic arthritis (JIA)

The side-effects reported during the studies in JIA are summarised in Appendix 20. Follow-up in these studies was generally for 1–2 years. Two studies followed children for up to 6 years.[233,239] Warady and colleagues followed children for 6 months only.[245] Three studies with bisphosphonates reported no side-effects.[237,238,241] Bianchi and colleagues[231] and Lepore and colleagues[232] reported gastrointestinal irritation with oral bisphosphonates. Two children discontinued treatment because of gastrointestinal side-effects;[231,232] in one of these children, oesophageal erosions healed on stopping treatment.[231] Four studies using intravenous administration of bisphosphonates reported a transient flu-like reaction (fever, muscle aches, bone pain) after the first infusion; symptoms were generally managed with paracetamol or ibuprofen and did not occur with further infusions.[233,235,239,240] Noguera and colleagues observed mild abdominal pain, nausea and vomiting after the first infusion.[233] In subsequent cycles, children received intravenous odansetron before pamidronate and did not experience any further problems. Five studies reported that growth appeared normal during treatment with bisphosphonates.[231,235,239,243,244]

The studies evaluating calcium and/or vitamin D did not report whether clinical side-effects occurred during treatment (Appendix 20).[245,251] One child was borderline for hypercalciuria at baseline and later developed abdominal pain; supplements were discontinued for 4 months then the child was able to complete the study.[245]

Osteogenesis imperfecta (OI)

In addition to the studies of bisphosphonates and calcium and/or vitamin D in JIA and connective tissue disease, 43 papers evaluated bisphosphonates, mainly pamidronate, in OI[248,252–293] (Appendix 23). These studies contributed greater numbers of children to the evaluation of safety in children as only limited numbers of children with JIA had been treated. Most reports were published as full papers. English abstracts only were available for two reports which were published in French[255] and Croatian[254] and so little information is available from these reports. One report was only published as a conference abstract[259] and four reports were published as letters.[273,289–291]

Larger studies were conducted in OI compared with JIA and children were followed for longer (generally 1–4 years). Rauch and colleagues[277] followed 165 children for 4 years. Zeitlin and colleagues[279] followed 125 children for 4 years (but did not report side-effects). Munns and colleagues[278] included 131 children in a study. Six smaller studies and case reports followed children for up to 10 years.[253,256,265,275,290,292] The age of patients varied from new-born infants up to 21 years old.

Thirty-two reports related to intravenous administration of pamidronate, three studies to oral pamidronate[268–270] and one study to both oral and intravenous pamidronate.[265] One study related to intravenous zoledronic acid.[252] Four studies related to oral administration of other bisphosphonates: alendronate,[271] clodronate[290] and olpadronate.[272,292] One study used both intravenous pamidronate and oral etidronate,[289] one used intravenous pamidronate and oral alendronate[275] and one used intravenous pamidronate and oral olpadronate.[253] The most commonly used dosage regimen (18 studies) for intravenous pamidronate, depending on the age of the child, was 0.25–1.0 mg/day for 3 days every 2–4 months. Nine studies used once-daily administration every 1–6 months. Oral pamidronate doses were 300–400 mg/week, 100 mg/day, and 250 mg/day.

The most common side-effect of treatment with intravenous pamidronate was a flu-like reaction, consisting of fever, rigors and bone pain, which occurred during the first infusion of bisphosphonate, and was reported in 18 studies with rates varying from 18 to 100%. The reaction was transient, the symptoms were managed with paracetamol and it did not occur during subsequent cycles. Robinson and colleagues[284] compared pretreatment with paracetamol and ibuprofen and found ibuprofen to be more effective in treating the flu-like symptoms. Abdominal pain, nausea and vomiting were also reported;[263,273] one study treated the symptoms with odansetron.[263] Flu-like symptoms were also reported with intravenous zoledronic acid.[252]

Eight studies reported transient decreases in calcium and phosphorus levels after treatment with intravenous pamidronate.[248,254,256,267,273,277,288,291] However, no symptoms of hypocalcaemia were

reported. Calcium levels returned to normal with or without calcium and/or vitamin D supplementation. Hogler and colleagues[253] recorded hypocalcaemia in 74% of children and hypophosphataemia in 82% of children after the first infusion of zoledronic acid. The decrease in calcium levels became less after the second and third infusions.[252] In one study, a girl with increased serum calcium levels developed microcalcifications of the renal papillae during treatment with intravenous pamidronate.[275] The calcium levels returned to normal after withdrawal of vitamin D supplements and the microcalcifications started to regress. Three studies noted no changes on renal ultrasound during treatment with intravenous pamidronate.[258,285,286]

Studies examined the effects of bisphosphonates on bone remodelling and fracture healing. In one study, bone turnover was suppressed to below that of normal children.[277] Falk and colleagues[257] observed non-union of a tibial fracture. Munns and colleagues[278] observed a non-significant delay in fracture healing. Two studies noted that fracture healing was not delayed and there were no instances of fracture non-union.[248,269] The linear growth of children was at least normal in four studies.[248,258,264,285] Van Persijn van Meerten and colleagues[253] noted sclerosis at various bone sites which disappeared on discontinuation of treatment with pamidronate. Devogelaer and colleagues reported that older radiopaque metaphyseal lines faded away indicating that dense bone was reabsorbed.[268] Glorieux and colleagues found no effects of commonly used doses of bisphosphonates on the growth plate and the bone ages of children corresponded with their chronological age.[248] Apart from this review, there is a report of iatrogenic osteopetrosis after administration of very high doses of intravenous pamidronate for idiopathic hyperphosphatasia[294] but, in a review of 20 children, Ward and colleagues found no problems when clinically relevant doses of bisphosphonates were administered.[295]

After infusion of pamidronate, respiratory distress occurred in four infants who already had respiratory compromise.[261] One infant died from respiratory infection and another from an unknown cause, but treatment was continued uneventfully in the other two children. Chien and colleagues noted subclinical hypocalcaemia in a 12-day-old infant even though the infant was receiving supplements.[267]

The outcome of pregnancy in two young women with OI and who had been treated with intravenous pamidronate for 5 and 7 years, respectively, was followed.[266] Pamidronate treatment was stopped during pregnancy. The two babies also suffered from OI. One baby had asymptomatic hypocalcaemia at birth which resolved by day 11. Calcium levels were not measured in the second baby but there were no symptoms of hypocalcaemia at birth.

The two studies of oral pamidronate[269,270] and four studies of other oral bisphosphonates[271,272,290,292] did not report any side-effects, including gastrointestinal effects.

Discussion

In two open studies of calcium and/or vitamin D supplementation in children with JIA, there was evidence of a beneficial effect on bone mass; however, the numbers of children recruited were small and it is not possible to draw any major conclusions about either efficacy or safety of these agents in this setting. The supplements were well tolerated in these studies. Unintentional high doses of vitamin D have resulted in potentially serious renal problems.[296]

Of the studies which reported on the use of bisphosphonates in children including those with JIA, there was some evidence of a consistency of effect in improving bone mass. There were insufficient data relating to effect on fracture risk. Overall, the quality of the evidence was poor in relation to study design (only one RCT), numbers of children studied, heterogeneity of subjects studied and therapeutic regimens used. Hence, although bisphosphonates appear to hold promise as an intervention in management of children with low bone mass, further studies are needed. The follow-up in the studies was generally 1–3 years, although Brumsen and colleagues[239] and Noguera and colleagues[233] followed patients for 6 years. JIA can be a life-long illness and it is unclear whether this duration of treatment is sufficient to reduce the risks of low BMD and fractures in adulthood.

Only small numbers of children with JIA were included and studies recruited a mixture of children with JIA and other connective tissue diseases. One study reported that they used a standard definition of JIA.[251] The other studies did not discuss how they defined arthritis in children and studies included a mixture of subtypes of disease. Therefore, it is not clear how the JIA children differ within and between studies.

Most studies recruited children with pre-existing poor bone health or fragility fractures, but two studies recruited children without current problems but who were at risk of low BMD and fractures because of JIA and long-term corticosteroid treatment.[229,236] Bone health also improved in these latter children.

Four studies included an intervention group of children treated with bisphosphonates and a control group of children receiving standard treatment.[229–232] However, none of the studies compared directly the results of intervention and control groups; the results were only compared with the group's own baseline. There were also differences in disease severity between groups. Acott and colleagues compared corticosteroid-treated children who had experienced fractures with corticosteroid-treated children who had not experienced fractures and had greater BMD.[230] Similarly, the control group of children recruited by Bianchi and colleagues had less severe disease which did not require corticosteroid therapy and had not experienced fragility fractures.[231]

There was considerable variation in the doses and schedules of bisphosphonates in the review but, even though bisphosphonates are not licensed for use in children, none of the authors explained their choice of dose. Although bisphosphonates were administered both orally and intravenously, it is not possible to compare any differences in effectiveness between the two routes because of heterogeneity in drugs and doses used and the heterogeneity of the study design with small numbers of children treated. It is not possible to determine the best agent, route of administration or duration of treatment from the available evidence.

In eight studies included in the systematic review, all children continued with their usual corticosteroid treatment, but in the other eight studies it was not clear whether children were receiving corticosteroids. It is not possible to assess whether maintenance of adequate calcium and vitamin D status in combination with bisphosphonate administration is more effective than bisphosphonates alone. Although 10 studies ensured adequate calcium and vitamin D status,[229–231,234,236,238,241–244] they did not report further details of how this was achieved. One case series[232] specifically did not allow supplementation and five studies did not report on calcium and vitamin status. The small numbers of patients and variation in study design further complicate any possible comparison.

The methods of assessment of outcome were a major weakness in most of the studies. All the studies included changes in BMD as an outcome. Brumsen and colleagues used DPA when first studying children, then later changed to DXA.[239] Bianchi and colleagues[231] described the methodology of density assessment using DXA in most detail. A standard protocol for measurement was used, each child was always scanned using the same machine and a quality control procedure was instituted. In other studies, detailed methodology was not reported but was probably inadequate. Hence the robustness of the scanning methodology in these studies is uncertain.

DXA does not measure the thickness of bone, only the scanned area, and estimates BMD as g/cm^2 (aBMD) rather than a true density. Hence, aBMD increases with bone size because of the greater thickness of larger bones. Interpretation of aBMD poses major challenges because of changes in bone size related to growth and puberty; children with chronic disease often have chronic growth and delayed puberty which will affect bone size. Therefore, aBMD should be adjusted for body size and one approach is calculation of BMAD by modelling the bone as a cube[84] or cylinder[84] (see Chapter 2). Two studies adjusted density for body size[231,234] and two calculated BMAD[229,235] Lepore and colleagues used CT scanning and thus estimated vBMD.[232] The fact that adjustments may not have been made to account for the size of children undermines the validity of the results and makes it difficult to compare results between studies. Ideally, reference data for calculating *Z*-scores should be obtained from large age-, sex- and ethnicity-specific local databases. Use of standard databases (for example, as provided by the manufacturer of DXA machines) can lead to inconsistencies in the diagnosis of osteopenia.[77] Bianchi and colleagues[231] and Gandrud and colleagues[235] used reference data from local children, but the other studies used manufacturers' data or did not state the source.

The method of reporting results varies between studies. Some studies report absolute values of BMC (g), BMD (g/m^2) or BMAD (g/m^3). Other studies report percentage change from baseline and others report *Z*-scores, making it hard to compare results between studies. It is not possible to ascertain the maximum improvement in BMD that can be attained through treatment with bisphosphonates.

A number of studies examined biochemical markers of bone turnover and noted changes in

levels during treatment. Few normative data are available for paediatric bone markers which are affected by age, sex and puberty. In addition, the relationship between markers and magnitude of change in BMD is unknown.

Both densitometry and bone markers are surrogate outcomes and the outcome of main interest and significance is reduction in fracture occurrence in the subjects as both children and adults. Although only short-term studies with bisphosphonates have been conducted, several showed a reduction in fractures during treatment with bisphosphonates. Longer-term studies are needed to show these effects are sustained.

The review of safety showed that both oral and intravenous bisphosphonates were generally well tolerated in children. A major concern has been about long-term effects. The anti-resorptive effects of bisphosphonates could damage bone but, although levels of bone markers were altered in some studies, there was no evidence of long-term effects. In addition, in a child with juvenile idiopathic osteoporosis, Hoekman and colleagues observed that all the biochemical markers of bone turnover returned to pretreatment levels after stopping bisphosphonate treatment, suggesting that there was no permanent inhibition of bone activity.[297] Several studies reported that fracture healing was not delayed. Linear growth was unaffected by treatment. Although sclerotic lines have occurred, they faded or disappeared. Two young women continued treatment with bisphosphonate until conception without untoward effects on themselves or their babies.[266]

Although low incidences of bone pain has been reported in adults after treatment with bisphosphonates for osteoporosis, severe bone pain has been reported frequently in adults with cystic fibrosis treated with bisphosphonates but can be controlled with corticosteroids.[298,299] The bone pain may be a reaction unique to cystic fibrosis related to the abrupt reduction in bone turnover expected after bisphosphonate dose.

Limitations of study

Although our review suggested that bisphosphonates appear to improve BMD in children with JIA, the evidence from our review is not conclusive. Because of the sparsity of data, we adopted a pragmatic approach and included all study designs, case series and case reports in the review of bisphosphonate treatment. Even so, only two studies of calcium and/or vitamin D could be included. The overall number of children treated was small (78). The quality of all studies including the RCT is poor. The studies are heterogeneous and of variable quality. For example, definitions of JIA are unclear and children of all different subtypes as defined by a range of standards were included, there are differences in dose and routes of administration of bisphosphonates and assessment and reporting of outcome are unclear. There were no comparisons with control groups even in RCTs and controlled studies. Because of this variability, it was not possible to combine results and estimate an overall health benefit. We only found short-term studies and the longer-term effects of these interventions, for example on bone health and growth, could not be determined in JIA. We were not able to determine whether children being treated with bisphosphonates also require supplementation with calcium and vitamin D in order to ensure that they are calcium and vitamin D replete. It is not known whether pharmacological doses of these agents are needed. Corticosteroid use in children is diminishing because of the effectiveness of new biological therapies and these developments could eventually reduce the problems of poor bone health in children with JIA. However, children with JIA can still develop low BMD in JIA even if not treated with corticosteroids. We could not distinguish whether the effectiveness of the interventions differs between children treated or untreated with corticosteroids.

Conclusions

- Bisphosphonates are a promising treatment for osteoporosis in children with JIA, but the quality of the current evidence is poor and better studies are needed to assess more clearly their role and permit licensing of these agents for treatment of children.
- The accurate assessment of outcome is crucial.
- There are still uncertainties about the use of bisphosphonates in children, including whether the positive effects of treatment continue over time, the length of treatment and the maximal bone mass gain that can be achieved. In particular, longer-term studies are needed to evaluate the effectiveness and safety of this treatment into adulthood.

Chapter 4

Long-term bone health in JIA

Objectives

The objective of this part of the study was to describe the occurrence of low bone mass and fractures in adults with JIA and compare it with that expected in the general population of adults.

Long-term follow-up of bone health

The review of outcome measures in Chapter 2 concentrated on how bone health can be assessed in children participating in clinical trials. Chapter 3 reviewed clinical studies of bisphosphonate treatment and calcium and/or vitamin D treatment in children; studies were short term. This chapter examines the longer-term effects of JIA. It is possible that adults with JIA (whether active, in remission or resolved) could have lower BMD and higher risk of fragility fractures than adults who have never suffered with JIA. This chapter briefly summarises the data available in healthy children and adults and then discusses the long-term studies available in children and adults with JIA. In addition, data from a further two cohorts of adults who have JIA are analysed.

BMD and fractures in children and adults without JIA

A large study used data from 84,129 children (aged <18 years) included in the UK GPRD, a large, computerised database of anonymised longitudinal medical records from UK primary care.[300] For all types of fracture, the fracture rate over an 11-year period was 133.1/10,000 person-years. Fracture rates were greater among boys than girls at all ages with the peak incidence for boys at 14 years and for girls at 11 years. After these ages there was a sharp decline in incidence. Clark and colleagues systematically reviewed published studies investigating the association between bone density and fractures in children.[26] Studies included children aged 16 years or younger who did not have a chronic illness likely to affect bone mass. Six studies found an association between low bone mass and fractures; standardised mean difference in mean bone mass between children with fractures and controls –0.32 [95% confidence interval (CI) –0.43 to –0.21, $p < 0.001$]. All studies measured bone density after the fracture had occurred, so it is possible that the reduction in bone mass may have been a consequence of previous fractures. A total of 6207 children (mean age 9.9 years) in the Avon Longitudinal Study of Parents and Children underwent a DXA scan at baseline, then fracture data were collected over the subsequent 2 years; 7.5% reported one fracture and 1.4% reported more than one fracture.[301] After adjustment for body size and other confounders, the odds ratio for risk fracture over 2 years per one SD decrease in BMC was 1.88 (95% CI 1.17 to 3.01). The age- and sex-specific incidences of fractures in otherwise healthy adults in England and Wales were determined from the GPRD 1988–98.[302] A total of 103,052 men and 119,317 women in a sample of 5 million adults sustained a fracture over 10.4 million and 11.12 million person-years of follow-up, respectively.

BMD may be used to predict the risk of fracture. In adults, a meta-analysis of 11 prospective cohort studies (90,000 person-years and 2000 fractures of any type) demonstrated that the risk of fracture appears to double for each one SD decrease in BMD.[24] The predictive risk was greater for fractures when BMD was measured at the site of the fracture. Thus BMD measured at the hip was a stronger predictor of hip fracture than bone mass measured at other sites.[24] In healthy girls, aged 3–15 years, each decrease of one SD in total body BMD nearly doubled the risk for new fractures at any site.[27]

BMD and fractures in children and adults with JIA

In contrast with healthy children and adults, there are fewer data relating to fracture risk in patients with JIA. Chapter 2 reviews how bone health reported as BMD or fractures can be assessed as an outcome measure in children with JIA. The longitudinal studies reported BMD and fractures but are are mostly short-term studies and followed up children for only 1 or 2 years.[19,164,170–172,174] In the longest study, Lien and colleagues assessed 105 children with JIA included and after a mean follow-up of 14.2 years (mean age at follow-up 17.0 ± 1.8 years) 41% of children had low total body BMC and 34% had low BMD.[164] Total body BMC was lower in children with polyarticular

disease compared with those with oligoarticular disease.

Three further studies examined the effects of JIA on bone mass in adults. In a cross-sectional study, 65 adult patients (mean age 32.2 years) with a history of JIA had reduced hip and lumbar spine BMD compared with healthy control subjects matched for age, sex, height and weight.[14] From WHO definitions, significantly more subjects in the JIA group had osteopenia and osteoporosis than would be expected in a normal population sample. Mean levels of markers of both bone formation and resorption were significantly increased in the JIA group, indicating increased bone turnover in these subjects compared with controls. Previous Steinbrocker functional class, polyarticular course and a history of corticosteroid treatment for more than 1 year were significantly associated with reduced BMD.[15] In a case–control study, Haugen and colleagues followed 229 adults with JIA.[16] The mean follow-up since diagnosis was 15.6 ± 2.4 years in women and 14.9 ± 2.1 years in men. Young adults with persistent disease had significantly lower BMD at radius, femoral neck, lumbar spine and total body, and significantly more osteopenia and osteoporosis, compared with healthy subjects. However, young adults who were in remission achieved the same BMD as healthy subjects. Only the number of months taking corticosteroids significantly affected BMD at all measured sites. French and colleagues retrospectively followed a cohort of 32 patients with JIA for a mean of 27.1 years.[15] The patients had a mean age 35 years at follow-up (range 19–53 years). A total of 41% of adults with a history of JIA were osteopenic at either the lumbar spine or femoral neck. Steinbrocker functional class, low physical activity, tobacco use and low calcium intake during adolescence were significantly associated with low BMD.

Burnham and colleagues used the UK GPRD to determine the risk of fracture in a population-based sample of individuals with childhood-onset arthritis.[22] Children and adolescents with a diagnostic criterion consistent with arthritis between 1 and 19 years of age were included and were sex- and age-matched with non-arthritis controls in the same GP practice. A total of 1939 subjects (median age at start of follow-up 17.3 years, range 1–96 years) with arthritis were included in the analysis and 207,072 controls (median age at start of follow-up 19.7 years, range 0–104 years). Subjects were followed for a median of 3.9 years. Subjects with childhood-onset arthritis received disease-modifying antirheumatic drugs (5.7%), corticosteroids (4.9%) and NSAIDs (54%); 12.7% of controls received NSAIDs ($p < 0.001$). A higher proportion of subjects with arthritis experienced fractures during the follow-up period: 129 (6.7%) in the arthritis group and 6910 (3.3%) in the control group ($p < 0.001$). The risk of fracture in subjects with arthritis was most pronounced during adolescence (age 10–15 years: incident rate ratio 3.13, 95% CI 2.21 to 4.33) and over the age of 45 years (incident rate ratio 3.97, 95% CI 2.23 to 6.59). In the subjects with arthritis, there were no significant associations between fracture risk and cumulative number of NSAID, DMARD or corticosteroid prescriptions. In both the arthritis and control groups, the most common sites of fracture were the forearm and wrist. A limitation of this study is that the diagnosis of JIA according to established criteria was not confirmed from the database or validation by GPs. The percentage of patients remaining on NSAIDs is lower than might be expected; this suggests that this cohort may have included individuals with non-chronic musculoskeletal disease, rather than JIA.

In a retrospective study by Murray and colleagues (only available as a conference abstract)[303] conducted in 103 children with a mean duration of JIA of 10.2 years attending Great Ormond Street Hospital, 23% of patients had experienced at least one fracture and 56% of these fractures were vertebral; 66% of children had received calcium and vitamin D supplementation and 9% had received bisphosphonates. Fractures occurred between 1 and 12 years of onset. The investigators commented that fractures were most common early in JIA and children with growth failure, severe erosive disease and those needing high doses of corticosteroids were at highest risk. A total of 52 children had lumbar spine BMD assessments; these were on average 2.0 SD less than expected (*Z*-score –2); 39% of these patients had osteoporosis as defined by the WHO criteria for adults.

Varonos and colleagues compared children with JIA and spinal fractures with children with JIA and no spinal fractures.[223] Children with spinal crush fractures had started treatment with corticosteroids at an earlier stage of disease. Elsasser and colleagues followed 63 children for 18 months.[224] Nine children had at least one crush fracture at baseline and four experienced further fractures during 18 months of follow-up. Five children without fractures at baseline experienced a fracture during follow-up. A case report described a girl who had experienced traumatic fractures and stress fractures of the limbs.[304]

Additional cohorts identified in this study

Data from two cohorts of adult patients with JIA were identified and have been analysed in this report to provide additional data on the long-term bone health of children and adults with JIA. Both cohorts included data on aBMD assessed using DXA and fractures.

The first set of long-term outcome data are derived from a cohort of patients studied by Dr Jon Packham, now at Staffordshire Rheumatology Centre, Haywood Hospital, Stoke-on-Trent. These patients were followed up from the Canadian Red Cross Memorial Hospital, Taplow, which was a national referral centre for JIA until the 1980s. After it closed, many patients were transferred to Wexham Park Hospital, Slough. Data concerning this cohort of patients have been published, focusing on education and employment,[305] functional outcome,[306] predictive factors for mood and pain[307] and social function, relationships and sexual activity.[308] They are not a true inception cohort, but are skewed towards patients with severe JIA still under medical follow-up. However, they do represent those patients most likely to be encountered in an adult rheumatology clinical practice. Data from a second population of patients have been collected by Dr Helen Foster, Arthritis Research Campaign Clinical Senior Lecturer in Paediatric Rheumatology, Medical School, Newcastle-upon-Tyne. This group of adults with JIA have been documented in a study of quality of life and psychosocial outcome.[309]

Taplow cohort

Methods

Patient assessment

A total of 259 adults (>18 years old) with childhood onset rheumatic disease, and either still attending clinics or with continuing contact with Wexham Park Hospital in the form of shared care, were identified from a computerised database, by manually searching patient lists and by reviewing patient notes. Local Research Ethics Committee approval was obtained. Patients eligible for study entry were sent letters describing the aims and requirements of the study and were asked to return a signed consent form. Non-responders were sent a second letter and subsequently contacted by telephone to ensure that their contact address was correct. Of these patients, 245 (95%) attended for an interview, clinical examination and notes review by the same rheumatologist (J Packham). The date of this interview and examination was used as the date of assessment for the study.

Data collected and used in this study

Data were collected for the patient's lifetime since onset of rheumatic disease, including date of birth, sex, height, weight, date of onset JIA, type of JIA (ILAR criteria),[3] treatment with oral corticosteroids, date of latest DXA scan, DXA scan results (g/cm^2) and date and site of any bone fractures. The DXA scans were requested because of suspected low BMD and/or fractures. All scans were performed on Lunar pencil scan. A few patients had been scanned more than once, in which case the latest scan result was used in the analysis.

Analysis

Data from the clinical examination, case notes review and patient interview were entered into an Access database. The data were double-checked and re-coded to allow analysis using STATA version 8. Only absolute aBMD (g/cm^2) values and not *Z*- or *T*-scores were available from the original data set; *T*- and *Z*-scores were subsequently determined by the Clinical Imaging Department, University of Manchester, using the reference database. Standardised fracture incidence ratios were calculated from a method based on the calculation of standardised mortality ratios, which used survival time data and assumed that each patient in the study only had one fracture during the follow-up period. Fracture rates in the population were obtained from the study of fractures in the GPRD.[302] Standardised fracture incidence ratios were calculated for all patients in the study, for men and women separately and for three different age groups (<30, 30–60 and >60 years old).

Results

Patient characteristics

A total of 245 patients were included in the study; 70 men (29%) and 175 women (71%). The mean age at review was 34 years with mean age at disease onset of 7 years and mean disease duration at review of 27 years (*Table 11*). A total of 7% of patients had the oligoarticular and 22% the extended oligoarticular subtype of JIA, 17% had the polyarticular subtype and 21% had the systemic subtype (*Table 1*). A total of 145 patients had received past or current treatment with oral corticosteroids for mean (SD) duration of 12 (10) years [12 (10) years for 36 men and 12 (10) years for 109 women].

TABLE 11 *Characteristics of all patients: mean ± SD (range)*

	All patients ***N* = 245**	**Men** ***N* = 70**	**Women** ***N* = 175**
Age at review (years)	34 ± 11 (18–77)	34 ± 11 (19–63)	34 ± 11 (18–77)
Age at onset of disease (years)	7 ± 4 (0.5–18)	8 ± 4 (1–17)	7 ± 5 (0.5–18)
Disease duration at review (years)	27 ± 11 (6–69)	26 ± 11 (7–53)	28 ± 11 (6–69)
Disease type: *N* (%)			
Systemic	52 (21%)	20 (29%)	32 (18%)
Oligoarticular	16 (7%)	2 (3%)	14 (8%)
Extended oligoarticular	54 (22%)	9 (13%)	45 (26%)
Polyarticular	41 (17%)	6 (9%)	35 (20%)
JRA	37 (15%)	5 (7%)	32 (18%)
Juvenile ankylosing spondylitis	32 (13%)	24 (34%)	8 (5%)
Juvenile psoriatic arthritis	13 (5%)	4 (5%)	9 (5%)

Bone mineral density

A total of 88 (36%) [14 men (20%) and 74 women (42%)] of the 245 patients had undergone a DXA scan of the lumbar spine (L2–L4) and/or hip. The mean age at the time of DXA scan was 35 years (35 years for women and 32 years for men). The mean duration of disease was 28 years. For all patients scanned, the mean aBMD was 1.07 g/cm^2 at the lumbar spine, 0.86 g/cm^2 for the right hip and 0.83 g/cm^2 for the left hip (*Table 12*). Mean *Z*- and *T*-scores at all three sites for all patients, and for men and women separately, were below zero (*Table 12*).

The numbers of patients with osteopenia and osteoporosis were determined based on their *T*-scores and using the WHO definitions.[310] Patients with aBMD greater than *T*-score –1 were classified as having normal aBMD and those with *T*-score aBMD below –2.5 were classified as having osteoporosis. A total of 43% of patients could be classed as having normal aBMD at the lumbar spine, 51% at the right hip and 43% at the left hip (*Table 13*); 48% of women had normal aBMD at the lumbar spine and 16% were classified as having osteoporosis at this site; 17% of men had normal aBMD at the lumbar spine and 50% were classified as having osteopenia and 33% as having osteoporosis at this site.

Fractures

Forty-eight of the 245 patients (19.6%) experienced one or more fractures since the onset of disease. Thirty-three of these patients experienced one fracture, 12 had two fractures, two had three fractures and one had five fractures. Fracture sites included mostly the femur (26 fractures) but also the humerus (6), forearm (12)

TABLE 12 *aBMD and Z-scores for DXA scans: mean (95% CI)*

aBMD	**All patients scanned**	**Men**	**Women**
Lumbar spine	*N* = 71	*N* = 12	*N* = 59
g/cm^2	1.07 (1.03 to 1.11)	1.06 (0.91 to 1.21)	1.08 (1.03 to 1.12)
T-score	–1.14 (–1.49 to –0.80)	–1.51 (–2.74 to –0.28)	–1.07 (–1.42 to –0.72)
Z-score	–0.73 (–1.02 to –0.45)	–0.78 (–1.77 to 0.22)	–0.73 (–1.02 to –0.43)
Right hip	*N* = 30	*N* = 4	*N* = 26
g/cm^2	0.86 (0.80 to 0.92)	0.86 (0.31 to 1.41)	0.87 (0.81 to 0.92)
T-score	–1.01 (–1.57 to –0.46)	–1.76 (–6.37 to 2.84)	–0.89 (–1.37 to –0.42)
Z-score	–0.87 (–1.37 to –0.36)	–1.43 (–5.39 to 2.54)	–0.78 (–1.25 to –0.31)
Left hip	*N* = 35	*N* = 5	*N* = 30
g/cm^2	0.83 (0.77 to 0.90)	0.77 (0.30 to 1.24)	0.84 (0.79 to 0.90)
T-score	–1.33 –1.90 to –0.77)	–2.47 (–6.39 to 1.45)	–1.15 (–1.60 to –0.69)
Z-score	–1.04 (–1.55 to –0.53)	–2.03 –5.44 to 1.38)	–0.88 (–1.31 to –0.44)

TABLE 13 *aBMD classified according to WHO*

	All patients scanned	Men	Women
Lumbar spine			
Normal	30 (43%)	2 (17%)	28 (48%)
Osteopenia	27 (38%)	6 (50%)	21 (36%)
Osteoporosis	13 (19%)	4 (33%)	9 (16%)
Right hip			
Normal	15 (51%)	1 (25%)	14 (56%)
Osteopenia	10 (35%)	1 (25%)	9 (36%)
Osteoporosis	4 (14%)	2 (50%)	2 (8%)
Left hip			
Normal	13 (43%)	1 (20%)	12 (40%)
Osteopenia	14 (46%)	1 (20%)	13 (43%)
Osteoporosis	3 (11%)	3 (60%)	5 (17%)

and tibia (8); vertebral crush fractures also occurred (7).

The calculated standardised fracture incidence ratio of observed to expected fractures was 1.92 (95% CI 1.42 to 2.55) for all patients ($p < 0.001$), 2.60 (95% CI 1.80 to 3.63) for women ($p < 0.001$) and 1.17 (95% CI 0.64 to 1.97) for men. When considered as three age bands, <30, 30–60 and >60 years, the calculated ratios were 1.20 (95% CI 0.70 to 1.92), 2.73 (95% CI 1.83 to 3.92, $p < 0.05$) and 8.96 (95% CI 1.09 to 32.37, $p < 0.001$).

Newcastle cohort

Methods

Patient assessment

Between 1996 and 2002, all patients attending a young adult rheumatology clinic and seen by the same rheumatologist (H Foster) and routinely offered a DXA scan as part of their clinical care were included in this study. A retrospective case notes review was then undertaken by a specialist registrar (N Kumar). Data were collected from clinical records within 3 months of the scan date and the scan date was regarded as the assessment date for this study. As this project was a review of case notes and the DXA scans were undertaken as routine practice, approval from an ethics committee was not needed. Patients were seen in outpatients by the same rheumatologist (H Foster) as part of their clinical care.

Data collected and used in this study

Data collected from the review of case notes included date of birth, sex, height, weight, JIA type, treatment with oral corticosteroids, date of latest DXA scan, DXA scan results (g/cm^2, *T*- and *Z*-scores) and occurrence of vertebral and peripheral fractures. All patients underwent a scan at the lumbar spine (L1–L4). All scans were undertaken on either a Hologic 4500A scanner or a Hologic Delphi scanner (previously a Hologic C2000 scanner). The scanners were validated by the department and were regarded as equivalent. A few patients had been scanned more than once, in which case the latest scan was used in the analysis. Scan results were recorded as aBMD (g/cm^2) and as *Z*- and *T*-scores.

Analysis

Data were entered into Excel spreadsheets by the Newcastle team. In Manchester, the spreadsheets were combined into a single sheet, the data were double checked and any duplicated data removed to allow analysis using STATA version 8.

Results

Patient characteristics

From a total of 98 patients, 11 (three men and eight women) were excluded from the analysis because data on BMD and fractures were missing. Therefore, 87 patients were included in this study; 16 men (18%) and 71 women (82%). The mean age at review was 29 years with a mean disease duration of 21 years (*Table 14*). The mean duration of corticosteroid treatment was 6 years. A total of 17% of patients had the pauciarticular subtype of JIA, 9% had the extended pauciarticular subtype, 47% had the polyarticular subtype and 14% had the systemic subtype (*Table 14*).

Bone mineral density

All 87 patients who underwent a DXA scan were included in the analysis of bone status. The mean

TABLE 14 *Characteristics of patients: mean ± SD (range)*

	All *N* = 87	Men *N* = 16	Women *N* = 71
Age at review (years)	29 ± 11 (14–66)	31 ± 14 (14–66)	29 ± 10 (14–59)
Disease type: *N* (%)			
Systemic	12 (14%)	5 (30%)	7 (10%)
Pauciarticular	15 (17%)	3 (19%)	12 (17%)
Extended pauciarticular	8 (9%)		8 (11%)
Polyarticular rheumatoid factor positive	18 (21%)	1 (6%)	17 (24%)
Polyarticular rheumatoid factor negative	23 (26%)	2 (13%)	21 (30%)
Juvenile psoriatic arthritis	5 (6%)	2 (13%)	3 (4%)
Enthesitis-related arthritis/juvenile ankylosing arthritis	4 (5%)	2 (13%)	2 (3%)
Other JIA	2 (2%)	1 (6%)	1 (1%)

TABLE 15 *aBMD and Z-scores for DXA scans: mean (95% CI)*

	All	Men	Women
Lumbar spine	*N* = 87	*N* = 16	*N* = 71
g/cm^2	0.99 (0.96 to 1.03)	1.03 (0.91 to 1.15)	0.98 (0.95 to 1.02)
T-score	–0.58 (–0.90 to –0.27)	–0.57 (–1.66 to 0.50)	–0.59 (–0.91 to –0.27)
Z-score	–0.31 (–0.63 to 0.00)	–0.25 (–1.27 to 1.90)	–0.33 (–0.66 to 0.00)

TABLE 16 *aBMD classified according to WHO recommendations*

	All patients	Men	Women
Lumbar spine	*N* = 87	*N* = 16	*N* = 71
Normal	52 (60%)	10 (62%)	42 (59%)
Osteopenia	30 (34%)	4 (25%)	26 (37%)
Osteoporosis	5 (6%)	2 (13%)	3 (4%)

aBMD for men and women was 0.99 g/cm^2 for the lumbar spine (*Table 15*). Men had a higher mean aBMD than women. Mean *Z*-scores for the lumbar spine were below zero for all patients and also for male and female patients considered separately. Mean *T*-scores were negative for all patients and for both sexes.

When *T*-scores were classified according to the WHO definitions for bone status, for lumbar spine, 34% of all patients, 25% of men and 37% of women were classified as having osteopenia and 4–13% as having osteoporosis (*Table 16*).

Fractures

Since the onset of JIA, two patients experienced vertebral fractures (one man, one woman) and four experienced peripheral fractures (four women).

Discussion

Large longitudinal studies using the GPRD provide age-related data on the occurrence of fragility fractures in adults and children. The relationship between low bone mass and increased risk of fractures in postmenopausal women is well recognised[24] but there also appears to be an association between low BMD and fractures in children.[26] There are relatively few long-term studies on the occurrence of low BMD and fragility fractures in children with JIA, with most studies only following children for 1 or 2 years. However, the long- and short-term data indicate that children with JIA have a lower BMD and more fractures than children without JIA. There are very few data on long-term bone health from adults who have JIA but studies indicate that low BMD persists into adulthood, although adults in

remission from JIA may attain the same BMD as healthy adults.[16] Further long-term outcome data are needed.

From the available data, any predictors of low BMD and fractures in children and adults with JIA remain uncertain. In children, those with more severe disease had lower BMD than would be expected. It is not clear whether corticosteroid treatment has an effect on the maximal BMD attained. In children in one short-term study,[171] corticosteroid treatment reduced BMD compared with healthy children but a second study noted no difference.[19] In addition, Murray and colleagues noted that fractures were more common in children treated with higher doses of corticosteroids compared with those on lower doses.[303] One study in adults examined the effects of corticosteroids and noted that longer treatment periods with corticosteroids reduced BMD compared with healthy adults.[16] Differences in treatment patterns may affect generalisability of results to more recent cohorts of children. The adults in these two cohorts studied are likely to have received heavy treatment with corticosteroids and methotrexate, whereas children now being diagnosed with JIA are less likely to receive such intense corticosteroid treatment and may receive etanercept rather than methotrexate. It is possible that these changes in treatment may improve accrual of bone mass in childhood compared with children treated several decades ago.

The two cohorts evaluated in this study included patients with JIA which had persisted into adulthood. However, these cohorts are likely to contain only the more severely affected patients compared with those whose disease had remitted and were no longer being treated. There were no healthy controls. However, calculation of standardised fracture incidences for the Taplow cohort using fracture data from healthy controls demonstrated increased occurrence of fractures in adults with JIA. As the GPRD allows multiple fractures, it is likely that the standardised fracture incidence ratios may be an underestimate. The ratios of observed to expected fractures were higher in women than men. Possible explanations may be that girls have more severe JIA than boys and that they may be more susceptible to the influence of JIA. Fracture ratios were also higher in older age groups compared with younger age groups of patients, possibly because adults with long-term disease have lower physical activity compared with healthy controls. In addition, disease could be more severe in these patients. Standardised fracture ratios were not calculated for the Newcastle cohort of patients because the date of onset of disease was not available. However, it should be possible to collect this information and calculate the ratios in future analyses. There was a higher incidence of fractures in patients in the Taplow study. The difference in fractures between the two studies may possibly be explained by the Wexham patients being specifically asked about fractures, whereas the Newcastle study relied solely on review of notes and some fractures may not have been recorded in the notes.

It is possible that BMD values in subjects could predict the likelihood of fracture. BMD and fracture data were available from the Taplow cohort of patients. However, not all patients had been scanned and the scans available had been undertaken at different body sites. The number of hip scans that could be undertaken was limited as some adults with JIA had bilateral hip replacements.

Limitations of study

The cohort of patients from Taplow consists only of patients with more severe JIA as they were all still under rheumatology care and therefore do not reflect the overall population of adults with JIA. In addition, only those patients with signs of low BMD underwent a DXA scan. In contrast, the cohort from Newcastle included a wider range of severities as the cohort included patients who had inactive disease but were still being followed by the clinic. All patients were offered a DXA scan in this clinic. Thus results from the two cohorts cannot be combined. Although drug treatment with calcium and bisphosphonates was recorded in both cohorts, missing details on dates and durations of treatment restricted further analysis. Treatment of patients in these cohorts dates back many decades and subsequent changes in treatment patterns with less intense use of corticosteroids and the introduction of etanercept may have improved the accrual of BMD and thus these cohorts may not reflect expectations for children being diagnosed with JIA now.

Conclusion

Adults with JIA may have persistent low BMD compared with an otherwise healthy population together with an increased risk of fracture.

Chapter 5

Systematic review of costs for managing children with JIA and low BMD or fragility fractures

Objectives

The objective of this part of the report was to review the costs of treating JIA with low bone density and/or fragility fractures with bisphosphonates and calcium and/or vitamin D.

Methods

Data sources and search strategy

MEDLINE (on Ovid, searched from1966) and EMBASE (on Ovid, from 1980) were searched, as were the ISI Web of Science Conference Proceedings (from 1990) and Cochrane Library (Wiley Interscience), including the Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database (EED) and Health Technology Assessment Database. The search strategies are listed in Appendix 24 and included terms to identify studies that discussed the costs of treating JIA. The strategies were based on those used by the NHS EED search strategy. The results of electronic searches were handled as for the searches for studies of effectiveness. Copies of full articles were obtained where relevant and bibliographies were checked for further relevant references. The main searches were run in January 2005.

Inclusion of studies

Included studies had to discuss the costs of treating children with JIA and low BMD and/or fragility fractures. All study types were included. Inclusion decisions were made by one reviewer (JT).

Results

Identification and exclusion of studies

The literature searching did not identify any studies which evaluated the cost of treating JIA with low BMD and/or fragility fractures.

Studies of general interest to the cost of JIA

As background information, any studies which appeared relevant to the costs of treating JIA were examined; 19 studies were identified. Fourteen studies were excluded from the review because they did not include cost data or included adult patients (Appendix 25). Five studies (four papers and one abstract) appeared relevant and were examined further. One recent study evaluated the burden and cost of illness in patients with JIA in Germany.[311] Twelve months of costs associated with JIA were estimated from a retrospective cohort of 215 patients with JIA after 17 years of follow-up. However, this study recruited adult patients who had been diagnosed with JIA as children and provided costs of treating the adults but not the costs of treating them as children. It only provided 3 months of data and was conducted in Germany. Therefore, because of the limited use of these data for a UK assessment of the costs of treating JIA, the study was excluded from the review. A second study evaluated the costs of treating JIA in the USA.[312] Three and 12 months of costs were estimated in 70 patients with JIA. The paper was from 12 years ago and described the US setting, so was not relevant to his project and was also excluded from the study.

A study was published since completion of our review. This comprehensive study was conducted from the Canadian healthcare perspective.[313] Bernatsky and colleagues estimated the mean direct medical costs for children with JIA as Can$3002 compared with Can$1315 for outpatient control children without chronic disease.[313] The higher cost for children with JIA was mainly because of higher drug costs although these children also had higher costs related to appointments with healthcare professionals and diagnostic tests.

Two studies only evaluated the cost of etanercept treatment of JIA and were found to be irrelevant to the review.[314,315] Haapasaari and colleagues[315] evaluated the costs of adding etanercept to existing treatment estimated in patients with JIA in Finland including a period of 3 months before start of treatment then 12 months of follow-up. Cummins and colleagues[314] undertook a UK health technology assessment of etanercept which involved a systematic review and economic

modelling. The authors used an adult cost–utility model for evaluating the outcomes and costs of treatment and had to make many assumptions. The assumptions included assuming that the CHAQ was equivalent to the Health Assessment Questionnaire (HAQ), JRA30 criteria for response rate in children were equivalent to ACR20 criteria in adults and the relationship between HAQ and utility and mortality claimed for rheumatoid arthritis applies in children with JIA. Further assumptions were made, including that the costs of etanercept for children were similar to those for adults, and resource use and costs for children were similar to those for adults. The authors concluded that the cost–utility model had uncertain validity in JIA because some very strong assumptions had to be made for which there was no evidence base. In addition, they identified some technical problems with the adult model. Hence neither of these studies with etanercept provided any useful information for the project. The fifth study was only published as a conference abstract and compared the costs and HRQoL of children with polyarticular JRA treated with methotrexate, etanercept or a combination of the two agents.[316] The cost of achieving a complete clinical remission was US$18,675, US$11,830 and US$25,260, respectively. The cost per QALY was US$9520, US$9600 and US$14,300, respectively.

Conclusions

- There are no studies evaluating the costs of treating children with JIA and low BMD and/or fragility fractures.
- There are few data evaluating the costs of treating JIA in general and the studies identified were not relevant to this project.

It was not possible to undertake any further work using published cost data. However, we had the opportunity to use primary resource data which are available from an ongoing UK longitudinal study within the arc Epidemiology Unit: the Childhood Arthritis Prospective Study (CAPS) (see Chapter 6).

Chapter 6

Assessment of cost of treatment for JIA

Objectives

Because the published clinical effectiveness and cost data for the treatment of children with JIA and low BMD and/or fragility fractures are limited, it was not possible to undertake economic modelling. There were no data on the cost of treating children with JIA and low BMD and fragility fractures. Neither were data available on the costs of overall treatment of JIA in the UK. These data are essential for modelling.

Therefore, as a starting point, the aim of this part of the study was to evaluate the overall cost of treating children with JIA.

Methods

Childhood Arthritis Prospective Study (CAPS)

Primary resource use data are being collected as part of an ongoing UK longitudinal study, CAPS, within the University of Manchester arc Epidemiology Unit. The recruitment target for the project is around 1000 children newly presenting with inflammatory arthritis. The aim of CAPS is to identify predictors of outcome, both short and long term, following presentation with childhood onset inflammatory arthritis and to identify the relative contributions of socio-demographic, clinical, psychological, laboratory and genetic factors in explaining outcome. The goal is to enhance the ability to provide an accurate prognosis during the course of the disease and to target complex therapies to those with the most appropriate need.

Children are recruited from four centres (Manchester, Liverpool, Newcastle and Glasgow). Appropriate Research Ethics Committee approval has been obtained for each of the centres. Each centre has its own dedicated nurse responsible for recruiting and following up the children. The current principal investigators for CAPS include Eileen Baildam (Royal Liverpool Children's Hospital), Joyce Davidson (Royal Hospital for Children, Glasgow) and Helen Foster (University of Newcastle).

The inclusion criteria are newly diagnosed children less than 16 years old with inflammatory arthritis of one or more joints which has persisted for at least 2 weeks. Children with JIA are classified according to the ILAR criteria[2,3] Exclusion criteria include arthritis subsequently diagnosed to be caused by infection, trauma, foreign body or haematological/oncological conditions and connective tissue disorders. Written consent is obtained from the child and parents.

Data are collected as part of routine clinical care at first presentation and study entry (baseline), 6 months and 1, 2, 3, 4 and 5 years. At each time point, children undergo a rheumatological examination by the consultant, a comprehensive case notes review is undertaken and the nurse completes an assessment form together with the child and parents. The nurse's assessment form includes the CHAQ/adolescent CHAQ, Child Health Questionnaire (CHQ), the General Health Questionnaire (GHQ-30), Moods and Feelings Questionnaire (MFQ-P/MFQ-C) and the Illness Perception Questionnaire (IPQ-P/IPQ-C).

Resource use

We extracted the resource use data from the CAPS database and used these data to compile patient-based costs. Resource use data were collected at baseline and at 6 and 12 months of treatment. The following resource use data are being collected in CAPS:

- paediatric rheumatologist appointments (number of visits)
- referrals to other specialists or care (splinting, admission, surgery, ophthalmologist, referral to nurse specialist, physiotherapy, occupational therapy, podiatry and other consultant appointments)
- hospital admissions
- medication used for JIA, including intra-articular corticosteroid injections: drug, trade name, date started, date stopped, route
- investigations [dates of full blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), rheumatoid factor, antinuclear antibody (ANA), HLA-B27, immunoglobulins]

- clinical imaging [dates of X-rays, magnetic resonance imaging (MRI), ultrasound scan, DXA scan].

In CAPS, the data are entered on to an Access database specifically designed for the purpose. The study was not originally designed as a resource use and costing study so we had to make assumptions (as described in the following sections) to suit the analysis of these data.

Consultant paediatric rheumatologist appointments

The number of appointments during the follow-up period were collected from report forms completed by the paediatric rheumatology nurse together with the child and family at baseline and follow-up.

Referrals to other specialists or care

Data collected included referrals to ophthalmologists, specialist paediatric rheumatology nurses, physiotherapists, occupational therapists, podiatrists, requirements for splinting and orthotics. Data were collected from the review of case notes report form at baseline and follow-up visits. Data were recorded as yes or no and the number of visits was recorded only in a few children as this was not needed in the original study. Therefore, the number of children who had been referred at baseline and at 6 and 12 months was calculated in order to get an estimate of the numbers of children affected (*Table 17*).

Although many children had been referred, it was not possible for staff to return to the original records and collect this detailed information in the time available. Therefore, the number of referrals had to be estimated for this analysis. After discussion with the nurse and consultants, it was apparent that there were no standard recommendations for referrals and that they varied considerably depending on the individual child and were not dependent on severity of disease or other factors. However, details of this resource use were needed as they were likely to contribute significant costs to the management of JIA. Therefore, an estimate of the number of appointments with each specialist based on published details of treatment approaches was developed. Some guidance was available for referral to ophthalmologists: 3-monthly screening check-ups for most children seem to be preferred. Estimates were also made for the length of an appointment where costs would have to be estimated from the cost per hour of staff – see the section 'Unit costs', p. 56). The estimates for each 6-month follow-up period were as follows:

- ophthalmologist: two appointments
- specialist nurse: three clinic visits with each visit lasting 30 minutes
- physiotherapist: six clinic visits with each visit lasting 30 minutes
- occupational therapist: two clinic visits with each visit lasting 30 minutes
- splinting: two clinic visits with each visit lasting 30 minutes
- podiatrist: three clinic visits with each visit lasting 30 minutes
- orthotics: three clinic visits with each visit lasting 30 minutes
- hydrotherapy: 24 clinic visits with each visit lasting 30 minutes
- psychologist: one clinic visit lasting 30 minutes
- dermatologist: one clinic visit
- endocrinologist: one clinic visit

TABLE 17 *Number of referrals from CAPS database at baseline and at 6 and 12 months follow-up (number of yes replies)*

	Baseline	Per 1000 children	6 months follow-up	Per 1000 children	12 months follow-up	Per 1000 children
Ultrasound	26	57	9	24	17	62
MRI	33	72	12	32	17	62
Bone scan	19	42	5	13	11	37
Splint	11	24	2	5	3	10
Admission	68	149	26	65	10	34
Surgery	16	35	7	19	10	34
Ophthalmology	227	497	153	405	118	397
Specialist nurse	105	230	60	159	36	121
Physiotherapist	22	48	106	281	76	279
Occupational therapist	54	118	40	106	28	103
Podiatry	26	57	21	55.7	22	81
Orthotics	NC	–	5	13	4	15
Other	66	144	27	72	25	84

- cardiologist: one clinic visit
- dietician: one clinic visit lasting 30 minutes.

Hospital admissions

Referrals for surgery were also collected but by 12 months none were JIA related (no joint replacements needed), so surgery was not included in this stage of the analysis. Admissions were also recorded but reasons were not stated, but it was assumed that these were mainly day case admissions related to intra-articular corticosteroid injections, which were already accounted for under drugs received.

Medication used for JIA

Data on the drugs administered were collected from the review of case notes at baseline and follow-up visits and concentrated on drugs prescribed by the consultant rheumatologist relevant to treatment of JIA. Data were also collected from forms completed by the nurse and child and family but the list of drugs differed from those recorded from the case notes review and also included over-the-counter and non-JIA drugs. The generic names of individual drugs were recorded and sometimes the trade names. However, the doses of drugs were not recorded as they had not been relevant to the original study design. Recommended doses were taken from the online British National Formulary (BNF) for Children (www.medicinescomplete.com/mc/bnfc/current/) and the BNF (www.medicinescomplete.com/mc/bnf/current/) for December 2005, as appropriate. The dose of rofecoxib (withdrawn from the UK) was obtained from the BNF for September 2000. The doses were then checked with paediatric rheumatologists from two centres participating in CAPS to ensure that they reflected local practice (*Table 18*). As ranges of doses were recommended, a representative dose was estimated for each drug.

Individual doses were then calculated for each child in the study from the weight (kg) and age of each child as recorded on the report forms. Where weights were missing for follow-up visits, they were calculated from weight at the baseline visit: regression of the weight data demonstrated a mean increase 1.33 kg per child per year, which was added to the baseline weights. For children in whom no weight was recorded either at baseline of follow-up, the weights were applied from national children's mean weights recorded in the Health Survey for England (www.iuc.nhs.uk/pubs/hlthsvyengupd). For methotrexate dosage, body surface area was calculated from height and weight using the equation of Mosteller: $\sqrt{[\text{height (cm)} \times \text{weight (kg)}/3600]}$.[317,318] Where heights were missing for follow-up visits, they were calculated from height at the baseline visit: regression of the weight data demonstrated a mean increase of 2.04 cm per child per year, which was added to the baseline heights. For children in whom no height was recorded either at baseline or follow-up, the heights were applied from national children's mean heights recorded in the Health Survey for England (www.iuc.nhs.uk/pubs/hlthsvyengupd). Thus, an appropriate dose could be calculated for all children receiving treatment with drugs.

The duration of treatment for each drug for each child was calculated from the recorded dates of starting and stopping treatment for each follow-up visit. If the start date was missing from a drug record at the follow-up visit, the stop date for the drug from the previous visit was used. If the stop date was missing, the date of the review of the case notes was used in its place. In addition, if the stop date was recorded as being later than the case date, the case date was used and not the stop date. Stop dates were still missing or inaccurate for 20% of drug courses and the duration of treatment could be calculated; the method of dealing with these missing data is described in the unit costs section.

A course of intravenous methylprednisolone was assumed to be 3 days if the duration of treatment was not cited. When the same dates were recorded for different follow-up visits, the duplicate entries were deleted from the analysis.

Intra-articular corticosteroid injections

Data on the number of injections were collected from the review of case notes at baseline and at follow-up visits. Recommended doses were taken from the BNF for Children and the BNF online for December 2005, as appropriate (*Table 19*). A representative dose was chosen for the CAPS analysis.

A separate table in the database listed the individual injections and their site (mostly ankle and knee joints), so it could have been possible to provide a cost for each injection; several patients had more than one injection to different joints on each occasion. However, as the injections took place under anaesthetic (see the next paragraph) and the children would only require one session of anaesthesia on each occasion regardless of the number of injections required, the analysis used a single injection, estimated as being for a large joint, and a single anaesthetic session.

TABLE 18 *Doses and cost of drugs used in CAPS*

Drug	Dose chosen for CAPS analysis, Children's BNF and BNF 2005	Cost chosen for CAPS analysis, Children's BNF and BNF 2005
NSAIDs and analgesics		
Celecoxib (oral)	200 mg/day	Tablets: 100 mg × 60 = £21.55
Codeine (oral)	1 month–12 years: 0.75 mg/kg four times daily 12–18 years 30 mg six times daily	Tablets: 15 mg × 20 = £0.70 Syrup: 25 mg/5ml × 100 ml = £0.90
Diclofenac (oral)	6 months–18 years: 0.65 mg/kg/day	Tablets: 25 mg × 84 = £2.33
Etoricoxib (oral)	>16 years: 90 mg/day	Tablets: 60 mg × 28 = £22.96
Ibuprofen (oral)	6 months–18 years: 10 mg/kg three times daily	Tablets: 200 mg × 84 = £1.69 Suspension: 500 ml = £3.05
Ibuprofen retard (oral)	6 months–18 years: 10 mg/kg × three times daily	Tablets: 800 mg × 56 = £6.74
Indomethacin (oral)	1 month–18 years: 0.75 mg/kg twice daily	Tablets: 25 mg × 20 = £0.51
Paracetamol (oral)	1–3 months: 45 mg × 3 3–12 months: 90 mg × 4 1–5 years 135 mg × 4 6–12 years: 375 mg × 4 12–18 years: 500 mg × 4	Tablets: 500 mg × 20 = £0.15 Suspension: 120 mg/5 ml × 100 ml = £0.41
Piroxicam (oral)	6–18 years Body weight <15 kg: 5 mg/day Body weight <15 kg: 5 mg/day Body weight 26–45 kg: 15 mg/day Body weight >46 kg: 20 mg/day	Tablets: 10 mg × 56 = £2.78
Rofecoxib (oral)	12.5 mg/day	Tablets: 12.5 mg × 28 = £20.99 Suspension: 12.5 mg/5 ml × 150 ml = £22.9
Corticosteroids		
Methylprednisolone (i.v.)	30 mg/kg/day	40 mg/ml × 1 ml = £2.87
Methylprednisolone (oral)	1 month–18 years: 0.25 mg/kg/day	Tablets: 2 mg × 30 = £3.23
Prednisolone (oral)	1 month–18 years: 0.25 mg/kg/day	Tablets: 1 mg × 28 = £0.53 Soluble tablets: 5 mg × 30 = £2.20
DMARDS		
Ciclosporin (oral)	1 month–18 years: 1.875 mg/kg/day	Tablets: 10 mg × 60 = £16.44 Suspension: 100 mg/ml × 50 ml = £82.00
Etanercept (s.c.)	800 μ/kg/week	25-mg vial = £89.38
Hydroxychloroquine (oral)	1 month–18 years: 5.75 mg/kg/day	Tablets: 200 mg × 60 = £4.55
Infliximab (i.v.)	3 mg/kg × 5 over 6 months	25-mg vial = £89.38
Leflunomide (oral)	Body weight <10 kg: 5 mg/day Body weight 10–40 kg: 10 mg/day Body weight >40 mg: 20 mg/day	Tablets: 10 mg × 30 = £51.13
Methotrexate (oral)	12.5 mg/m^2/week	Tablets: 2.5 mg × 28 = £3.27
Methotrexate (s.c.)	12.5 mg/m^2/week	25 mg/ml × 2 ml = £4.58
Naproxen (oral)	1 month–18 years: 7.5 mg/kg twice daily	Tablets: 250 mg × 28 = £1.57
Sulfasalazine (oral)	2–18 years: 22.5 mg/kg twice daily	Tablets: 500 mg × 112 = £7.36
Ophthalmic preparations		
Atropine (eye drops)	8 drops/day	0.5% 10 ml = £2.32
Betamethasone (eye drops)	8 drops/day	10 ml = £2.32
Cyclopentolate (eye drops)	8 drops/day	0.5% × 5 ml = £0.97
Dexamethasone (eye drops)	8 drops/day	10 ml = £2.95
Prednisolone (eye drops)	8 drops/day	10 ml = £2.00
Prednisolone forte (eye drops)	8 drops/day	10 ml = £3.05

continued

TABLE 18 *Doses and cost of drugs used in CAPS (cont'd)*

Drug	Dose chosen for CAPS analysis, Children's BNF and BNF 2005	Cost chosen for CAPS analysis, Children's BNF and BNF 2005
Supplements		
Calcium, Calcichew (oral)	1 month–4 years: 0.25 mmol/kg four times daily 5–12 years: 2.0 mmol/kg four times daily 12–18 years: 10 mmol four times daily	Tablets: 1.25 g (Calcium 500 mg or 12.6 mmol) × 100 = £9.33
Ferrous sulfate (oral)	4 mg/kg/day	Tablets: 200 mg= 65 mg iron × 20 = £0.64
Folic acid (oral)	5 mg/week	Tablets: 5 mg × 20 = £0.44 Syrup: 2.5 mg/ml × 150 ml = £9.16
Sodium feredetate (oral)	4 mg/kg/day	Liquid: 190 mg/5 ml = 27.5 mg iron/5 ml × 100 ml = £0.89
Other		
Domperidone (oral)	Body weight <35 kg: 400 μg/kg three times daily Body weight >35 kg: 15 mg three times daily	Tablets: 10 mg × 30 = £2.51
Lansoprazole (oral)	Body weight <30 kg: 0.75 mg/kg/day Body weight >30 kg: 22.5 mg/day	Tablets: 15 mg × 28 = £10.86
Omeprazole (oral)	1 month–2 years: 700 μg/kg/day Body weight 10–20 kg: 10 mg/day Body weight >20 kg: 20 mg/day	Tablets: 10 mg × 28 = £11.40
Ondansetron (oral)	1–12 years: 4 mg three times daily 12–18 years: 8 mg three times daily	Tablets: 4 mg × 30 = £107.91 Syrup: 4 mg/5ml × 50 ml = 35.97
Ranitidine (oral)	1–6 months: 1 mg/kg three times daily 6 months–12 years: 3 mg/kg twice daily 12–18 years: 150 mg twice daily	Solution: 75 mg/5ml × 300 ml = £20.76 Tablets: 150 mg × 60 = £7.26
Pamidronate (i.v.)	⩾1 year: 1mg/kg over 4 hours, on 3 consecutive days <1 year: 0.5 mg/kg over 4 hours, on 3 consecutive days	3 mg/ml × 10 ml = £55.00[a]

[a] From BNF for March 2007.

TABLE 19 *Doses and cost of intra-articular injections used in CAPS*

Drug	Dose chosen for CAPS analysis, Children's BNF and BNF 2005	Cost chosen for CAPS analysis, Children's BNF and BNF 2005
Depomedrone (methylprednisolone acetate)	40–80 mg	40 mg/ml × 2 ml = £5.13
Triamcinolone acetonide (and hexacetonide)	10 mg for finger and toe joints, 20 mg for small joints, 40 mg for large joints	40 mg/ml × 1 ml = £1.70

It was assumed that all children treated were booked into the hospital as a day case and would receive either a general anaesthetic or nitrous oxide. After discussion with paediatric rheumatologists, it was confirmed that for the analysis a general guideline could be applied in that children under 8 years old would need a general anaesthetic but older children could have nitrous oxide, although in practice this would vary depending on the number of joints to be treated and the individual child (*Table 20*).

In practice, for intra-articular injection under general anaesthetic the child comes to the ward then down to theatre where they are under general anaesthetic for 15–30 minutes for the injection, then they return to the ward until well enough to go home. The child spends about 4–5 hours in hospital in total. For nitrous oxide, the procedure takes 15–30 minutes depending on how relaxed or stressed is the child, and the child is usually in hospital for about 2 hours.

TABLE 20 *Replies from paediatric rheumatologists concerning administration of corticosteroid injections*

CAPS centre	Reply regarding anaesthesia requirement
Liverpool, consultant 1	No strict age demarcation Depends on child (cooperation), joint (for some joints such as subtalars we always use general anaesthetic whatever the age) No child under 8 years old would have Entonox
Liverpool, consultant 2	Usually under 8 years old have general anaesthetic and over 8 years old have Entonox. Also hips and toes have general anaesthetic together with multiple joints over 3–4 joints
Glasgow	Depends on individual child If 1 or 2 joints would do most aged over 8 years with Entonox rather than general anaesthetic. Have general anaesthetic if younger or need multiple joints injected
Newcastle	Usually under 8 years old have general anaesthetic and over 8 years old have Entonox, but depends on child, number and site of joints. For multiple joints or relatively inaccessible joints irrespective of age would prefer general anaesthetic

When the same injection date was recorded several times during the case notes review, the duplicate entries were deleted from the analysis.

Investigations

Resource data for haematology, platelets, white blood cells, lymphocytes, neutrophils, erythrocyte sedimentation rate, CRP, ANA, B27 and immunoglobulin were collected from the review of case notes at baseline and follow-up visits. The tests were recorded as the date of test.

Clinical imaging

Resource use data from X-ray, ultrasound, MRI and bone scans were collected from the review of case notes at baseline and follow-up visits. Imaging procedures were just recorded as yes or no, but as it is unlikely that many children would have had more than one of each image procedure in each follow-up period, it was assumed that they had just one investigation.

Unit costs

Consultant paediatric rheumatologist appointments and referrals to other specialists or care

Most unit costs for appointments and referrals were obtained from Reference Costs 2004 (national average unit costs published by the Department of Health) (www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en) and the Unit Costs of Health and Social Care 2005 published by the Personal Social Services Research Unit (PSSRU), University of Kent[319] (*Table 21*). The finance department for the Manchester Children's University Hospital also provided local costs for certain aspects of care: paediatric rheumatology appointments, paediatric ophthalmology appointments and paediatric day-case admittance. As these were local costs and cannot be published, they were not used in the analysis but confirmed that the costs used in the study were appropriate.

NHS Reference Costs provided only one cost for paediatric clinic appointments of any type. This was used for the rheumatology appointments, but for other appointments the specific speciality cost was used even if it were presumed to be for an adult. Where different costs were provided for a first appointment and follow-up appointment, the cost of the follow-up appointment was used as patients were estimated as having more than one appointment and also it was not known whether the first appointment was really included in the database. The PSSRU provides a range of costs for any resource use; costs for patient contact were chosen as they related directly to patient care in the clinic.[319]

The cost of a hydrotherapy appointment was based on information and data in a study of the use of hydrotherapy in children with JIA.[320] Two physiotherapists are needed for an appointment lasting 29 minutes. The costs for the physiotherapists were taken from the PSSRU Costs of Health and Social Care 2005, per hour of patient contact. The fixed costs of a hydrotherapy appointment (to cover maintenance of the hydrotherapy pool) were obtained from the same study and were inflated to 2005 costs using Hospital and Community Health Services (HCHS) pay and price inflation.[319] The fixed costs were then added to the staff costs after inflation to give the total costs of the appointment.

TABLE 21 *Costs of appointments with health professionals involved in care of JIA*

Appointment/referral	Cost (£)	Source of cost
Paediatric rheumatologist appointment	133.00	Department of Health Reference Costs 2004, paediatric clinic follow-up appointment
Ophthalmologist appointment	55.00	Department of Health Reference Costs 2004, ophthalmology clinic follow-up appointment
Specialist nurse visit	16.50	PSSRU Costs of Health and Social Care 2005, per hour of patient contact
Physiotherapist visit	21.00	PSSRU Costs of Health and Social Care 2005, per hour of patient contact
Occupational therapy	22.50	PSSRU Costs of Health and Social Care 2005, per hour of patient contact
Splinting	22.50	No specific costs so used occupational health costs. PSSRU Costs of Health and Social Care 2005, per hour of patient contact
Podiatry	45.00	Department of Health Reference Costs 2004, podiatry follow-up appointment
Orthotics	45.00	No specific costs so used podiatry costs. Department of Health Reference Costs 2004, follow-up appointment
Dietician visit	17.50	PSSRU Costs of Health and Social Care 2005, per hour of patient contact
Endocrinologist appointment	121.00	Department of Health Reference Costs 2004, endocrinology clinic follow-up appointment
Dermatologist appointment	62.00	Department of Health Reference Costs 2004, dermatology clinic follow-up appointment
Cardiologist appointment appointment	95.00	Department of Health Reference Costs 2004, cardiology clinic follow-up
Psychologist appointment	38.50	PSSRU Costs of Health and Social Care 2005, per hour of patient contact
Hydrotherapy	61.10	See text for method of calculation

Medication used for JIA

The costs of drugs were obtained from the BNF for Children and the BNF for December 2005 (*Table 18*). As rofecoxib (Vioxx) has now been withdrawn from the UK, costs were obtained from an older edition of the BNF (September 2000). Based on year 2000 prices, costs were inflated to 2005 costs using HCHS pay and price inflation.[319] Costs of generic drugs were used throughout as it was not clear whether generic or branded drugs had been used. As indicated in the section describing calculation of dosage, stop dates were still missing or inaccurate for 20% of drug courses; the duration of treatment could not be calculated and the costs of drug treatment could not be applied. For these drugs, the missing cost was replaced with the mean cost of treatment with this drug.

Where drugs of different strength tablets were available, the cost of the lowest strength tablet was used to calculate the total cost as children would be receiving the lower dose. Where drugs were available as liquid formulation or tablets, it was assumed that children aged less than 12 years would receive syrup or suspension of soluble tablets whereas older children would be able to take tablets. For calculating the cost of eye drops, it was assumed that there were 200 drops in one 10-ml bottle and that patients would need two drops twice per day in both eyes and the bottle would have a 28-day expiry.

Intra-articular corticosteroid injections

The costs of drugs were obtained from the BNF for Children and the BNF for December 2005 (*Table 18*). Data from a previous RCT study were used for the cost of day-case surgery for children having corticosteroid injections.[321] The mean total cost per child per surgical incident was £89.30; this cost was for 2000 and was inflated to 2005 costs using HCHS pay and price inflation.[319] Although the difference in anaesthetics at different ages had been discussed (see the section 'Resource use', p. 51), only this single cost was available for day-case surgery in children and so it was assumed that there was no difference in cost used for children having general anaesthetic or nitrous oxide. The cost of day-case surgery was added to the cost of the corticosteroid injection in the analysis.

Investigations and clinical imaging

The costs of tests, investigations and clinical imaging were taken from the NHS Reference Costs 2004 (*Table 22*). None of the reference costs were

TABLE 22 *Costs of tests, investigations and clinical imaging used in care of JIA*

Investigation	Cost (£)	Source of cost
Blood and biochemistry	Haematology 32.28 Immunology 8.16 Biochemistry 1.88 Other 8.44	Department of Health Reference Costs 2004
X-rays	195.92	Manchester Children's University Hospital
MRI	224	Department of Health Reference Costs 2004 (band F1: MRI of body parts)
Ultrasound	32	Department of Health Reference Costs 2004 (band B3: body sections not maternity)
Bone scan	142	Department of Health Reference Costs 2004 (band H: whole body bone scan as well as parts of body)

specific to children. However, costs for X-rays were not available from here or any other database and the cost provided by the Manchester Children's University Hospital was used; the same cost applied to all body sites.

Analysis

Resource use and costs were analysed using STATA version 8. CAPS is an ongoing study and children are being followed for 5 years in total but are still being recruited, so this analysis will evaluate the costs of treating patients up to12 months since diagnosis.

Results

Patients

A total of 457 children with JIA have been recruited to CAPS and 297 of these have attended a 12-month follow-up visit. It was not yet possible to calculate attrition of patients at this stage, for a number of reasons. Some patients who are still ill may have delayed or missed follow-up visits and may return to the clinic at a later date. Other children may have remission of JIA; some of these children may later present again with a relapse.

The mean age at entry (289 children) was 8.2 years (SD 4.3 years), range 1.3–16.9 years. Age could not be calculated for eight children because the date of first attendance was not recorded. Of these 297 patients, 191 were female (64%) with a mean age at study entry of 7.8 years (SD 4.4 years, range 1.3–16.6 years) and 106 were male (36%), with mean age 8.8 years (SD 4.1 years, range 1.4–16.9 years). When considered by disease subtype, 17 children (5.8%) had systemic disease, 139 had oligoarthritis (47.4%), 17 had extended oligoarthritis (5.8%), 41 had polyarthritis RF negative (14.0%), nine had polyarthritis RF positive (3.1%), 24 had enthesitis-related arthritis (8.2%), 17 had psoriatic arthritis (5.8%), 12 had unclassifiable disease (4.1%) and 17 had other inflammatory arthritis (5.8%). JIA subtype was not classified in four children.

A total of 124 children were treated in the Liverpool study centre, 36 in Glasgow, 111 in Manchester and 23 in Newcastle. The study centre classification was incorrect in three patients.

Costs of treatment

Table 23 summarises the cost of treating the 297 children with JIA for 1 year; the mean total cost per child was £1649. The highest cost component was appointments with paediatric rheumatologists

TABLE 23 *Cost of treatment per child for 12 months* (n = *297)*

	Paediatric rheumatologist appointments	Referrals to other specialists/care	Clinical imaging	Laboratory tests	Drugs	Total
Mean (SD) (£)	742 (479)	385 (332)	309 (861)	37 (32)	175 (272)	1649 (1093)
Range (£)	266–3990	0–1954	0–5345	0–277	0–2705	401–6967
	45%	23%	19%	2%	11%	100%

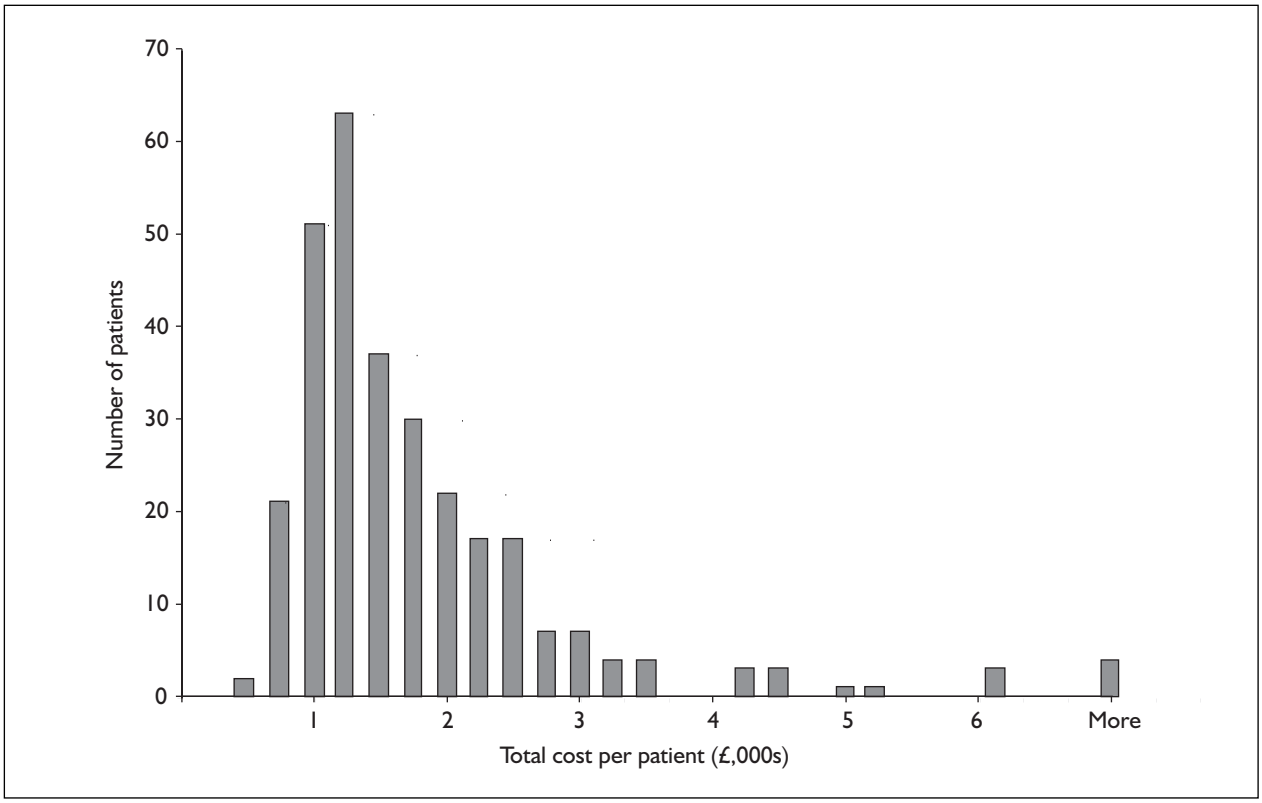


FIGURE 4 *Distribution of individual total costs of management of children with JIA for the first year after diagnosis*

TABLE 24 *Costs of treatment (£) by study centre: mean cost per child (SD) range* (n = *294)*

Centre	*N*	Paediatric rheumatologist appointments	Referrals to other specialists/care	Clinical imaging	Laboratory tests	Drugs	Total cost
Liverpool	124	858 (627) 266–3990 54%	265 (326) 0–1954 17%	268 (530) 0–4198 17%	37 (42) 0–277 2%	159 (292) 0–2704 10%	1587 (1014) 490–6032 100%
Glasgow	36	595 (255) 399–1729 38%	423 (238) 0–1000 28%	217 (884) 0–5345 14%	48 (14) 20–68 3%	255 (354) 15–2073 17%	1538 (1039) 579–6519 100%
Manchester	111	610 (259) 399–1862 37%	404 (278) 0–1938 24%	432 (1173) 0–5345 26%	36 (24) 0–123 2%	180 (239) 0–1288 11%	1662 (1255) 401–6967 100%
Newcastle	23	1000 (405) 266 ± 1995 47%	922 (117) 661–992 42%	105 (374) 0–1763 5%	32 (21) 0–66 1%	117 (112) 0–363 5%	2177 (559) 1002–3406 100%

then referrals to other specialists and care. Some children did not receive any care associated with JIA other than appointments with the paediatric rheumatologist.

Figure 4 summarises the distribution of total costs of management for the children with JIA including the 2.5th centile (£599) 50th centile (£1285) and 97.5th centile (£5569).

Table 24 and *Figure 5* summarise the costs of treating children at each of the four study centres. The mean total cost per child varied between £1538 and £2177. Again, the highest cost component at each centre was appointments with paediatric rheumatologists.

Table 25 and *Figure 6* summarise the costs of treating children in each of the nine different JIA

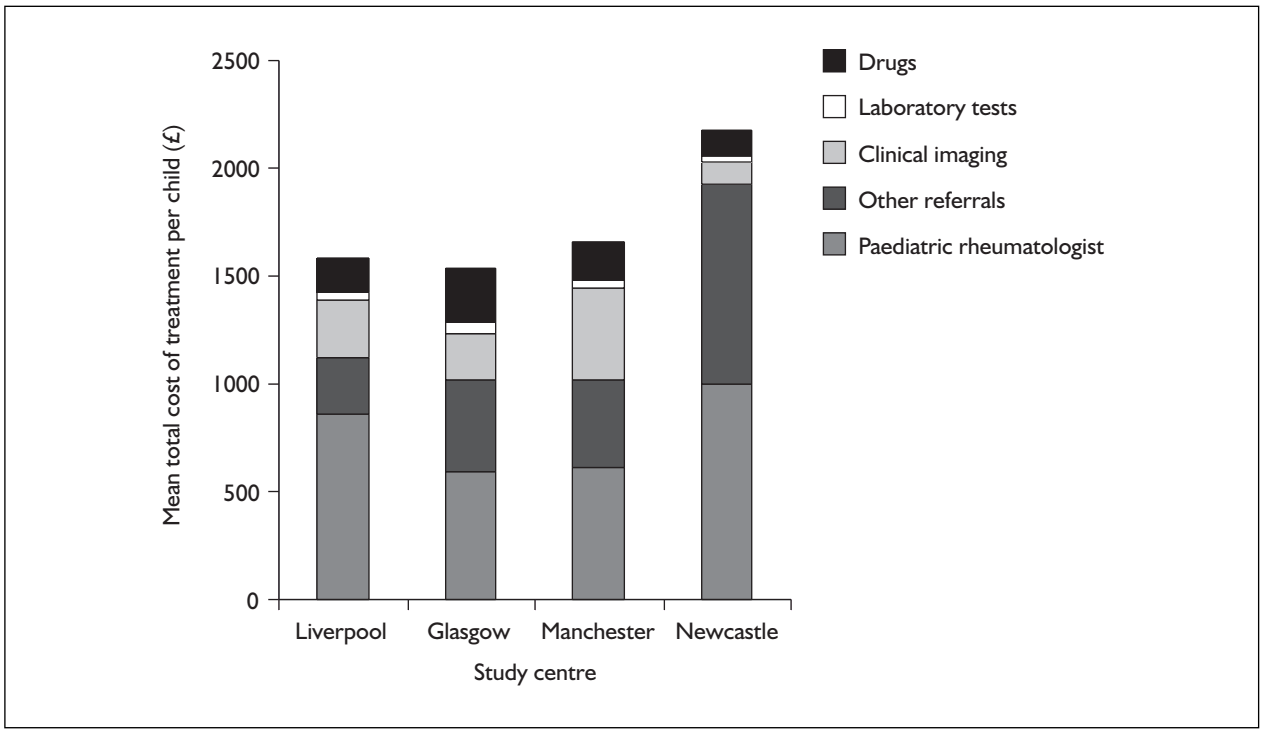


FIGURE 5 *Mean total cost of treatment per child according to study centre, including cost components*

subtypes; the numbers in some groups are fairly low. The highest component cost was the cost of appointments with paediatric rheumatologists.

Discussion

There are no published studies evaluating the costs of treating children with JIA and low BMD and/or fragility fractures. There are few data evaluating the costs of treating JIA in general and the studies identified were not relevant to this project. It was not possible to undertake economic modelling in this study because of limited effectiveness data and the lack of published cost data.

Key findings

This prospective cohort study demonstrated that, in the first 12 months after diagnosis, children with all JIA disease subtypes consume large but highly variable quantities of health service resources. It is not known whether this consumption pattern persists after this time. The largest component of health provider costs was consultant rheumatology appointments, followed in order of magnitude by: referrals to other specialists, clinical imaging, drugs and laboratory tests. The right-skewed distribution of costs suggests that a few high cost outliers increased the mean costs for the group overall, and within individual disease subgroups. It is not clear from these data whether different disease subgroups are associated with different levels of resource consumption. Data from a larger cohort, over a longer period, are required to substantiate these results further.

Limitations of study

There were limitations of this analysis. The CAPS study was not primarily designed to assess resource use and cost data, so we had to make many informed assumptions about treatment from the data that were available. For example, the length and number of appointments was estimated, dose of drugs estimated, one session of anaesthetic was assumed to be sufficient for any number of joint injections and only one clinical image per follow-up was assumed. Hence it is possible that some costs are conservative estimates of the true costs. These data can be collected as the study continues and accuracy of subsequent analyses should be increased. More patients are being recruited to the study, so numbers will increase and there will be higher numbers in the different subgroups, hence it may be possible to compare the costs of treatment in these different groups. Analyses will be undertaken at later stages of follow-up, up to 5 years, and so it will be possible to estimate the cost of longer durations of treatment. The children in the study are not undergoing routine assessment of bone density but

TABLE 25 *Costs of treatment (£) by JIA subtype: mean cost per child (SD) and range* (n = *293)*

JIA subtype	*N*	Consultant paediatric rheumatologist appointments	Referrals to other specialists/ care	Clinical imaging	Laboratory tests: blood and biochemistry	Drugs	Total cost
Systemic	17	1072 (780) 399–3591	262 (399) 0–1592	227 (249) 0–1035	49 (58) 0–223	319 (383) 16–1288	1929 (925) 560–4053
Oligoarthritis	139	689 (398) 266–3325	365 (271) 0–1122	350 (1019) 0–5345	30 (21) 0–98	144 (168) 0–1122	1579 (1163) 490–6967
Extended oligoarthritis	17	782 (420) 399–1862	594 (385) 126–1702	142 (192) 0–708	58 (39) 12–154	36 (498) 0–2073	1912 (730) 686–3368
Polyarthritis RF negative	41	834 (379) 399–1862	511 (416) 0–1938	291 (828) 0–5345	44 (25) 7–121	163 (142) 0–622	1843 (982) 867–6519
Polyarthritis RF positive	9	680 (458) 399–1862	494 (301) 126–978	125 (160) 0–392	62 (20) 30–92	248 (410) 0–1288	1608 (740) 875–2745
Enthesitis-related arthritis	24	848 (611) 399–3192	357 (435) 0–1954	483 (1097) 0–4198	44 (53) 0–277	253 (569) 0–2704	1981 (1395) 730–5003
Psoriatic arthritis	17	563 (197) 266–1064	352 (215) 0–700	118 (155) 0–452	37 (21) 7–65	147 (132) 0–2704	1217 (369) 791–2260
Unclassifiable	12	964 (980) 399–3990	240 (326) 0–1032	421 (493) 0–1278	24 (23) 0–63	128 (217) 0–780	1778 (1478) 702–6032
Other inflammatory arthritis	17	579 (282) 399–1463	321 (291) 0–992	305 (906) 0–3781	27 (24) 0–78	62 (86) 0–262	1290 (958) 401–4324

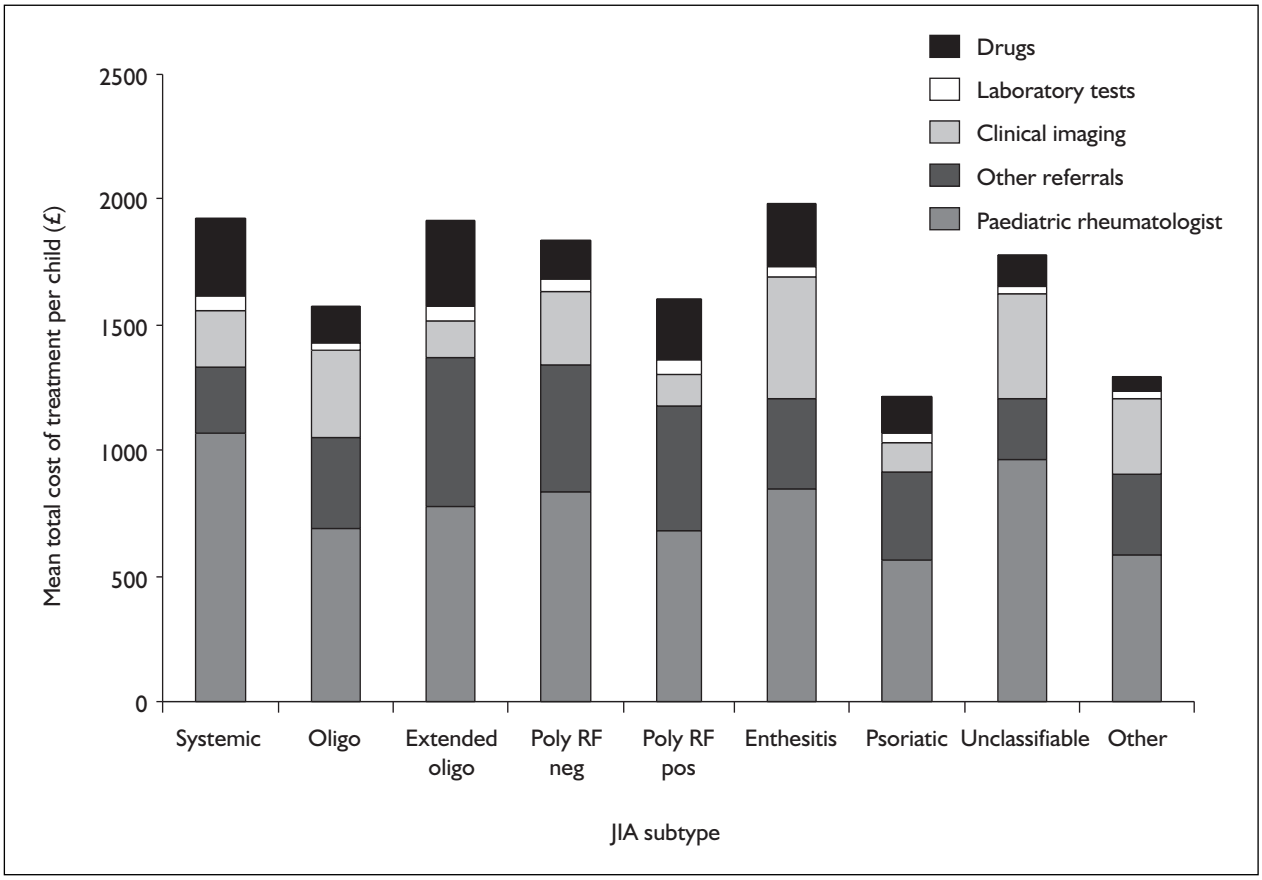


FIGURE 6 *Mean total cost of treatment per child according to JIA subtype, including cost components*

future analyses may be able to incorporate management of bone disease. It was not possible to calculate the loss to follow-up because the reasons for non-attendance are not clear.

CAPS was not designed specifically to evaluate bone health. However, it is a study of routine care and, as the study progresses, it is expected that the costs of managing any children with JIA who have low BMD and fractures will be incorporated into future analyses.

Implications for future costing studies and economic evaluation

Prospective studies of costing of treatment should consider all aspects of JIA management, which requires input from many different parts of the health service. The National Institute for Health and Clinical Excellence (NICE) has issued clear guidelines on the minimum requirements for health technology assessments that are to be used to inform NHS decision-making.[322] These guidelines are often referred to as the 'NICE reference case'. The reference case requires cost data in health technology assessments to have a perspective that includes both the NHS and personal social services (PSS).The cost data presented here are retrospective and we were not able to include PSS costs. Other work in JIA has included both NHS and PSS costs. A health technology assessment report published in 2005 evaluated the detailed cost of a hydrotherapy programme in JIA and included the costs of physiotherapy, inpatient admissions, GP appointments, district nurses, hospital consultant appointments (rheumatology, ophthalmology, haematology, nephrology, orthopaedics, orthodontist and ear nose and throat), referrals to podiatrists, psychologists, occupational therapists and social workers and also diagnostic testing (blood counts, liver function, X-ray, MRI, ultrasound, ECG, gastroscopy and barium meal) and time away from work for parents.[320] All these elements need to be included.

Studies in JIA so far have only looked at 1 year of management, but future studies should examine costs of longer-term management after 2 or 3 years of treatment. Studies should also examine ongoing developments in treatment. More children are now being treated with biological agents such as etanercept. These are more expensive drugs but may reduce the incidence of poor bone health, thus reducing the overall cost of management – this should be considered in future studies.

This costing study demonstrates the importance of patient-based cost data to allow the characterisation of inter-patient variation. These types of data are essential for economic evaluation, to allow differences in treatment intensity between interventions to be identified. As with other chronic disease costs, studies should also consider costs falling outside the health service, such as costs to PSS. Costs to parents and patients need to be identified, as do indirect costs, for example, time off school. Improvements in management may also be of benefit to families as they may reduce the considerable financial burdens that can be faced by them.

Conclusions

- In the first 12 months after diagnosis, children with all JIA disease subtypes consume large but highly variable quantities of health service resources.
- The largest component of health provider costs was consultant rheumatology appointments.
- The right-skewed distribution of costs suggests that a few high-cost outliers increased the mean costs for the group overall, and within individual disease subgroups.
- Data from a larger cohort, over a longer period, are required to substantiate these results further.

Chapter 7
Discussion

Key findings

This project has contributed new findings in four key aspects of JIA research:

1. The critical appraisal of outcomes suggests that DXA appears to be the current most reliable estimate of bone health for clinical trials in these children. However, it has some limitations (size dependency, no separate measure of cortical and trabecular bone provided) and QCT (axial and peripheral) should be considered for inclusion in future studies if feasible.
2. A systematic review of trials of bisphosphonates, calcium and vitamin D in children with JIA yielded very few comparative data. The lack of effectiveness data precluded an economic evaluation. There is some evidence for the effectiveness of bisphosphonates in children with JIA at risk of low BMD and fragility fractures; little evidence is available for calcium and/or vitamin D.
3. Assessment of long-term outcome data suggests that the problems of low bone mass persist into adulthood with adults with JIA at greater risk of fracture than otherwise healthy adults.
4. The cost of treating children with bisphosphonates and calcium and/or vitamin D has not yet been evaluated. A retrospective cohort study has generated observational patient-based cost data and demonstrated that, in the first 12 months after diagnosis, children with all JIA disease subtypes utilise large but highly variable quantities of health service resources. It is not known whether this consumption pattern persists after this time.

Review of outcome measures for assessing bone health in children with JIA

Poor assessment of outcome was a key criticism of the studies identified in the systematic review of effectiveness. Although it is true that different types of trial may need different outcome measures, the use of outcomes in trials appeared to be highly variable, precluding direct comparison of studies.

From the systematic review of outcome measures, BMD measured using DXA appears to be the best and most practical measure of outcome of bone health in clinical trials. However, standard methods of measurement and interpretation of results should be used so that the technique is reproducible between different study centres and groups. Further investigation could ascertain whether QCT is suitable for future more widespread use. However, there are no clear definitions for osteopenia and osteoporosis in children and various criteria have been used.[77] Unlike adults, no prospective studies have identified a fracture threshold in children for any given *Z*-score.

It is hard to determine from the studies reviewed whether biochemical markers of bone turnover are useful as an outcome measure. In adults, biochemical bone markers are sensitive to changes early on in the treatment with bisphosphonates of osteoporosis.[211] Changes in bone markers during treatment have been associated with reductions in fractures.[211] Similar information would be useful for treatment of children. More studies of markers are needed and in the longer term it may be possible to use markers as outcome measure when they are better understood.

A few studies in the systematic review assessed more subjective outcome measurements, noting improvements in pain and disability of children with JIA after bisphosphonate treatment. However, HRQoL was not assessed using validated instruments in any studies of bone disease in JIA and there were very few data in JIA generally. Ideally, an HRQoL measure should be validated specifically for use in children with low BMD; current instruments for osteoporosis are specific for adults. However, it is unlikely that any instruments would be able to assess health status associated with fractures as the effects of fractures are generally limited to a certain period of time and the instrument would have to be applied during this time. However, there may be problems with the assessment of health status in children receiving treatments such as bisphosphonates, which are likely to provide more benefits in the long term by increasing peak bone mass and reducing fractures than in the short term. The

child is unlikely to experience any immediate improvements in health status and could even feel less well because of any side-effects associated with the drugs; hence the child may not be prepared to suffer adverse effects now in spite of potential benefits some time in the perceived distant future. Therefore, HRQoL could probably not be used as a primary measure of health status but could be used as a secondary measure alongside other outcome measurements and would enable health effects in different studies to be compared.

Of the instruments available, the disease-specific CHAQ and the generic CHQ instruments seem to be most widely used in JIA and are associated with the most evidence. New instruments are being developed and may be applicable to JIA; the adult EQ-5D is being adapted for children and will include a question on pain.[65]

An ideal outcome measure would be the occurrence of new fragility fractures. However, it would be difficult, if not impossible, to recruit sufficient children to use fractures as a primary outcome in a clinical trial. However, fracture data should be reported alongside other measures and may be appropriate as the primary measure in the longer term studies; a study like CAPS would be able to assess fractures as an outcome.

Effectiveness of bisphosphonate and calcium and/or vitamin D in children with JIA

The systematic review of studies administering bisphosphonates to children with JIA indicated that bisphosphonates may be effective for both prevention and management of low BMD and fragility fractures in these children. However, the available evidence is not conclusive and it is unlikely that existing data would support licensing of bisphosphonates for these children. As discussed in Chapter 3, the quality of the evidence is poor. Overall, existing studies are heterogeneous and of variable quality. For example, definitions of JIA are unclear, there are differences in dose and routes of administration of bisphosphonates and assessment of outcome is unclear. There were no comparisons with control groups even in RCTs and controlled studies. Better studies are needed to assess more clearly the role of bisphosphonates. Bisphosphonates were generally well tolerated in the short term and this finding was supported by studies in children with OI. However, the longer-term effects, for example on bone health and growth, are unknown.

A recent general review supports our findings that there are still many unanswered questions about the use of bisphosphonates in children.[323] The optimum dose and frequency of administration and length of treatment have not been defined. For example, 18 months of treatment may be sufficient and then treatment can be stopped. The maximal BMD gain that can be achieved is not known. It is not clear whether the positive effects of treatment continue over time. Follow-up after the end of treatment is needed in order to examine the longer-term effects, for example at 2 years, and this would also allow further evaluation of safety. A further question is whether treatment should be limited to children with pre-existing low BMD and/or fractures or should be offered to children thought to be at risk of these problems.

There is limited evidence on the use of calcium and/or vitamin D to prevent or treat low BMD and fragility fractures; only two therapeutic studies were identified in the systematic review. In addition, from the review of bisphosphonate treatment it is uncertain whether children being treated with bisphosphonates also require supplementation with calcium and vitamin D in order to ensure that they are calcium and vitamin D replete. It is not known whether pharmacological doses of these agents are needed.

Corticosteroid use in children is diminishing because of effectiveness of new biological therapies and these developments could eventually reduce the problems of poor bone health in children with JIA. However, children with JIA can still develop low BMD in JIA even if not treated with corticosteroids: up to 30% of post-pubertal females with mild to moderate JIA who have never been treated with corticosteroids have a low BMD.[21] Therefore, a further question to be answered is whether children treated with corticosteroids and those untreated should be studied and analysed separately.

Bone health in adults with JIA

Although several studies have demonstrated the increased prevalence of low BMD and fractures in children with JIA, there are limited data in adults with JIA. Published studies indicate that adults with JIA have lower BMD than healthy adults. Data from the two cohorts analysed in this study confirm that BMD is low in adults with JIA, with many patients classified as having osteopenia or osteoporosis according to WHO guidelines.

Calculation of standardised fracture ratios for the Taplow cohort demonstrated higher fracture rates in adults with JIA compared with expected values in otherwise healthy adults.

As discussed in Chapter 4, further analyses to investigate potential predictors of low BMD and fragility fractures may be possible for both cohorts of patients. The evidence from the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D only considered short-term follow-up of children. However, the problems of low BMD and fragility fractures associated with JIA can persist into adult life, but the studies reviewed did not address whether treatment with bisphosphonates would have long-term effects on peak BMD attained as an adult. If bisphosphonates increased the peak BMD achieved, they could also reduce the risk of fractures in adults with JIA. As discussed, changes in treatment patterns with less intense use of corticosteroids and the introduction of etanercept may improve accrual of bone mass in children currently diagnosed with JIA compared with those diagnosed and treated several decades ago.

Costs of treating JIA

The literature review found no published studies evaluating the costs of treating children with JIA and low BMD and/or fragility fractures. There are few data evaluating the costs of treating JIA in general and the studies identified were not relevant to this project.

Unit costs were attached to patient-based resource use data collected as part of the CAPS study. Preliminary analysis demonstrated that, in the first 12 months after diagnosis, children with all JIA disease subtypes consume large, but highly variable quantities of health service resources. It is not known whether this consumption pattern persists after this time. The largest component of health provider costs was consultant rheumatology appointments, followed in order of magnitude by referrals to other specialists, clinical imaging, drugs and laboratory tests. Data from a larger cohort, over a longer period, are required to substantiate these results further.

Studies in JIA so far have only examined 1 year of management, but future studies should examine costs of longer-term management after 2 or 3 years of treatment. Costing of treatment should consider all aspects of health and PSS resource consumption. Studies should also consider indirect costs, for example, time off school and time away from work for parents.[320] Studies should also examine ongoing developments in treatment. More children are now being treated with biological agents such as etanercept; these are more expensive drugs but may reduce the incidence of poor bone health, thus reducing the overall cost of management – this should be considered in future studies. It was not possible to undertake economic modelling in this study because of the limited effectiveness data and the lack of cost data. Future studies examining low BMD and fragility fractures in these children may be able to include a cost-effectiveness or cost–utility evaluation if an appropriate outcome measure is available.

Implications for practice and policy

In conclusion, bisphosphonates may have a role in the prevention and treatment of low BMD and fragility fractures in children with JIA; studies suggest they are effective and well tolerated. However, the quality of the evidence is poor and better-designed, longer-term studies are needed to confirm the potential benefits. There are very few data supporting the use of calcium and/or vitamin D and further studies are needed. There are many uncertainties around the management of children with JIA, including the effect of both disease and treatment on long-term bone health and further studies are needed. In particular, the problems of poor bone health persist into adulthood; adults with JIA have increased numbers of fractures compared with expected values in otherwise healthy adults.

The lack of evidence in JIA and bone disease reflects a wider gap in evidence available to support paediatric prescribing. The recent National Service Framework for Children recommends that children who require ongoing health interventions have access to high-quality care.[324] This access is reduced by the lack of evidence to support physicians in providing safe and effective treatments. Recognition of this deficiency has led to the development of the Medicines for Children Research Network, which aims to improve the quality of research in this area (www.liv.ac.uk/mcrn/).

The American Society for Bone and Mineral Research (ASBMR) Pediatric Bone Initiative has recommended that procedures to test the efficacy of drugs in paediatric bone disease should be standardised and should incorporate the unique

needs of paediatric clinical trials.[325] Outcomes should be assessed at different developmental stages as children grow, taking into account age-appropriate normal values. Physical and cognitive growth and development should be monitored. Adverse events should be monitored using laboratory tests and clinical measurements. Longer term surveillance studies are needed after treatment. Placebo-controlled studies are essential to determine if changes are a result of treatment or other differences. Multicentre studies will provide larger numbers of patients and ensure that numbers in different age, pubertal and racial groups are adequate. The ASBMR recommended that bisphosphonates and calcium and vitamin D nutrition should be studied in children. The ASBMR also made suggestions for the outcomes that should be used in studies of paediatric bone health.[325] Longitudinal studies of DXA should be conducted in various age groups to examine if DXA BMD values in childhood can predict adults predisposed to low BMD and fragility fractures. Further study of bone markers is needed. The period over which to assess fracture prevention should be defined and also the fracture threshold that determines success or failure. Fractures would be the ideal outcome measure, but a study with this end-point would require large numbers of patients and long-term follow up. However, fracture data could be routinely collected for local and other registers.

The potential problems of conducting studies of bone health in children were demonstrated in a prospective randomised trial, comparing pamidronate with calcium and calcitriol supplements for the management of corticosteroid-induced osteoporosis in children, which was unsuccessful.[326] Only 12 patients were enrolled into the study over 4 years. Lumbar spine aBMD increased in five children treated with bisphosphonates: mean annual increase $8.76 \pm 5.2\%$ compared with $6.6 \pm 4.0\%$ in seven calcium/vitamin-treated children. An additional 11 patients were treated outside the study, three had radiological evidence of fractures and four received bisphosphonate treatment. In the 11 patients, the mean change in aBMD was $3.72 \pm 2.5\%$. Out of the total 23 patients, three had JIA; the others had other conditions requiring corticosteroid treatment including juvenile dermatomyositis, Crohn's disease, irritable bowel syndrome and autoimmune hepatitis. The authors identified a number of reasons for trial failure in this setting, which is in accord with those discussed during this review. The children in the study had multiple underlying diagnoses, and children of different ages with different rates of bone mass accrual were recruited, so it is difficult to separate and quantify the relative contributions of puberty, hormone replacement therapy, state of health and bisphosphonate treatment on outcome. In addition, a large number of changes in disease management are likely. Some additional suggested problems included the unwillingness of parents to involve children in the trial of a potentially toxic product unlicensed for use in children and a lack of parental belief in the seriousness of childhood osteoporosis and its relationship to fracture risk.

However, an Arthritis Research Campaign-funded multi-centre longitudinal double-blind placebo-controlled RCT in children with JIA, juvenile SLE, vasculitis and juvenile dermatomyositis is ongoing and will be addressing a number of the issues described above. The study consists of two arms running concurrently: prevention of corticosteroid-induced osteopenia and treatment of corticosteroid-induced osteopenia. It is planned to recruit 150 children to each arm of the study. In the prevention arm of the study, children about to start corticosteroid treatment will be randomised to receive either placebo (and an adequate calcium and vitamin D intake) or treatment with 1-α-hydroxycholecalciferol 15 ng/kg/day (and an adequate calcium and vitamin D intake). In the treatment arm of the study, children who have received more than 3 months of corticosteroid therapy will be randomised to 1-α-hydroxycholecalciferol 15 ng/kg/day (and an adequate calcium and vitamin D intake) or risedronate 1 mg/kg orally (and an adequate calcium and vitamin D intake). Children will be treated and followed for 1 year. The primary outcome measures include lumbar spine BMD and BMC (assessed using DXA). The secondary outcome measure is the development of new fragility fractures. The results from this study should help to answer questions about the role of bisphosphonates and calcium and vitamin D supplementation in children with JIA.

NICE has issued clear guidelines on the minimum requirements for health technology assessments that are to be used to inform NHS decision-making.[322] These guidelines are often referred to as the 'NICE reference case'. The reference case requires health technology assessments to have the following characteristics:

- Comparators should be alternative therapies routinely used in the NHS.
- Cost perspective should include the NHS and PSS.

- Outcomes should include all health effects on individuals.
- The type of economic evaluation used should be a cost-effectiveness analysis.
- Any synthesis on evidence on outcomes should be based on a systematic review.
- Health benefits should be measured using QALYs.
- QALYs should be derived from standardised and validated generic instruments.
- The method of preference elicitation should be a choice-based method.
- The preference data should be from a representative sample of the public.
- A discount rate of 3.5% should be applied to both costs and outcomes.

QALYs all have the same weights, regardless of other characteristics of individuals receiving the health benefits.

During this study, it became clear that the data are not available for a health technology assessment of interventions to prevent and manage osteoporosis in JIA that complies with these criteria. Key omissions are:

- The lack of comparative effectiveness data.
- The limitations of outcomes in that they do not assess all health effects on individuals and QALY measurement has not been carried out.
- The lack of prospective resource use and cost data in the appropriate patient group.

Recommendations for research

Specific areas of research required are described in the following list:

1. The ongoing Arthritis Research Campaign-funded RCT has initiated a trial of bisphosphonates and 1-α-hydroxycholecalciferol (hydroxylated derivative of vitamin D) in children with JIA. This is a placebo-controlled double-blind RCT which will incorporate two studies. The first study is examining prevention of glucocorticoid-induced osteopenia in children with juvenile rheumatic disease. Children with JIA or connective tissue disease and starting treatment with corticosteroids are recruited to the study and randomised to either placebo (and an adequate calcium intake) or 1-α-hydroxycholecalciferol (and an adequate calcium intake) for 12 months. The second study is examining treatment of established glucocorticoid-induced osteopenia in children with juvenile rheumatic disease. Children with JIA or connective tissue disease who are established on corticosteroid therapy for at least 3 months and have a low BMD compared with expected values will be recruited and will be randomised to either 1-α-hydroxycholecalciferol (and an adequate calcium intake) or risedronate 1 mg/kg once weekly (and an adequate calcium intake) for 1 year. For both studies, the primary outcome measures are lumbar spine bone area, BMC and BMD and the secondary outcome measure is occurrence of fragility fractures. Levels of biochemical markers of bone turnover are also being recorded. It is planned to recruit 150 patients to each study. Thus, this study should address some of the research issues raised in this chapter. First, it should be possible to determine the effectiveness of risedronate in terms of both BMD and fractures when used as prevention and treatment of low BMD children with JIA; these will be corticosteroid-treated children who are calcium and vitamin D replete; more safety data will be made available in this study. Information on the effects of JIA and risedronate on bone markers will also be available. However, this study will only answer some questions about treatment with bisphosphonates and those remaining include whether risedronate is the best bisphosphonate to use in this situation and whether the route of administration, dose and duration of treatment are optimal. It may not be possible to answer questions about the long-term effectiveness and safety of bisphosphonates. This study will only consider corticosteroid-treated children, and problems of low BMD in non-corticosteroid-treated children with JIA will still need to be examined. The effectiveness of 1-α-hydroxycholecalciferol for prevention of low BMD in children with JIA should also be determined in this study. Again, further data on long-term effectiveness and safety of this agent will be needed.
2. Longer-term follow-up of studies with bisphosphonates and calcium and/or vitamin D are needed to determine the longer-term effect of treatment on both bone mass, fracture risk and also safety. It is unlikely that a long-term RCT specifically to address this issue would be feasible, but it might be possible to continue to follow children long term at the end of the Arthritis Research Campaign-funded RCT (described in recommendation 1) through a cohort study. Children in CAPS could also be followed into adulthood. Further cohort studies

could be initiated to follow other groups of children receiving bisphosphonates and calcium and/or vitamin D. Clinicians should select treatment in these observational studies and bone health (including BMD and fractures) of the children would be followed systematically. Studies should recruit adults with a history of JIA and follow their long-term outcome. In addition, HRQoL costs should be explored within these studies.

3. Increased treatment with biologicals and reduced use of corticosteroids could possibly change the clinical pattern of JIA in that the occurrence of low BMD is reduced and treatment with bisphosphonates may not be so crucial. The effects of ongoing developments in treatment should be incorporated into future research. In particular, the effects of corticosteroid treatment or non-treatment on long-term bone health should be clarified. A cohort study of children with newly diagnosed JIA should examine the effects of disease and current management approaches on bone health in these children.
4. Future analyses of the Taplow and Newcastle cohorts of patients described in the report may provide further information concerning the association between BMD and fractures and data concerning the risk factors for low BMD and fractures in adults including disease type, disease severity and duration, treatment with corticosteroids, other treatments including DMARDs, calcium and vitamin D supplementation and the effects of treatment with bisphosphonates. Data concerning JIA and fractures in these studies were obtained, however, using retrospective case note review. Large prospective studies are needed in order to determine the predictors of bone mass and fractures in adults with JIA.
5. Most evidence to date relates to the use of DXA for assessing bone health in children. Longitudinal studies of DXA should be conducted to determine whether bone mass measured by DXA predicts bone mass and fracture risk in adults.
6. Most current evidence relates to the use of DXA for assessing bone health in children. Further evaluation of other quantitative imaging techniques is needed. In particular, QCT (central or peripheral) has advantages over DXA in providing a true volumetric BMD and may provide uniquely useful information on the differential effects of disease and treatment on cortical and trabecular bone. Comparative studies are needed to ascertain whether QCT is suitable for more widespread use in children. Given the lower radiation exposure, pQCT may be preferable. Some of this information might be available from long-term cohort studies suggested in recommendation 2.
7. Biochemical markers of bone turnover may be more sensitive than densitometry to changes in bone turnover. Reference ranges for markers of bone formation and bone resorption in healthy children need to be established, including how these change with age. More studies are needed looking at their performance in children with JIA. The effect of treatment on markers in children with JIA should be assessed.
8. An HRQoL measure should be validated specifically for use in children with low trauma fractures. However, as discussed in Chapter 2, it may be difficult to detect changes in HRQoL caused by fractures using such an instrument.
9. Future studies should examine costs of management of bone health in JIA in both the short and medium term. A cost-effectiveness or cost–utility evaluation could be incorporated. Future studies examining bone health in children should have an economic component.

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Contribution of authors

Judith Thornton (Research Associate) was responsible for designing and running the electronic search strategies, screening search results, checking bibliographies for further studies, retrieval of papers, screening retrieved papers against inclusion criteria, appraising quality of papers, abstracting data from papers, data management for the reviews, writing a protocol amendment, obtaining the data on the two cohorts of patients, restructuring the databases and checking them for errors and duplicated information, analysis of the cohort data, checking the resource use database for the CAPS study for errors and duplicated information, collection of referral information and unit costs for the CAPS study, analysis of the CAPS resource use and cost data, interpreting data, writing and editing the report, organising project team meetings and telephone meetings with external advisors, keeping minutes of meetings and writing abstracts and papers for submission to a conference and a journal. Darren Ashcroft (Clinical Senior Lecturer) was involved in the conception of the review, designing the review and economic analysis, securing funding for the review and economic analysis, interpreting data, providing support and advice on the systematic reviews, assisting with writing the protocol amendment, assisting with analysis of the cohort data and analysis of the CAPS cost data, providing general advice on the systematic reviews and cost analysis and reviewing the report. Terence O'Neill (Senior Lecturer) was involved in the conception of the review, designing the review and economic analysis, securing funding for the review and economic analysis, interpreting data, providing a clinical perspective, assisting with writing the protocol amendment, analysis of the cohort data, providing general advice on the systematic reviews and reviewing the report. Rachel Elliott (Clinical Senior Lecturer) was involved in the conception of the review, designing, coordinating and securing funding for the review and economic analysis, interpreting data, assisting with writing the protocol amendment, assisting with the cost analysis of CAPS, providing general advice on the systematic reviews and cost analysis and reviewing the report. Judith Adams (Professor of Radiology) was involved in the conception of the review, designing the review and economic analysis, securing funding for the review and economic analysis, interpreting data, providing a clinical perspective, analysis of the cohort data, providing general advice on the systematic reviews and reviewing the report. Chris Roberts (Senior Lecturer in Medical Statistics) was involved in the conception of the review, designing the review and economic analysis, securing funding for the review and economic analysis and provided help with statistics and analysis. Madeleine Rooney (Senior Lecturer and Consultant Rheumatologist) was involved in performing previous work that was the foundation of the current study, securing funding for the review and economic analysis and providing a clinical perspective. Deborah Symmons (Professor of Rheumatology and Musculoskeletal Epidemiology) was involved in the conception of the review, designing the review and economic

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Paper published in another peer-reviewed journal relating to this research

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Appendix 1

Search strategies: review of patient-based outcome measures

MEDLINE

1 Health Status/ [27958]
2 health status.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [45929]
3 "Quality of Life"/ [49768]
4 ("quality of life" or "health-related quality of life").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [71810]
5 Health Status Indicators/ [9689]
6 "Outcome and Process Assessment (Health Care)"/ or Patient Satisfaction/ or "Outcome Assessment (Health Care)"/ or Treatment Outcome/ [286787]
7 patient-based outcome measure$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [24]
8 QUESTIONNAIRES/ [130378]
9 questionnaire$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [196308]
10 ("childhood health assessment questionnaire" or "CHAQ").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [116]
11 ("childhood arthritis impact measurement scale$" or "CHAIMS").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [4]
12 ("juvenile arthritis self-report index" or "JASI").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [6]
13 ("juvenile arthritis functional assessment scale" or "JAFAS" or "juvenile arthritis functional assessment report" or "JAFAR").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [16]
14 ("juvenile arthritis quality of life questionnaire" or "JAQQ").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [5]
15 ("childhood arthritis health profile" or "CAHP").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [9]
16 ("child health questionnaire" or "CHQ").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [238]
17 ("pediatric quality of life inventory scale$" or "PedsQL" or "Peds QL").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [43]
18 ("quality of my life questionnaire" or "QoMLQ").mp. [mp=title, original title, abstract, name of substance word, subject heading word] [0]
19 (utility or utilities).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [48282]
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [582423]
21 exp CHILD/ [1068545]
22 exp INFANT/ [654417]
23 exp ADOLESCENT/ [1088311]
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Appendix 2

Summaries of studies assessing bone health in healthy children using DXA

Study	Design	Subjects	Site of measurement	Results
Glastre *et al*., 1990[91]	Cross-sectional	135 children, 1–15 years, Caucasian	Lumbar spine	BMD increased with age in boys and girls; the increase was steepest at puberty. There were no significant differences between BMD in girls and boys except at age 12 years when BMD was higher in girls probably because of the earlier onset of puberty in females. BMD also highly correlated with height, weight, body surface area and bone age
Ponder *et al*., 1990[92]	Cross-sectional	184 children, 5–12 years, 99 white, 45 black, 40 Hispanic	Lumbar spine	Weight, height and age were highly correlated with BMD
Southard *et al*., 1991[93]	Cross-sectional	218 children, 1–19 years, 134 F, 84 M, 162 white, 56 black	Lumbar spine	BMD greatest in children who were heaviest, oldest and most advanced in sexual maturity. No significant difference between boys and girls or blacks and whites in any age group. The greatest increase in BMD correlated with growth spurt of early childhood (1–4 years) and puberty (12–17 years)
Faulkner *et al*., 1993[94]	Cross-sectional	234 children, 8–16 years, 110 M, 124 F	Total body, head, upper limbs, lower limbs, trunk, pelvis	At all sites BMD and BMC increased significantly with age. There was a significant effect on BMC at the head (boys having greater BMC), upper limbs (boys having greater BMD) and pelvis (girls having greater BMD)
Zanchetta *et al*., 1995[95]	Cross-sectional	778 children, 2–20 years, 433 F, 345 M, Caucasian	Total body, lumbar spine, femoral neck, trochanter, radius, Ward's triangle	Total body BMC reached maximum in 16-year-old group with difference between boys and girls becoming significant in 17-year-old group. Femoral neck, trochanter and Ward's triangle BMD in girls increased until 14 years of age with no significant difference between age groups older than 13 years. In boys there were no differences between age groups after 16 years. Radius BMD increased in girls and boys. Differences between boys and girls were only significant after 16 years for lumbar spine; boys had greater BMD. BMC and BMD at all sites (except radius in girls) increased with increased Tanner stage
Ogle *et al*., 1995[96]	Cross-sectional	265 children and adults, 4–26 years, 137 M, 128 F	Total body	BMC increased with age until 15.7 years in females and in males until 17.4 years. There was almost no overlap in BMC values between the sexes after puberty
Faulkner *et al*., 1996[97]	Cross-sectional	977 children, 8–17 years, 506 F, 471 M, >98% Caucasian	Total body, proximal femur, lumbar spine	At all sites BMC and BMD increased with age. Significant age by sex interaction at total body BMC and BMD. No sex differences until age 14 years for BMC and 16 years for BMD when male values became significantly greater. Sex by age interaction for BMC at lumbar spine; young women had significantly greater BMC at 12–13 years but by 17 years, male values were greater. No age by sex interaction for lumbar spine BMD. Significant age by sex interaction at femoral neck: males had significantly greater BMC beginning at 14 years; no interaction effect for BMD and males had higher values at all ages. BMC and BMD values levelled off in women between 16 and 21 years and there was no significant difference in BMC or BMD at any of the sites between 17 and 21 years

continued

Study	Design	Subjects	Site of measurement	Results
Boot *et al.*, 1997[98]	Cross-sectional	500 children, 4–20 years, 205 M, 95 F, 444 Caucasian, 21 black, 35 Asian	Lumbar spine, total body	Total body and spine BMD and spine BMAD increased with age. The increase was higher during puberty than before puberty. Girls had higher spine BMD and BMAD at all ages. There was no difference in total body BMD. Weight correlated with all three BMD variables after adjustment for age. After adjustment for age the Tanner stage was significantly associated with all three BMD variables in girls and with spine BMD in boys. Ethnicity was not associated with BMD or BMAD in boys. Asian girls had a lower total body BMD than Caucasian girls. BMD and BMAD of black children did not differ from other children
Maynard *et al.*, 1998[99]	Cross-sectional	148 children, 8–18 years, Caucasian, 75 M, 73 F	Total body, head, arms, spine, pelvis, legs	Significant sex differences in BMC at ages 15–18 years for the total body and legs, at ages 12 and 15–18 years for arms and pelvis, at 11–13 years and 16–18 years for the spine, and 10–11 years for the head. Significant sex differences in BMD at ages 16–18 years for total body, arms and legs; at 12–13 and 16–18 years for the pelvis; at 12–14 and 18 years for the spine; and at 13–18 years for the head
Molgaard *et al.*, 1998[100]	Cross-sectional	343 children, 5–19 years, 201 F, 142 M, Caucasian	Total body	BMC depended on bone area, height, age and pubertal stage. BMD depended on age and pubertal stage
Lotborn *et al.*, 1999[101]	Cross-sectional	396 children, 15 years old, 184 M, 212 F, Caucasian	Total body	Boys had significantly higher BMC and bone mineral area than girls but no difference for BMD. BMC and BMD higher with later stages of puberty. BMD was higher for girls from one regional area of Sweden than the other but no difference for boys
Horlick *et al.*, 2000[102]	Cross-sectional	336 children, age range 6–11 years, 172 F, 164 M, 135 Asian, 79 black, 122 white	Total body	BMC significantly greater in boys than girls with sex effect independent of ethnicity. BMC was significantly greater in black compared with non-black children. The ethnic difference was a function of BA and weight
Ellis *et al.*, 2001[103]	Cross-sectional	982 children, 5–18 years, 537 F, 445 M, 407 European-American, 285 black, 290 Mexican-American	Total body	In boys, there were no statistically significant differences between ethnic groups for BMC, BA and BMD except for BMD of the African-American group, which was significantly higher than for European-Americans. In girls, African-Americans had significantly higher BMC and BMD than the European-American and Mexican-American girls
Henderson *et al.*, 2002[104]	Cross-sectional	256 children, 3–18.5 years, 117 M, 139 F, 212 Caucasians, 25 African-Americans, 19 other	Proximal femur, distal femur, lumbar spine	BMD increased with age. No statistically significant difference in BMD distal femur between boys and girls at any age. BMD distal femur was greater in African–Americans than in Caucasians and other race groups at all ages
Van der Sluis *et al.*, 2002[105]	Cross-sectional	444 children and adults, 4–20 years, 188 M, 256 F, Caucasian	Lumbar spine, total body. Corrected for size using Kroger *et al.*, 1995	BMD and BMAD increased with age and pubertal stage. The maximal increase was around the age of 13 years in girls and 15 years in boys

continued

Study	Design	Subjects	Site of measurement	Results
Binkley *et al*., 2002[106]	Cross-sectional	231 children and adults, 5–22 years, 107 M, 124 F	Total body	Total body BMC and total body bone area reached a plateau in girls at approximately 15 years but continued increasing in boys
Arabi *et al*., 2004[107]	Cross-sectional	363 children, 10–17 years, 184 M, 179 F, Lebanese	Lumbar spine, femoral neck, subtotal body, forearm, total hip, trochanter. Corrected for size using Katzman *et al*., 1991[82]	In both sexes BMD, BMC and BMAD increased with age and pubertal stages at all skeletal sites except for femoral neck BMAD in boys. Mean BMD in these Lebanese children were significantly lower than Western normative values. Children of lower socio-economic status tended to have lower BMD
Henry *et al*., 2004[108]	Cross-sectional	132 children, 11–19 years, 63 M, 69 F, Caucasian	Lumbar spine, femoral neck, radius. Corrected for size using Kroger *et al*., 1992[84]	BMC and bone volume increased with age in both males and females. Approximately 80–90% of peak values were attained by late adolescence. vBMD at the spine and distal radius (in women) increased gradually but vBMD at the femoral neck and ultradistal radius in men remained almost constant. During consolidation bone size continued to increase with little change in vBMD
Cromer *et al*., 2004[109]	Cross-sectional	422 girls, 12–18 years, 264 black, 158 non-black	Lumbar spine, femoral neck. Corrected for size using Katzman *et al*., 1991[82]	Lumbar spine and femoral neck BMD increased with age and weight. BMD was higher in black than non-black subjects
Willing *et al*., 2005[110]	Cross-sectional	428 children, 4.5–6.5 years, 200 M, 228 F, Caucasian	Total body, lumbar spine, proximal femur	Boys had higher age–height–weight-adjusted means for most BMD and BMC measures except spine BMD. BMC and BMD increased with height quartile. Mean BMD and BMC were similar for boys and girls except hip BMD, which was higher for boys. Total body BMC was higher for boys at height quartiles 1 and 3
Lu *et al*., 1994[111]	Cohort, follow-up period up to 2 years	266 children and adults, 4–27 years, 136 M, 130 F, 53 followed longitudinally	Total body, lumbar spine, femur	BMD of all sites increased significantly with age. BMD peaked at 17.5 years in boys and 15.8 years in females, except for femoral neck BMD in females, which peaked at 14.1 years. Males had higher peak total body BMD. Peak L2–L4 BMD was similar in males and females. Before peak BMD weight was best predictor of total BMD and L2–L4 BMD in both sexes
Sabatier *et al*., 1999[112]	Cohort, follow-up period 2 years	395 children and adults, 10–24 years, all F, Caucasian	Lumbar spine	In multiple regression, BMD and BMC relative gains were highly correlated with height and weight relative gains and with time since menarche. The four peri-menarcheal years beginning with first pubertal signs are essential for bone acquisition with 46.7% of adult BMC acquired during this period
Nguyen *et al*., 2001[113] (follow-up to Maynard *et al*., 1998)[99]	Cohort, follow-up period 4.3 years	186 children and adults, 6–36 years, 94 M, 92 F, Caucasian	Total body, arms, spine, pelvis	No sex differences in BMC or BMD during the prepubertal stage; however, females had significantly higher BMD of the pelvis and BMC and BMD of the spine during puberty, and postpubertal males generally had significantly higher BMC and BMD than their female counterparts. In addition the longitudinal rate of bone accumulation in both sexes increased rapidly during childhood and adolescence and was nearly complete at the end of puberty. Peak BMC and BMD was achieved between the ages of 20 and 25 years and occurred earlier in females than males.

Appendix 3

Summaries of studies assessing bone health in healthy children using QCT and pQCT

Study	Design	Subjects	Site of measurement	Results
Gilsanz *et al*., 1988[119]	Cross-sectional	101 children undergoing CT because of trauma, 2–18 years, 58 M, 43 F, white	Spine	Compared with prepubertal children, pubertal adolescents had significantly higher trabecular bone density and more compact bone in the spine. After controlling for puberty, vertebral bone density failed to correlate with age, sex, weight, height, surface area and body mass index
Gilsanz *et al*., 1991[120]	Cross-sectional	75 black girls and women, 2–20 years, compared with 75 white females matched for age and sexual development	Spine	Vertebral bone density did not differ between black and white girls before puberty. Bone density increased during puberty in each racial group but the magnitude of the increase from prepubertal values was substantially greater in black than in white subjects (34 vs 11%)
Fujita *et al*., 1999[121]	Cross-sectional	83 children and adults, 6–19 years, 47 M, 36 F, Japanese	Distal radius Trabecular 4% site Cortical 15% site Single slice	Relative cortical volume and density increased with age in boys and girls but there was no significant increase in trabecular bone
Neu *et al*., 2001[122]	Cross-sectional	371 children and adults, 6–23 years, 185 M, 186 F, white	Distal radius 4% site Single slice	Total vBMD remained stable between 6 and 15 years, then increased by 30% in girls and 46% in boys. Boys had a higher total vBMD than girls from 6 to 11 years and >18 years. Trabecular vBMD did not change with age in girls but increased by 10% in boys after 15 years. Males had higher trabecular vBMD than females
Moyer-Mileur *et al*., 2001[123]	Cross-sectional	84 girls, mean age 12.8 ± 0.8 years	Distal and midshaft tibia 10 and 66% length from distal end Single slice	Body weight was the most important predictor and determinant of total and cortical bone density and strength. Menarche, age, weight-bearing physical activity, calcium intake, height and body mass index were minor but significant predictors of bone density and strength. There were no significant predictors of trabecular BMD and strength. Total and cortical bone mineral content and vBMD measurements from pQCT were significantly related to lumbar spine and femoral neck measurements from DXA
Binkley and Specker, 2000[124]	Cross-sectional	101 children, 3–4 years, 53 M, 48 F	Distal tibia 20% site Single slice	Total cross-sectional area, cortical area and cortical thickness correlated with weight. In a regression model, weight was the only predictor of total cross-sectional area; cortical thickness was predicted by height. Both height and weight predicted the cortical area
Binkley *et al*., 2002[106]	Cross-sectional	231 children and adults, mean 11.6 years (range 5–22), 107 M, 124 F, 226 white, 3 Asian, 2 native American	Distal tibia 20% site Single slice	Prepubertal expansion of the tibia reached a plateau in girls at 14 years and continued until 18 years in boys. Tibial cortical density increased during the age of puberty more gradually in females than males. Total body BMC and total body bone area from DXA reached a plateau in girls at approximately 15 years but continued increasing in boys

continued

Study	Design	Subjects	Site of measurement	Results
Volta *et al*., 2004[125]	Cross-sectional	726 children and adults, 8.4–20.9 years, 260 M, 466 F, white	Radius	aBMD and vBMD from QCT and BUA progressively increased with age and correlated with age, height and BMI. Measures increased according to pubertal stage. BUA showed a positive significant correlation with aBMD and vBMD
Loro *et al*., 2000[126]	Cohort. Mean follow-up 3 years	40 children, depending on Tanner stage and sex mean ages were 12.3 ± 1.0 to 15.6 ± 0.9 years, 20 M, 20 F, white	Femur, midshaft Lumbar spine	Measurements of the cross-sectional dimensions of the femurs and lumbar vertebral bodies and of the density of cancellous bone at the beginning of puberty accounted for 62–92% of the variations seen at sexual maturity on average 3 years later. No correlation between caloric intake and calcium and CT parameters

Appendix 4

Summaries of studies assessing bone health in healthy children using QUS

Study	Design	Subjects	Site of measurement	Results
Schonau *et al.*, 1994[131]	Cross-sectional	218 children and young adults, 0–30 years, 100 M, 118 F	Calcaneus, thumb, patella	SOS in thumb and patella increased with age and peaked at 20–25 years. SOS in calcaneus showed no increase after puberty
Mughal *et al.*, 1996[132]	Cross-sectional	58 children, 7–17 years, 33 white (16 M, 17 F), 25 black (11 M, 14 F)	Calcaneus	BUA significantly correlated with total body BMD from DXA. The relationship between BUA and total body BMD was not affected by gender, race, weight or Tanner stage of breast development. BUA and BMD correlated with age and weight
Mughal *et al.*, 1997[133]	Cross-sectional	367 children, 6–15 years, 193 F, 174 M, white	Calcaneus	Boys had higher calcaneal BUA values than girls but only significant in age ranges 10–11 and 12–13 years. For the combined groups there were significant positive correlations between BUA and age, height and weight
Sundberg *et al.*, 1998[134]	Cross-sectional	280 children, 148 M, 132 F, 11–16 years, 98% Caucasian	Calcaneus	Boys had higher values for BUA than girls at age 13 and 15 years. BUA, SOS and SI correlated with age, height and weight. Significant positive correlations between QUS parameters and BMD from DXA and SXA
Lum *et al.*, 1999[135]	Cross-sectional	125 children and young adults, 90–25 years, 69 F, 56 M, 30 Asian, 38 black, 39 Hispanic, 18 white	Calcaneus	BUA and SOS increased with age and pubertal development during adolescence. Among females, Tanner stage was a stronger predictor than age for all QUS measurements. QUS measurements correlated moderately with DEXA of the spine, femoral neck and total body BMD and spine BMAD
Sawyer *et al.*, 2001[136]	Cross-sectional	311 children, 6.6–20 years, 204 F, 107 M, >95% Caucasian	Calcaneus	BUA, SOS and SI increased with age until plateau at age 16–18 years. There was no gender difference in age-related gains. Weight and height were correlated with all QUS parameters. After adjusting for age and weight, physical activity had no independent effect on BUA and contributed only 1.4% and 1% to the variance in SOS and SI, respectively
Wunsche *et al.*, 2000[137]	Cross-sectional	3299 children, 1623 F, mean age 11.5 ± 3.3 years, 1676 M, mean age 11.4 ± 3.4 years, Caucasian	Calcaneus	BUA increased with age in boys and girls and significantly greater for 18-year-old subjects compared with 6-year-old subjects. BUA significantly higher in 9- and 11-year-old boys than in girls. BUA significantly higher in 13–17-year-old girls compared with boys. SOS was nearly constant throughout aging. SOS was higher in 7-year-olds and 13–17-year-old girls compared with boys. BUA increased with height and weight in boys and girls. There was no correlation between SOS, height and weight
Van den Bergh *et al.*, 2000[138]	Cross-sectional	491 children, 6–21 years, 262 F, 229 M, Caucasian	Calcaneus	BUA increased with age. SOS increased with age in girls but not in boys. Tanner stage was significantly correlated with BUA but not SOS. BUA though not SOS increased with number of years since menarche. In boys, age, weight and foot length were independent predictors for BUA and age and foot length for SOS. In girls, age and weight were independent predictors for BUA and age was the only predictor for SOS

continued

Study	Design	Subjects	Site of measurement	Results
Lequin *et al.*, 2001[139]	Cross-sectional	120 children, 53 M, age 4.5–18 years, 67 F, age 1–19 years, Caucasian	Calcaneus, tibia	In girls, calcaneal SOS and BUA correlated with skeletal age. For tibial ultrasound, there was good correlation between skeletal age and SOS in girls and modest correlation in boys. In girls only Tanner stage was a significant determinant for SOS, BUA and quantitative ultrasound index
Volta *et al.*, 2004[125]	Cross-sectional	726 children, 8.4–20.9 years, 260 M, 466 F, white	Calcaneus	BUA and aBMD and vBMD from QCT progressively increased with age. Significant positive of BUA with aBMD and vBMD. SOS less significant. BUA significantly lower in pubertal stages 1 and 2 compared with 4 and 5
Ikeda *et al.*, 2004[140]	Cross-sectional	632 adolescents, 12–17 years, 321 M, 311 F, Japanese	Calcaneus	BUA and SOS correlated with age in males though not females. BUA showed a weak positive correlation with body size in both sexes, though after adjusting for age the effect in females became non-significant. SOS showed no correlation with body size in either sex. Positive significant correlation of SOS and BUA with BMD (depending on sex and site) when adjusted for age and body size
Micklesfield *et al.*, 2004[141]	Cross-sectional	177 girls, 7.5–11.7 years, 73 black, mean age 9.7 ± 0.8 years, 40 white, mean age 9.6 ± 0.6 years, 64 mixed origin, mean age 9.8 ± 0.8 years	Calcaneus	BUA and SOS were higher in the black girls and girls of mixed ancestral origin than in white girls. Covarying for age and weight did not affect these results. Walking energy expenditure and calcium score were correlated with SOS for the whole group
Lequin *et al.*, 1999[142]	Cross-sectional	53 children, 23 F (6–19 years), 30 M (6–17 years)	Tibia (4 sites)	No significant difference in SOS between girls and boys. No difference in SOS between dominant and non-dominant leg
Van Rijn *et al.*, 2000[143]	Cross-sectional	146 children, 58 M (7.6–23.4 years), 88 F (7.6–23.5 years)	Tibia	Lumbar spine and total body BMD from DXA had strong significant correlations with tibial QUS in boys and girls. Introduction of height, body weight or Tanner stage into regression analysis failed to reach significance. Lumbar spine BMAD also showed significant correlations with QUS
Lequin *et al.*, 2000[144]	Cross-sectional	596 children, 309 F (6.1–19.9 years), 287 M (6.1–19.6 years)	Tibia	A statistically significant correlation between SOS, age and skeletal age in boys and girls. In girls, there was a significant increase in mean SOS among all Tanner stages except stages 2 and 3. In boys, a significant increase in mean SOS was observed between Tanner stages 2 and 3 and between stages 4 and 5
Lappe *et al.*, 1995[145]	Cross-sectional	568 children 8–18 years, 331 F, 237 M, white	Patella	In simple linear regression, AVU positively correlated with age and Tanner stage in both sexes. Height and weight were positively correlated with AVU in both sexes whereas dietary intake of calories, protein and calcium were negatively correlated with AVU in males but not females

continued

Study	Design	Subjects	Site of measurement	Results
Lappe *et al*., 1998[146]	Cross-sectional	65 children, 38 F (8.2–10.8 years), 27 M (8.3–10.7 years), white	Patella	No significant difference between boys and girls for AVU. No difference in AVU in those with or without history of fracture. There was a significant negative correlation between apparent velocity of ultrasound and activity. When simple regression was performed by gender only the girls activity was correlated with AVU. Weight also predicted AVU in girls
Halaba and Pluskiewicz, 1997[147]	Cross-sectional	433 children, 9–15 years, 226 F, 207 M, Caucasian	Phalanx (2–5 fingers)	Boys had lower mean SOS values than girls, but up to age 11 years the values were not significantly different. An increase in values was observed in girls at 11 years and in boys 2 years later. Regression analysis showed that in girls the main factor influencing SOS was age and in boys height and weight
Baroncelli *et al*., 2001[148]	Cross-sectional	1083 children, 3–21 years, 587 M, 496 F, white	Phalanx (2–5 fingers)	Mean SOS increased significantly with age in both sexes. There was no difference between the sexes until age 11 years then females had significantly higher SOS than males at ages 12, 13 and 14 years. No difference in SOS between sexes in pubertal stages 1, 2 and 5 but females had significantly higher mean SOS than males at stages 3 and 4. Independent predictors of SOS were weight, body mass index, pubertal stage and mean width of fingers in males and age, pubertal stage, and mean width of fingers in females
Daly *et al*., 1997[149]	Case–control	33 male gymnasts, mean age 9.4 ± 1.1 years, 40 normally active controls matched for age (mean age 9.4 ± 1.1 years) height and weight	Calcaneus, distal radius, prox phalanx of index finger	Gymnasts had a significantly greater SOS in calcaneus, distal radius and phalanx than non-gymnasts. There were no differences in calcaneal BUA between the groups. Distal radius SOS correlated with calcium intake in all subjects and training time in the gymnasts
Lehtonen-Veromaa *et al*., 2000[150]	Case–control	184 peripubertal girls, 11–17 years, (65 gymnasts, 63 runners, 56 non-athletic controls), Caucasian	Calcaneus	Mean BUA and SOS significantly higher in pubertal gymnasts than controls. Mean SOS in prepubertal runners significantly higher than controls. The amount of physical activity correlated weakly but significantly with BUA and SOS values in the pubertal and prepubertal groups. In the whole group calcaneal BUA and SOS correlated with BMD of the femoral neck and lumbar spine
Lappe *et al*., 2000[151]	Cohort, follow-up period 3 years	328 children, 184 F mean age at baseline 11.8 ± 2.1 years, 144 M mean age at baseline 11.7 ± 2.1 years	Patella	At baseline, AVU values were significantly higher in girls than boys. At 3 years, girls continued to have higher AVU values. Both males and females experienced significant increase in AVU values over the 3-year period. The rate of change of AVU peaked at an earlier age in females and maximum accumulation rates in both genders occurred at ages at which highest rates were seen with densitometry

AVU, apparent velocity of ultrasound; DEXA, dual energy X-ray absorptiometry; SI, stiffness index.

Appendix 5

Search strategies: review of quantitative imaging techniques as an outcome measure in JIA

MEDLINE

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34 13 and 18 and 33 [453]

Appendix 6

Studies excluded from review of quantitative imaging techniques as an outcome measure

Study	Reason for exclusion
Cetin A, Celiker R, Dincer F, Ariyurek M. Bone mineral density in children with juvenile chronic arthritis. *Clin Rheumatol* 1998;**17**:551–3	Measurement using dual-photon absorptiometry
Ebbesen EN, Thomsen JS, Beck-Nielsen H, Nepper-Rasmussen HJ, Mosekilde L. Age- and gender-related differences in vertebral bone mass, density, and strength. *J Bone Miner Res* 1999;**14**:1394–403	Adults
Fantini F, Beltrametti P, Gallazzi M, Gattinara M, Gerloni V, Murelli M, *et al*. Evaluation by dual-photon absorptiometry of bone mineral loss in rheumatic children on long-term treatment with corticosteroids. *Clin Exp Rheumatol* 1991;**9** Suppl 6:21–8	Measurement using dual-photon absorptiometry
Fewtrell MS. British Paediatric and Adolescent Bone Group. Bone densitometry in children assessed by dual x-ray absorptiometry: uses and pitfalls. *Arch Dis Child* 2003;**88**:795–8	Review paper
Fulkerson JA, Himes JH, French SA, Jensen S, Petit MA, Stewart C, *et al*. Bone outcomes and technical measurement issues of bone health among children and adolescents: considerations for nutrition and physical activity intervention trials. *Osteoporosis Int* 2004; **15**:929–41	Review paper
Henderson RC. The correlation between dual-energy X-ray absorptiometry measures of bone density in the proximal femur and lumbar spine of children. *Skeletal Radiol* 1997; **26**:544–7	Children with non-connective tissue disease
Hopp R, Degan J, Gallagher JC, Cassidy JT. Estimation of bone mineral density in children with juvenile rheumatoid arthritis. *J Rheumatol* 1991;**18**:1235–9	Measurement using dual-photon absorptiometry
Kaga M, Takahashi K, Suzuki H, Moriwake T, Makino H, Yamamoto K, *et al*. Ultrasonic assessment of tibia in Japanese children and adolescents. *Osteoporos Int* 1997;**7**:67	Conference abstract
Kovanlikaya A, Loro ML, Hangartner TN, Reynolds RA, Roe TF, Gilsanz V. Osteopenia in children: CT assessment. *Radiology* 1996;**198**:781–4	Children with non-connective tissue disease
Leonard MB, Shults J, Elliott DM, Stallings VA, Zemel BS. Interpretation of whole body dual energy X-ray absorptiometry measures in children: comparison with peripheral quantitative computed tomography. *Bone* 2004;**34**:1044–52	Use of pQCT to aid interpretation of DXA
Leonard MB. Assessment of bone health in children and adolescents with cancer: promises and pitfalls of current techniques. *Med Pediatr Oncol* 2003;**41**:198–207	Review paper
Lequin C, van Rijn RR, Robben SGF, Keinan DD, van Kuijk C. Quantitative ultrasound of the tibia: precision in a pediatric population. *Osteoporos Int* 1997;**7**:300	Conference abstract
Povoroznjuk VV, Tatarchuk TF, Mazur IP, Tkachenko LP. Use of ultrasound densitometry for evaluation of bone tissue in children. *Osteoporos Int* 1997;**7**:298	Conference abstract
Rooney M, Davies UM, Reeve J, Preece M, Ansell BM, Woo PM. Bone mineral content and bone mineral metabolism: changes after growth hormone treatment in juvenile chronic arthritis. *J Rheumatol* 2000;**27**:1073–81	Measurement using dual-photon absorptiometry
Roth J. Bone mass in adolescents with early-onset juvenile idiopathic arthritis: comment on the article by Lien, *et al*. *Arthritis Rheum* 2004;**50**:2036	Musculoskeletal abnormalities and bone geometry
van Rijn RR, Van DS, I, Link TM, Grampp S, Guglielmi G, Imhof H, *et al*. Bone densitometry in children: a critical appraisal. *Eur Radiol* 2003;**13**:700–10	Review paper

Appendix 7

Summaries of studies included in the review of quantitative imaging techniques as an outcome measure in JIA: DXA

Bisphosphonate studies are included in the effectiveness section of the report (Chapter 3).

Study	Design	Subjects	Controls	Site of measurement	Results
Shore *et al.*, 1995[73]	Cross-sectional	224 children with bone mineral disorders secondary to a variety of conditions including rheumatological disease, prolonged corticosteroid therapy, Gaucher disease, idiopathic hypercalciuria, mean age 10.1 years, 117 F, 107 M		Distal third radius, lumbar spine	After controlling for age, sex, weight and height, partial correlations were very small for lumbar BMD with radial BMD and with cortical thickness (from hand X-rays), and slightly better for radial BMD with cortical thickness. *Z*-scores also correlated poorly with no meaningful correlation for lumbar BMD with radial BMD
Henderson *et al.*, 1997[159]	Cross-sectional	48 children with JIA, systemic (2), polyarticular (28) pauciarticular (18) mean age 8.1 ± 1.9 years, 37 F, 11 M, Caucasian	25 healthy controls, mean age 7.7 ± 1.7 years, 14 F, 11 M, Caucasian	Total body, skull, arms, hips, legs and trunk	Overall mean total body BMD scores did not differ between JIA and controls. However, 29.2% of the JIA children had low total body BMD whereas only 16% would be expected to have low values based on the standard normal distribution. The JIA subjects with low total body BMD were significantly younger, had significantly more active articular disease, greater physical function limitation, higher erythrocyte sedimentation rate, higher joint count severity score, lower BMI and more protein and vitamin D in their diet compared with children with normal total body BMD
Pereira *et al.*, 1998[160]	Cross-sectional	62 children with JIA, polyarticular (29) pauciarticular (21) systemic (12), 5–18 years, 36 F, 26 M, Brazilian	157 healthy controls, 5–18 years, 88 F, 69 M	Lumbar spine, left femoral neck, distal one-tenth radius	Decreased lumbar spine, femoral neck and radius BMD in 50–60% of children with JIA compared with controls. Children treated with corticosteroids had significant bone loss in distal radius and lumbar spine but not in femoral neck. BMD loss in polyarticular, pauciarticular and systemic disease, highest in polyarticular children (not significant). There was a significant difference in disease duration between the children with decreased BMD and those with no BMD decrease in the same regions
Brik *et al.*, 1998[20]	Case–control	17 children with systemic JIA, mean 14.9 ± 4.5 years, 10 receiving corticosteroids for at least 12 months before study, 6 M, 11 F	18 age- and sex-matched healthy children, mean age 14.5 ± 4.8 years, 6 M, 12 F	Lumbar spine, femoral neck	Children with systemic JIA treated with corticosteroids had significantly reduced BMD in lumbar spine and femoral neck compared with controls. BMD of JIA children not treated with corticosteroids was not different from controls

continued

Study	Design	Subjects	Controls	Site of measurement	Results
Kotaniemi *et al.*, 1999[17]	Cross-sectional	111 children with JIA, oligoarticular (36) polyarticular (75), 38 M with mean age 12.7 ± 2.5 years, 73 F, 12.6 ± 2.6 years, Finnish	66 healthy controls of same age	Lumbar spine, femoral neck. Corrected for size using Kroger *et al.*, 1992[84]	Compared with healthy controls, BMD and vBMD were significantly reduced at the femoral neck. Lumbar spine BMD was significantly reduced in both sexes with JIA but BMAD was reduced in boys only. Body size, physical activity and calcium intake were positive and disease activity and corticosteroids negative determinants of BMD in JCA
Chlebna-Sokol *et al.*, 1999[161]	Cross-sectional	30 children with JIA, oligoarticular (6) polyarticular (17) and systemic (7), 5–18 years, 24 F, 6 M		Total body, lumbar spine	Osteoporosis (*Z*-score <–1.5) diagnosed in 12 (40%) children. BMD (expressed as *Z*-score) correlated negatively with disease duration
Henderson *et al.*, 2000[21]	Cross-sectional	36 children with JIA, polyarticular (25), pauciarticular (11), mean age 16.0 ± 1.8 years, all F, 35 Caucasian, 1 African-American	51 healthy controls, mean age 16.1 ± 1.6 years, all female, 50 Caucasian, 1 African-American	Total body, lumbar spine. Corrected for size using Molgaard *et al.*, 1997[87]	3.9% of control subjects and 5.6% of JIA children were osteopenic (WHO criteria) at the lumbar spine. None had osteoporosis. Total body BMC was slightly higher (4.5%) in controls than JIA children. Compared with JIA patients with normal total body BMC, those with low total body BMC were lighter, shorter and had greater number of involved joints
Njeh *et al.*, 2000[162]	Cross-sectional	22 children with JIA, mean age 11.7 ± 2.9 years, 15 F, 7 M		Total body, lumbar spine	Mean spine BMD significantly lower compared with the normal ranges: 45% had a *Z*-score <–1.5 for spine and 23% for total body. BMD significantly associated with age, height and weight. BMD significantly negatively associated with duration of disease
Ellis *et al.*, 2001[103]	Cross-sectional	106 children, CF (42), dermatomyositis (29), liver disease (15), Rett syndrome (6), HIV (14), mean ages varied according to disease type and sex 7.7 ± 2.2 to 12.5 ± 3.3 years	982 children, 5–18 years, 537 F, 445 M, 407 European-American, 285 black, 290 Mexican-American	Total body	In boys, only the CF children had significantly lower BMC than controls. CF, HIV and liver disease groups had significantly lower BMD than controls. Girls in the CF, HIV, liver disease and Rett syndrome groups had lower BMC compared with healthy controls. Only the JDM and CF groups had a mean BMD within the normal range. 39 patients had *Z*-scores <–1.5, 22 had *Z*-scores <–2.5

continued

Study	Design	Subjects	Controls	Site of measurement	Results
Mul *et al.*, 2002[68]	Cross-sectional	27 rheumatic diseases treated with high-dose corticosteroids JIA (13), SLE (6), periarteritis nodosa (2), polymyositis (2), dermatomyositis (2), Takayashu arteritis (1), mixed connective tissue disease (1), mean age 11.46 ± 4.16 years, 11 M, 16 F		Total body, lumbar spine Corrected for size using Kroger, 1995	Total body and lumbar spine BMD SD scores were significantly lower than normal. CHAQ score correlated with BMD lumbar spine. No significant correlation of BMD with cumulative dose or duration of corticosteroid treatment
Fielding *et al.*, 2003[163]	Cross-sectional	42 children with chronic disorders associated with osteopenia, including JIA (2), SLE (3), mean age of all children 14.5 ± 2.9 years, 26 F, 16 M, 67% Caucasian, 19% Asian-American, 12% Hispanic, 2% African-American		Total hip, femoral neck, lumbar spine, whole body. Corrected for size using Carter *et al.*, 1992[83]	Mean aBMD and BMAD below average for age at all sites
Lien *et al.*, 2003[164]	Cross-sectional	105 children with JIA, systemic (15), pauciarticular (73), polyarticular (17), mean age at follow-up 17.0 ± 1.8 years, 80 F, 25 M, Caucasian		Total body, lumbar spine, hip, forearm	41% of adolescents with early-onset JIA had low total body BMC and 34% had low total body BMD. Low total body BMC was less frequent in groups with systemic onset than the other two groups. Compared with adolescent JIA patients with normal total body BMC those with low total body BMC were lighter, shorter, had longer duration of active disease and higher number or active and restricted joints
Hartman *et al.*, 2004[165]	Cross-sectional	40 children with chronic rheumatic disease, JIA (32), SLE (6), dermatomyositis (2), mean age 9.9 ± 4.3 years, 27 F, 13 M		Lumbar spine	BMD *Z*-score <–1 SD in 45% of children. Reduced BMD correlated with age at disease onset and corticosteroid treatment. BMD correlated negatively with disease duration and methotrexate therapy. BMD lower in patients with polyarticular compared with oligoarticular disease
Alsufyani *et al.*, 2005[166]	Cross-sectional	36 children with connective tissue diseases, SLE (25), juvenile dermatomyositis (7), systemic vasculitis (4), mean age 11.4 ± 2.9 years, 33 F, 3 M, 14 Caucasian, 13 Asian, 6 East Indian, 3 Canadian First Nations		Lumbar spine, hip, total body	An abnormal *Z*-score (one or more sites) found in 15/25 children with SLE and 3/11 JDM/vasculitis patients. Children with low BMD tended to be younger, have received higher doses of corticosteroids and were more often prepubertal than those with normal BMD. There was no relationship between disease activity at the time of the study and BMD

continued

Study	Design	Subjects	Controls	Site of measurement	Results
Kotaniemi *et al.*, 1993[167]	Case–control	43 children with JIA, polyarthritis treated with corticosteroids, mean age 12.4 ± 3.0 years, all F, Finnish	44 healthy controls, mean age 12.7 ± 3.6 years, all F	Lumbar spine, femoral neck. Corrected for size using Kroger *et al.*, 1992[84]	Girls with JIA had reduced BMD, bone size and vBMD at both the lumbar spine and femoral neck. In the JIA group the femoral BMD and vBMD and the spine bone width correlated negatively with mean corticosteroid dose
Pepmueller *et al.*, 1996[168]	Case–control	41 children with JIA (21 oligoarticular, 20 polyarticular), mean age 10.1 ± 4.3 years, 7 M, 34 F	62 healthy children, mean age 11.3 ± 4.2 years, 30 M, 34 F	Patients: total body, non-dominant arm including 1/3 and 1/10 radius, lumbar spine. Controls: arm and body scans only	BMD (DXA) was decreased at all sites in JIA children compared with controls. For total body scan, this applied to both children with oligoarthritis and polyarthritis. Divergence from normal increased with age and was greatest in postpubertal children. BMD corrected for age, height, weight and bone area was decreased at cortical sites (radius, upper and lower extremities and total body)
Celiker *et al.*, 2003[67]	Case–control	28 children with JIA, oligoarticular (7), polyarticular (15), systemic (1), SLE (1), Juvenile AS (4), mean age 11.0 ± 4.13 years, 12 M, 16 F	45 healthy controls, mean age 11.13–2.21 years, 24 M, 21 F	Lumbar spine	BMD significantly lower in JIA children compared with controls (mean 0.533 vs 0.636 g/cm^2, $p < 0.001$). JIA children treated with corticosteroids had significantly lower BMD than healthy controls (mean 0.492 vs 0.636 g/cm^2, $p < 0.005$). The non-corticosteroid group had lower BMD than the control group (0.595 g/cm^2, not significant). Age of children and age of onset significantly correlated with BMD
Lilleby *et al.*, 2005[169]	Case–control	70 children and young adults with childhood onset SLE, mean age 26.4 ± 9.9 years, 53 F, 17 M, Norwegian	70 healthy age- and sex-matched controls, mean age 26.7 ± 10.0 years	Femoral neck, lumbar spine, total body, distal one-third radius	BMD lumbar spine (mean 1.03 vs 1.16 g/cm^2), total body (1.07 vs 1.12), radius (0.56 vs 0.61) and femoral neck (0.95 vs 1.05) were significantly lower in children with SLE compared with controls. The reduction in BMD of the lumbar spine was significantly greater than that of the total body. In multiple regression, a higher cumulative corticosteroid dose was significantly associated with lower BMC of the lumbar spine and femoral neck. Decreased lumbar BMD was also related to male sex
Kotaniemi *et al.*, 1998[170]	Cohort, 12 months follow-up, controlled	105 children with JIA, polyarticular (69), oligoarticular (36), polyarticular with mean age 12.4 ± 2.8 years, oligoarticular 13.2 ± 2.1 years, 71 F, 34 M	65 healthy controls: mean age 12.8 ± 3.5 years, 37 F, 28 M	Lumbar spine, femoral neck. Corrected for size using Kroger *et al.*, 1992[84]	At baseline, BMD and BMAD were decreased at the lumbar spine (mean 0.786 vs 0.940 g/cm^2 and 0.296 vs 0.309 g/cm^3) and femoral neck (0.746 vs 0.962 g/cm^2 and 0.343 vs 0.368 g/cm^3) in polyarticular children compared with healthy controls. In oligoarticular children, BMD and BMAD were only significantly

continued

Study	Design	Subjects	Controls	Site of measurement	Results
					decreased at femoral neck. In polyarticular children, the acquisition of BMD and BMAD was significantly decreased at the femoral neck (4.1 vs 7.4% and 0.8 vs 3.6%) but remained the same at the spine compared with controls. In oligoarticular children, the increase in BMD and BMAD at the femoral neck was similar to that in controls, but significantly increased at the spine (7.4 vs 4.9% and 3.6 vs 1.0%) compared with the change in the controls. Bone mineral gain was significantly delayed at the lumbar spine in children treated with corticosteroids
Bianchi *et al*., 1999[171]	Cohort, 18 months follow-up	32 children with JIA, oligoarticular (13), systemic (10), polyarticular (9), 2.6–15.4 years, 25 F, 7 M	45 healthy children matched for age and sex	Total body, lumbar spine	Pubertal stage and disease activity significantly influenced the yearly change in BMD. During treatment with methotrexate, BMD increased but the increase was less than in healthy children. BMD did not correlate with either methotrexate dose or length of therapy. Treatment with corticosteroids reduced BMD increase, in particular in the spine
Perez *et al*., 2000[19]	Cohort, 12 months	13 children with rheumatic disease, JIA (6), spondyloarthropathy (1), dermatomyositis (4), SLE (2). 7 treated with corticosteroids and 6 not treated with corticosteroids, age range 8–16 years, 12 F, 1 M		Total body	BMD was similar in both corticosteroid-treated and non-corticosteroid treated children at baseline and follow-up
Falcini *et al*., 2000[172]	Cohort, 12 months	53 chronic rheumatic disease, JIA (29), SLE (13), juvenile dermatomyositis (11), mean age 13.02 ± 2.69 years, 41 F, 12 M	55 healthy children matched for age, sex, pubertal stage, weight	Lumbar spine	Mean values BMD lower than in healthy controls and were significantly below the normal range when corrected for age and sex. BMD correlated with age, height, weight and Tanner pubertal stage but not sex
Stewart *et al*., 2003[173]	Cohort, mean follow-up 28.2 months	15 juvenile dermatomyositis, age range 4.8–22.9 years, 9 F, 6 M, Caucasian		Lumbar spine	Of the 15 patients, 10 had active disease. Baseline BMD measurements showed osteopenia or osteoporosis in the majority (6/10 with active disease, 4/5 with inactive disease). 14 had serial BMD measurements. Persistent or worsening osteopenia was documented in all patients who had active disease except for three who had been treated with bisphosphonates because of vertebral compression fractures

continued

Study	Design	Subjects	Controls	Site of measurement	Results
Lien *et al.*, 2005[174]	Cohort, 24 months, controlled	108 children with JIA, systemic (5), oligoarthritis (64), polyarthritis RF negative (30), polyarthritis RF positive (3), spondyloarthropathy (3), psoriatic (3), mean age 10.1 ± 3.2 years, 63 F, 45 M (100 at follow-up, mean age 12.2 ± 3.2 years, 58 F, 42 M)	108 healthy controls, mean age 10.1 ± 3.2 years, 63 F, 45 M (100 at follow-up, mean age 12.3 ± 3.2 years, 58 F, 42 M)	Total body, lumbar spine, hip, radius. Corrected for size using Kroger *et al.*, 1992[84]	No difference in bone measurements at baseline but the healthy children had significantly greater gains than JIA children in total body BMC (difference 35 g, $p = 0.035$) and distal radius BMC (0.08 g, $p < 0.001$). There was a trend towards higher gains in femoral neck BMC and total femoral BMC. BMC was low or very low (Z-score <–2) in 24% of JIA children and 12% of healthy children at follow-up
Treatment with growth hormone					
Bechtold *et al.*, 2004[175]	Cohort, 4 years follow-up	11 prepubertal children with JIA (systemic or polyarticular receiving corticosteroids) and growth retardation, mean age 10.3 ± 2.0 years, 4 M, 7 F. Treated with growth hormone for 4 years		Lumbar spine. Corrected for size using Kroger *et al.*, 1992[84]	aBMD and vBMD significantly lower than in a healthy reference population at baseline. After 4 years of treatment, vBMD increased from 0.198 to 0.232 g/cm^3 ($p < 0.03$)

AS, ankylosing spondylitis; CF, cystic fibrosis; JDM, juvenile dermatomyositis.

Appendix 8

Summaries of studies included in the review of quantitative imaging techniques as an outcome measure in JIA: QCT and pQCT

Bisphosphonate studies are included in the effectiveness section of the report (Chapter 3).

Study	Design	Subjects	Controls	Site of measurement	Results
Fredericks *et al.*, 1990[177]	Cross-sectional	132 children idiopathic juvenile osteoporosis (7), OI (3), corticosteroid-treated children (14: 8 nephrotic syndrome, 6 collagen disease), chronic renal failure (17), vitamin D-resistant rickets (4), thalassaemia (54), 3–15 years	37 ambulant children undergoing CT for other reasons and with normal bone status	Lumbar spine	Children with idiopathic osteoporosis, OI and some with prolonged corticosteroid therapy had low values for trabecular BMC compared with the controls. Children with chronic renal failure had high trabecular BMC
Lettgen *et al.*, 1996[178]	Case–control	27 children with rheumatic disease	27 age- and sex-matched healthy controls	Ultradistal radius	Trabecular and total BMD were lower in children with rheumatic disease than controls. There was no difference in BMD in children with systemic or non-systemic disease. BMD did not correlate with duration of disease or corticosteroid medication

Appendix 9

Summaries of studies included in the review of quantitative imaging techniques as an outcome measure in JIA: QUS

Bisphosphonate studies are included in the effectiveness section of the report (Chapter 3).

Study	Design	Subjects	Controls	Site of measurement	Results
Njeh *et al.*, 2000[162]	Cross-sectional	22 children with JIA, systemic (7), psoriatic (6), oligoarthritis (3), polyarthritis negative (5), polyarthritis positive (1), mean age 11.7 ± 2.9 years, 15 F, 7 M		Tibia	Total body and spine BMD from DXA was lower in children compared with normative data. BMD *Z*-scores were negatively associated with duration of disease and lower in those taking corticosteroids. Spine and total body BMD correlated significantly with tibial SOS. Weight and height were strong predictors of BMD; however, only weight was a significant predictor of SOS
Brukx and Waelkens, 2003[152]	Cross-sectional	41 children at risk of low BMD, 15 M, 26 F, and 226 healthy children, 121 M, 105 F, aged 7.0–18.4 years		Calcaneus	Among children at risk of low bone mass, QUS parameters (BUA, SOS and quantitative ultrasound index) correlated with DXA measurements at one or more sites. Among healthy children there were no significant differences in QUS parameters between age and pubertal stage groups
Fielding *et al.*, 2003[163]	Cross-sectional	42 children and adults referred for DXA scan because of chronic disease associated with osteopenia including organ transplantation, cystic fibrosis, anorexia nervosa, chronic corticosteroid therapy and OI, mean age 14.5 years (range 9.0–20.9 years), 26 F, 16 M		Calcaneus	aBMD and vBMD from DXA below expected at all sites. Correlations between *Z*-scores for DXA and ultrasound parameters were modest (r = 0.3–0.6)
Baroncelli *et al.*, 2003[179]	Cross-sectional	135 children and adults with bone and mineral disorders including long-term corticosteroid or chronic anticonvulsant treatment, JIA (4 pauciarticular, 5 polyarticular), coeliac disease, disuse osteoporosis, β-thalassaemia major, survivors of acute lymphoblastic leukaemia, liver transplantation, calcium deficiency, hypophosphataemic rickets, 3–21 years, 64 M, 71 F		Phalanx	Mean SOS, cortical area to total area ratio (CA/TA), lumbar aBMD from DXA, radial BMD from SPA and lumbar vBMD were significantly reduced compared with normative data. Positive correlation between SOS and CA/TA, lumbar aBMD and lumbar vBMD. In children with previous fracture mean values of SOS, CA/TA ratio, lumbar aBMD, lumbar vBMD, expressed as *Z*-scores were significantly lower among those children with a recent facture

continued

Study	Design	Subjects	Controls	Site of measurement	Results
Jaworski *et al.*, 1995[180]	Case–control	18 children with osteopenia (OI, juvenile osteoporosis, corticosteroid treatment), mean age 10.2 ± 2.6 years	71 healthy children, mean age 10.2 ± 2.6 years, age- and sex-matched	Calcaneus	SOS, BUA and stiffness values increased with age. BUA, SOS and stiffness correlated with BMD measured with DXA at heel, lumbar spine and total body (r = 0.67–0.83 in pooled sample). SOS, BUA and stiffness were significantly lower in osteopenic compared with normal children
Falcini *et al.*, 2000[172]	Case–control	53 children, JIA (29), SLE (13), dermatomyositis (11), mean age 13.02 ± 2.69 years, 12 M, 41 F	55 healthy children matched for age, sex, pubertal stage and weight	Calcaneus	BMD from DXA and BUA lower in children with rheumatic disease than healthy children. BUA was statistically significantly correlated with BMD at lumbar spine. The relationship between BUA and BMD was not affected by age, sex, weight, height or Tanner stage. BMD and BUA correlated with age, weight, height and Tanner stage
Hartman *et al.*, 2004[165]	Case–control	40 children with chronic rheumatic diseases: 32 JIA (21 pauciarticular, 6 polyarticular, 5 systemic), 6 SLE, 2 dermatomyositis, mean age 9.9 ± 4.3 years, 27 F, 13 M	64 healthy age and sex matched from reference database	Tibia, radius	BMD from DXA and SOS Z-scores <–1 in 45% and 38% of chronic rheumatic disease children, respectively. Reduced BMD and SOS values correlated with age at disease onset and corticosteroid treatment. Only DXA correlated negatively with disease duration. Significant correlation between BMD lumbar spine and SOS radius but not SOS at tibia

Appendix 10

Search strategies: review of biochemical markers of bone turnover as an outcome measure

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32 DERMATOMYOSITIS/ [3514]

33 juvenile dermatomyositis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [343]

34 dermatomyositis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [3934]

35 Systemic Lupus Erythematosus/ [22641]

36 systemic lupus erythematosus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [25390]

37 SLE.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [11828]

38 VASCULITIS/ or SYSTEMIC VASCULITIS/ [10481]

39 vasculitis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [16923]

40 Connective Tissue Disease/ [3878]

41 connective tissue diseases.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [1694]

42 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [109461]

43 22 and 27 and 42 [140]

Appendix 11

Studies excluded from the review of biochemical markers of bone turnover as an outcome measure

Study	Reason for exclusion
Cadogan J, Blumsohn A, Barker ME, Eastell R. A longitudinal study of bone gain in pubertal girls: anthropometric and biochemical correlates. *J Bone Miner Res* 1998;**13**:1602–12	Healthy children
Crofton PM, Kelnar CJ. Bone and collagen markers in paediatric practice. *Int J Clin Pract* 1998;**52**:557–65	Review paper
Davies UM, Rooney M, Preece MA, Ansell BM, Woo P. Treatment of growth retardation in juvenile chronic arthritis with recombinant human growth hormone. *J Rheumatol* 1994; **21**:153–8	Data on BMD and biochemical markers published elsewhere[18]
de Ridder CM, Delemarre-van de Waal HA. Clinical utility of markers of bone turnover in children and adolescents. *Curr Opin Pediatr* 1998;**10**:441–8	Review paper
Jedrzejczyk-Goral B, Owczarek H, Nahaczewska W, Prusek W. Markers of bone turnover in children with juvenile chronic arthritis. *Adv Clin Exp Med* 2001;**10**:157–64	Not published in English
Jedrzejczyk-Goral B, Prusek W, Owczarek H, Nahaczewska W. Markers of bone turnover in children with juvenile chronic arthritis – Part II. *Adv Clin Exp Med* 2003;**12**:449–59	Not published in English
Kopec Z, Prusek W, Owczarek H, Galinski A. Hydroxyproline changes in children with juvenile chronic polyarthritis in relation to age and pharmacological treatment. *Reumatologia* 1992;**30**:134–40	Not published in English
Davies UM, Jones J, Reeve J, Camacho-Hubner C, Charlett A, Ansell BM, *et al*. Juvenile rheumatoid arthritis. Effects of disease activity and recombinant human growth hormone on insulin-like growth factor 1, insulin-like growth factor binding proteins 1 and 3, and osteocalcin. *Arthritis Rheum* 1997;**40**:332–40	Data on BMD biochemical markers published elsewhere[18]
van Coeverden SCCM, Netelenbos JC, de Ridder CM, Roos JC, Popp-Snijders C, Delemarre-van de Waal HA. Bone metabolism markers and bone mass in healthy pubertal boys and girls. *Clin Endocrinol* 2002;**57**:107–16	Healthy children
Zoch-Zwierz W, Rudobielska M, Jarzabska-Szorc W. Evaluation of the degree of bone changes based on the determination of blood serum alkaline phosphatase isoenzymes in children with rheumatoid arthritis. *Pediatr Pol* 1981;**56**:127–32	Not published in English

Appendix 12

Summaries of studies included in the review of biochemical markers of bone turnover outcome measure

Bisphosphonate studies are included in the effectiveness section of the report (Chapter 3).

Study	Design	Patients	Controls	All markers measured	Results
Reeve *et al.*, 1993[213]	Clinical trial, follow-up 1 year	34 children with JIA treated with corticosteroids randomised to treatment with prednisone (n =17, 16 completed study, mean age 10.56 ± 3.68 years, 6 M, 11 F) or deflazacort (n = 17, 15 completed study, mean age 10.25 ± 3.92 years, 6 M, 11 F). 21 systemic, 10 polyarticular, 3 pauciarticular		Serum ALP, OC. Urinary HYP/Cr	No significant difference between the mean trends for two treatment groups for ALP, HYP/Cr or plasma OC. OC or HYP/Cr did not predict spinal bone mineral changes during trial
Polito *et al.*, 1995[214]	Cross-sectional	20 children with active JIA (7 oligoarticular, 9 polyarticular, 4 systemic), mean age 10.7 (SEM 1.2) years, 5 M, 15 F, never treated with corticosteroids		Serum ALP, OC	OC was normal in all children. ALP increased in 6 children. No significant relationship between OC, ALP and BMC
Chlebna-Sokol *et al.*, 1999[161]	Cross-sectional	Total of 30 children with JIA (17 polyarticular, 6 oligoarticular, 7 systemic), 24 F, 6 M, 5–18 years, 12 treated with corticosteroids		Serum and urinary excretion of total ALP and bone-specific alkaline phosphatase (BALP), urinary HYP and HYP/Cr	ALP and BALP within expected limits and no significant differences between children with or without osteoporosis (based on BMD). HYP excretion higher in children with osteoporosis compared with non-osteoporosis children ($p < 0.06$)
Henderson *et al.*, 2000[21]	Cross-sectional	36 girls with JIA (25 polyarticular, 11 pauciarticular), mean age 16.0 ± 1.8 years. No previous corticosteroid therapy		Serum OC, BALP, ICTP	OC and ICTP levels were significantly higher in children with low total body BMC compared with those with normal BMC and were significantly negatively correlated with total body BMC. There were no differences for the other measures and their values were within previously published normal ranges
Lien *et al.*, 2003[164]	Cross-sectional	42 children with early onset JIA and low total body BMC. All 103 children: 15 systemic, 73 pauciarticular, 17 polyarticular, mean age 17.0 ± 1.8 years, 80 F, 23 M. 29/42 treated with corticosteroids	61 children with early-onset JIA and normal total body BMC. 45/61 treated with corticosteroids	Mean of 14.2 years after disease onset. Serum BALP, OC, ICTP, urinary DPD	No significant differences between low and normal BMC groups for BALP, OC, ICTP, urinary DPD

continued

Study	Design	Patients	Controls	All markers measured	Results
Bardare *et al.*, 1991[215]	Case–control	36 children with JIA: 13 pauciarticular, mean age 8.9 years (range 5–13), 9 F, 4 M, never treated with corticosteroids; 8 polyarticular, mean age 9.4 years (range 7–14), 4 F, 4 M, all treated with corticosteroids; 15 systemic, mean age 11.4 years (range 7–17), 10 F, 5 M, all treated with corticosteroids	45 healthy children, mean age 9.6 years (range 5–14), 25 F, 20 M	ALP, HYP	At baseline there was no difference in OC and ALP between severity subgroups; no variation after 1 year
Hillman *et al.*, 1994[216]	Case–control	44 children with JIA (24 polyarthritis, 20 oligoarthritis), mean age 9.7 ± 4.7 years, 28 F, 16 M. Excluded those receiving systemic corticosteroids within the past year	37 healthy children, mean age 11.8 ± 3.8 years, 18 F, 19 M	Serum OC, BALP, TRAP	OC, BALP and TRAP were significantly decreased in JIA
Pepmueller *et al.*, 1996[168]	Case–control	41 children with JIA (21 oligoarticular, 20 polyarticular) mean age 10.1 ± 4.3 years, 7 M, 34 F	62 healthy children, mean age 11.3 ± 4.2 years, 30 M, 34 F	Serum OC, BALP, PICP, TRAP	OC, BALP and TRAP were significantly lower in children with JIA. PICP and UrDPyr:Cr in children with JIA were similar to controls. The results were similar when children treated with corticosteroids were excluded. Laboratory markers of disease severity were highly correlated with decreases in markers of bone formation but not with those of resorption
Brik *et al.*, 1998[20]	Case–control	17 children with systemic JIA, mean 14.9 ± 4.5 years, 10 receiving corticosteroids for at least 12 months before study, 6 M, 11 F	18 age- and sex-matched healthy children, mean age 14.5 ± 4.8 years, 6 M, 12 F	Serum OC and alkaline ALP	OC and ALP were similar in children with JIA (both corticosteroid and non-corticosteroid groups) and controls
Falcini *et al.*, 1998[217]	Case–control	47 children with JIA, 33 with active disease, 14 in remission, (23 pauciarticular, 17 polyarticular RF negative, 7 systemic), 34 F, 13 M, mean age 7.13 ± 4.1 years	47 age- and sex-matched healthy children, mean age 8.06 ± 3.4 years	ALP, OC, PICP, ICTP	ALP, OC, PICP and ICTP were not significantly different from controls. OC and ICTP were significantly lower in children with active disease compared with inactive disease. OC and ICTP were significantly lower in polyarticular and systemic disease compared with pauciarticular disease. No difference in active disease treated with corticosteroids compared with those treated with NSAIDs or NSAIDs plus methotrexate

continued

Study	Design	Patients	Controls	All markers measured	Results
Pereira *et al.*, 1998[160]	Case–control	62 children with JIA (29 polyarticular, 21 pauciarticular, 12 systemic), 36 F, 26 M, 5–18 years, 14 currently treated with corticosteroids	157 healthy children, 88 F, 69 M, 5–18 years	Serum OC, BALP. Urinary to HYP/Cr and DPD crosslinks to creatinine ratio (DPD/Cr)	OC, BALP, DPD/Cr and HYP/Cr values were decreased in healthy girls more than 12 years of age and in healthy boys more than 14 years of age compared with younger children from the same population. Lower levels of OC and BALP were observed in younger children with JCA (girls less than 13 years; boys less than 15 years) compared with healthy children of the same age. Older girls with JCA (13 years and over) were found to have increased HYP/Cr and DPD/Cr values compared with older healthy children
Lilleby *et al.*, 2005[169]	Case–control	70 children and young adults with childhood onset SLE, mean age 26.4 ± 9.9 years (range 9.8–49.3), 53 F, 17 M	77 healthy age- and sex-matched children, mean age 26.7 ± 10.0 years (range 9.6–49.6)	Serum OC, BALP, CTP, DPD	DPD was significantly higher in adults ⩾20 years than in controls but there was no difference for children <20 years. There were no significant differences in any other markers of bone turnover
Bianchi *et al.*, 1990[219]	Cohort, controlled, 1 year follow-up	36 children with JIA (13 pauciarticular mean age 7.9 years, 8 polyarticular mean age 9.4 years, 15 systemic mean age 11.4 years), 23 F, 13 M, 23 treated with corticosteroids	45 healthy children, 25 F, 20 M, mean age 9.6 years	Plasma ALP, OC, urinary HYP	At baseline plasma no significant differences in ALP/urinary HYP between JIA groups or controls. No variation in these parameters during follow-up. OC within normal range at baseline and no differences between disease groups. After 1 year OC decreased in all patients. Both ALP and OC correlated negatively with age
Reed *et al.*, 1990[220]	Cohort, 14 months follow-up	113 children with chronic rheumatic disease (37 polyarticular, 21 pauciarticular, 12 systemic, 13 systemic–polyarticular JIA, 13 juvenile dermatomyositis, 17 SLE), 1.5–21 years, 31 M, 82 F. 62 active, 23 inactive, 28 remitted during study		Serum OC	OC levels were reduced in those with active disease even before corticosteroid therapy. Those with inactive disease or whose disease remitted had normal OC levels despite use of corticosteroids. Reduced levels of OC were predictive of radial BMC in subsample. In those who had repeat OC measurements, changes (increase) observed only in those whose disease remitted

continued

Study	Design	Patients	Controls	All markers measured	Results
Lien *et al.*, 2005[174]	Cohort, follow-up 2 years	108 children with early JIA (5 systemic, 64 oligoarthritis, 30 polyarthritis RF negative, 3 polyarthritis RF positive, 3 spondylarthropathy, 3 psoriatic arthritis) mean age 10.1 ± 3.2 years, 45 M, 63 F, 35 ever treated with corticosteroids	108 healthy children matched for age, sex, race and county of residence, mean age 10.1 ± 3.2 years, 45 F, 63 M	Serum BALP and OC, serum ICTP, urinary DPD	BALP and OC were lower in patients at baseline and follow-up. ICTP and DPD in patients were higher at baseline but lower at follow-up. In patients with JIA, higher ICTP and bone-specific ALP were independent predictors of change in total body BMC from baseline to follow-up
Treatment with growth hormone					
Davies *et al.*, 1997[327]	Clinical trial, follow-up 1 year	18 prepubertal children with JIA and growth retardation, mean age 9.8 ± 2.0 years, 7 M, 11 F. Received recombinant human growth hormone for 1 year (either 12 or 24 IU/m^2/week)	18 healthy children, 10 F, mean age 8.5 ± 2.2 years, 8 M, mean age 8.5 ± 1.3 years	ALP, OC	At baseline healthy children had higher OC than JIA children. OC correlated with height (SD score). Mean OC level increased during treatment with growth hormone although it remained lower than the control values. Significant negative correlation between CRP and OC level
Touati *et al.*, 2000[221]	Cohort, follow-up 2 years	14 children with systemic JIA receiving chronic corticosteroid therapy. Mean age 9 years and 8 months, 8 M, 6 F. Treated for 1 year with growth hormone. Followed for a further 12 months		Serum ALP, OC, PICP, urinary PYD, DPD, HYP	Bone metabolism markers were normal at baseline. OC, PICP, HYP, PYD, DPD significantly increased during treatment and returned to pretreatment values after growth hormone was stopped. ALP increased significantly with treatment and remained significantly higher after 1 year without treatment. OC was best predictive variable for the growth response to growth hormone
Bechtold *et al.*, 2004[175]	Cohort, follow-up 4 years	11 prepubertal children with JIA (systemic or polyarticular receiving corticosteroids) and growth retardation, mean age 10.3 ± 2.0 years, 4 M, 7 F. Treated with growth hormone for 4 years		ALP, PICP, urinary DPD	Markers of bone formation (ALP, PICP) and resorption (DPD) increased significantly during treatment, indicating a high bone turnover. This was partly due to puberty. Increase in PICP and DPD correlated with the increase in mean vBMD. No correlation between markers of bone metabolism and disease activity

BALP, bone-specific alkaline phosphatase; HYP, hydroxyproline; HYP/Cr, hydroxyproline:creatinine ratio; PYD, pyridinoline; SEM, standard error of the mean; UrDPyr:Cr, urinary deoxypyridinoline:creatinine ratio.

Appendix 13

Search strategies for the review of fractures as an outcome measure

MEDLINE

1 (fracture$ adj10 (bone$ or vertebra$ or femur$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [33511]
2 FRACTURES/dt, ec, ep, et [Drug Therapy, Economics, Epidemiology, Etiology] [5929]
3 HUMERAL FRACTURES/ or FEMORAL NECK FRACTURES/ or TIBIAL FRACTURES/ or FEMORAL FRACTURES/ or RADIUS FRACTURES/ or HIP FRACTURES/ or SPINAL FRACTURES/ [37997]
4 1 or 2 or 3 [61622]
5 exp CHILD/ [1047913]
6 exp INFANT/ [642483]
7 exp ADOLESCENT/ [1065930]
8 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler or baby or babies or pediatric or paediatric).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [2144024]
9 5 or 6 or 7 or 8 [2144024]
10 Arthritis, Juvenile Rheumatoid/ [5946]
11 (arthriti$ adj3 (juvenile$ or child$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [7268]
12 (oligoarticular arthritis or oligoarthritis or polyarticular arthritis or polyarthritis or pauciarticular arthritis or systemic arthritis or psoriatic arthritis or enthesitis-related arthritis or undefined arthritis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [7712]
13 Arthritis, Rheumatoid/ [3348]
14 DERMATOMYOSITIS/ [4047]
15 juvenile dermatomyositis.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [360]
16 dermatomyositis.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [4780]
17 Lupus Erythematosus, Systemic/ [30344]
18 systemic lupus erythematosus.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [22157]
19 SLE.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [13584]
20 VASCULITIS/ [7478]
21 vasculitis.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [16553]
22 Connective Tissue Diseases/ [3083]
23 connective tissue disease$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] [6684]
24 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 [116866]
25 4 and 9 and 24 [112]

MEDLINE In-Process & Other Non-Indexed Citations

1 (fracture$ adj10 (bone$ or vertebra$ or femur$)).mp. [mp=title, original title, abstract, name of substance word] [804]
2 [FRACTURES/dt, ec, ep, et [Drug Therapy, Economics, Epidemiology, Etiology]] [0]
3 HUMERAL FRACTURES/ or FEMORAL NECK FRACTURES/ or TIBIAL FRACTURES/ or FEMORAL FRACTURES/ or RADIUS FRACTURES/ or HIP FRACTURES/ or SPINAL FRACTURES/ [0]
4 1 or 2 or 3 [804]
5 [exp CHILD/] [0]
6 [exp INFANT/] [0]
7 [exp ADOLESCENT/] [0]
8 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler or baby or babies or pediatric or paediatric).mp. [mp=title, original title, abstract, name of substance word] [16429]
9 5 or 6 or 7 or 8 [16429]
10 Arthritis, Juvenile Rheumatoid/ [0]
11 (arthriti$ adj3 (juvenile$ or child$)).mp. [mp=title, original title, abstract, name of substance word] [90]
12 (oligoarticular arthritis or oligoarthritis or polyarticular arthritis or polyarthritis or pauciarticular arthritis or systemic arthritis or psoriatic arthritis or enthesitis-related arthritis

or undefined arthritis).mp. [mp=title, original title, abstract, name of substance word] [118]
13 Arthritis, Rheumatoid/ [0]
14 DERMATOMYOSITIS/ [0]
15 juvenile dermatomyositis.mp. [mp=title, original title, abstract, name of substance word] [9]
16 dermatomyositis.mp. [mp=title, original title, abstract, name of substance word] [55]
17 Lupus Erythematosus, Systemic/ [0]
18 systemic lupus erythematosus.mp. [mp=title, original title, abstract, name of substance word] [374]
19 SLE.mp. [mp=title, original title, abstract, name of substance word] [270]
20 VASCULITIS/ [0]
21 vasculitis.mp. [mp=title, original title, abstract, name of substance word] [235]
22 Connective Tissue Diseases/ [0]
23 connective tissue disease$.mp. [mp=title, original title, abstract, name of substance word] [71]
24 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 [894]
25 4 and 9 and 24 [0]

EMBASE

1 (fracture$ adj10 (bone$ or vertebra$ or femur$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [37469]
2 Fracture/ [12842]
3 FRAGILITY FRACTURE/ or DISTAL TIBIA FRACTURE/ or STRESS FRACTURE/ or HUMERUS FRACTURE/ or ULNA FRACTURE/ or LEG FRACTURE/ or ARM FRACTURE/ or VERTEBRA FRACTURE/ or LIMB FRACTURE/ or RADIUS FRACTURE/ or TIBIA SHAFT FRACTURE/ or TIBIA FRACTURE/ or SPINE FRACTURE/ or PROXIMAL TIBIA FRACTURE/ [16497]
4 1 or 2 or 3 [49776]
5 exp Child/ [504807]
6 exp Infant/ [140532]
7 exp Adolescent/ [333406]
8 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler$ or baby or babies or pediatric or paediatric).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [812952]
9 5 or 6 or 7 or 8 [961123]
10 Juvenile Rheumatoid Arthritis/ [4657]
11 (arthritis adj3 (juvenile$ or child$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [6345]
12 ("oligoarticular arthritis" or oligoarthritis or "polyarticular arthritis" or polyarthritis or "pauciarticular arthritis" or "systemic arthritis" or "psoriatic arthritis" or "enthesitis-related arthritis" or "undefined arthritis").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [7339]
13 RHEUMATOID ARTHRITIS/ or CHRONIC ARTHRITIS/ or ARTHRITIS/ or PSORIATIC ARTHRITIS/ [61854]
14 DERMATOMYOSITIS/ [3525]
15 juvenile dermatomyositis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [343]
16 dermatomyositis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [3945]
17 Systemic Lupus Erythematosus/ [22696]
18 systemic lupus erythematosus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [25446]
19 SLE.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [11845]
20 VASCULITIS/ or SYSTEMIC VASCULITIS/ [10502]
21 vasculitis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [16954]
22 Connective Tissue Disease/ [3890]
23 connective tissue diseases.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] [1698]
24 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 [109753]
25 4 and 9 and 24 [175]

Appendix 14

Studies excluded from the review of fractures as an outcome measure

Study	Reason for exclusion
Maenpaa HM, Soini I, Lehto MU, Belt EA. Insufficiency fractures in patients with chronic inflammatory joint diseases. *Clin Exp Rheumatol* 2002;**20**:77–9	Did not distinguish adults and children
Murray KJ, Boyle RJ, Woo P. Pathological fractures and osteoporosis in a cohort of 103 systemic onset juvenile idiopathic arthritis patients. *Arthritis Rheum* 2000;**43**:S119	Conference abstract
Yee CS, Crabtree N, Skan J, Amft N, Bowman S, Situnayake D, *et al*. Prevalence and predictors of fragility fractures in systemic lupus erythematosus. *Ann Rheum Dis* 2005; **64**:111–13	Adults
Maenpaa H, Savolainen A, Lehto MUK, Belt EA. Multiple stress fractures in a young girl with chronic idiopathic arthritis. Extended case report. *Joint Bone Spine* 2001;**68**:438–42	Case report

Appendix 15

Summaries of studies included in the review of fractures as an outcome measure

Study	Design	Subjects	Controls	Results	Comments
Elsasser *et al.*, 1982[224]	Cohort study	63 children with JIA	For determination of normal BMD: 49 normal Swiss children, 28 healthy English children (children of staff or siblings of patients)	At entry, 9 children had at least one spinal crush fracture; during the ensuing 18 months, four developed further crush fractures. Five children with intact spines experienced a crush fracture during the same period. Association between fractures, corticosteroid therapy and also duration of bed rest	BMD measurements using CT densitometer. At baseline, 22 children had trabecular bone density values more than 2 SDs below normal. Seven of these children had crush fractures at baseline, four developed them during follow-up. One child had a normal BMD when diagnosed and subsequently developed crush fractures although BMD only fell by a small amount over 18 months
Varonos *et al.*, 1987[223]	Case-control	23 children with JIA treated with corticosteroids (19 systemic, 3 polyarticular, 1 pauciarticular persisting) with at least one radiographic vertebral fracture, age <16 years	23 children with JIA treated with corticosteroids (6 systemic, 5 polyarthritic, 10 pauciarticular becoming polyarthritis, 2 pauciarticular persisting), without evidence of vertebral fracture, age <16 years	Mean number of fractures in cases with fracture was 3.3 (range 1–15). No difference in age of onset between cases and controls, but fracture cases had started treatment with corticosteroids at earlier stage of disease. Inverse correlation between mean daily dose of corticosteroids and time to first vertebral collapse	

Appendix 16

Drugs and proprietary names used in the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D

Drug name	Proprietary names
Bisphosphonates	
Alendronic acid/alendronate/sodium alendronate	Fosamax, Onclast
Etidronic acid/disodium etidronate/etidronate	Didronel, Didronel PMO
Risedronic acid/risedronate sodium/risedronate	Actonel
Clodronic acid/disodium clodronate/clodronate[a]	Bonefos, Loron, Ostac
Pamidronic acid/disodium pamidronate/pamidronate[a]	Aredia
Calcium and vitamin D	
Vitamin D/calcitriol/calciferol/ergocalciferol/alfacalcidol/ colecalciferol/cholecalciferol/dihydrotachysterol	One-alpha, Rocaltrol, Calcijex, AT 10, Alfarol, Onealfa, Oxarol, AlfaD, Silkis, Tachyrol, Calderol, Delta-D, DHT, Hectorol, Hytakerol, Zemplar
Calcium/calcium gluconate/calcium lactate/calcium chloride	Adcal, Cacit, Calcichew, Calcium-500, Calcium-sandoz, Sandocal, Ostram, Phos-ex, Cal-citrate, Cal-lac, Calphron, Citracal, Neo-calglucon, Oyster calcium, Phos-ex, Phoslo, Posture, Prelief, Super citracal
Calcium and vitamin D	Adcal-D3, Cacit D3, Calceos, Calcichew D3, Calcichew D3 forte, Calfovit D3, Caltrate plus, Caltrate, haliborange calcium plus vitamin D, Osteocare, Porosis D, SPHP

[a] Drug not indicated for osteoporosis or not recommended for use in children but early searches indicated that it had been used in some studies and appropriate terms were added to search strategies.

Appendix 17

Search strategies for the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D

MEDLINE

1 (bisphosphonate$ or bis-phosphonate$ or biphosphonate$ or bi-phosphonate$ or diphosphonate$ or di-phosphonate$ or amino-bisphosphonate$).mp. [8972]
2 exp Diphosphonates/ [10635]
3 (alendronic acid or alendronate sodium or alendronate$ or onclast or fosamax or clodronic acid or disodium clodronate or clodronate$ or ostac or bonefos or loron or etidronic acid or disodium etidronate or etidronate$ or didronel or didronel PMO or pamidronic acid or disodium pamidronate or pamidronate$ or aredia or risedronic acid or risedronate sodium or risedronate$ or actonel).mp. [4762]
4 vitamin D.mp. [24193]
5 exp Vitamin D/ [26318]
6 (calciferol or ergocalciferol or alfacalcidol or one-alpha or calcitriol or rocaltrol or calcijex or colecalciferol or cholecalciferol or dihydrotachysterol or AT 10 or alfarol or onealfa or oxarol or alfaD or silkis or tachyrol or calderol or delta-D or DHT or hectorol or hytakerol or zemplar).mp. [1181703]
7 calcium.mp. [312920]
8 Calcium, Dietary/ [5897]
9 (calcium gluconate or calcium lactate or adcal or calcit or calcichew or calcium-500 or calcium sandoz or sandocal or calcium chloride or ostram or phos-ex or cal-citrate or cal-lac or calphron or citracal or neo-calglucon or oyster calcium or phos-ex or phoslo or posture or prelief or super citracal).mp. [52235]
10 (calcium and vitamin D).mp. [13431]
11 (adcal-D3 or cacit D3 or calceos or calcichew D3 or calcichew D3 forte or calfovit d3 or caltrate plus or caltrate or haliborange calcium plus vitamin D or osteocare or porosis D or SPHP).mp. [19]
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 [1486229]
13 Osteoporosis/ [19057]
14 corticosteroid induced osteoporosis.mp. [132]
15 (corticosteroid induced osteoporosis or glucocorticoid induced osteoporosis or glucocorticosteroid induced osteoporosis).mp. [478]
16 osteoporosis.mp. [30036]
17 (fracture$ adj10 (bone$ or vertebra$ or femur$)).mp. [31760]
18 (bone adj5 mass).mp. [8692]
19 (bone adj5 densit$).mp. [24283]
20 BMD.mp. [7583]
21 Bone Density/ [19290]
22 FRACTURES/dt, ec, ep, et [Drug Therapy, Economics, Epidemiology, Etiology] [5671]
23 osteogenesis imperfecta.mp [2745]
24 Osteogenesis imperfecta/ [2493]
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26 exp CHILD/ [1031968]
27 exp INFANT/ [63943]
28 exp ADOLESCENT/ [1048225]
29 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler or baby or babies or pediatric or paediatric).mp. [2109364]
30 26 or 27 or 28 or 29 [2109364]
31 12 and 25 and 30 [4118]

MEDLINE In-Process & Other Non-Indexed Citations

1 (bisphosphonate$ or bis-phosphonate$ or biphosphonate$ or bi-phosphonate$ or diphosphonate$ or di-phosphonate$ or amino-bisphosphonate$).mp. [203]
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4 vitamin D.mp. [353]
5 [exp Vitamin D/] [0]

6 (calciferol or ergocalciferol or alfacalcidol or one-alpha or calcitriol or rocaltrol or calcijex or colecalciferol or cholecalciferol or dihydrotachysterol or AT 10 or alfarol or onealfa or oxarol or alfaD or silkis or tachyrol or calderol or delta-D or DHT or hectorol or hytakerol or zemplar).mp. [31901]
7 calcium.mp. [3660]
8 Calcium, Dietary/ [0]
9 (calcium gluconate or calcium lactate or adcal or cacit or calcichew or calcium-500 or calcium sandoz or sandocal or calcium chloride or ostram or phos-ex or cal-citrate or cal-lac or calphron or citracal or neo-calglucon or oyster calcium or phos-ex or phoslo or posture or prelief or super citracal).mp. [377]
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12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 [35418]
13 Osteoporosis/ [0]
14 corticosteroid induced osteoporosis.mp. [4]
15 (corticosteroid induced osteoporosis or glucocorticoid induced osteoporosis or glucocorticosteroid induced osteoporosis).mp. [18]
16 osteoporosis.mp. [708]
17 (fracture$ adj10 (bone$ or vertebra$ or femur$)).mp. [636]
18 (bone adj5 mass).mp. [322]
19 (bone adj5 densit$).mp. [694]
20 BMD.mp. [438]
21 Bone Density/ [0]
22 FRACTURES/dt, ec, ep, et [Drug Therapy, Economics, Epidemiology, Etiology] [0]
23 osteogenesis imperfecta.mp [51]
24 Osteogenesis/imperfecta/ [0]
25 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 [1702]
26 [exp CHILD/] [0]
27 [exp INFANT/] [0]
28 [exp ADOLESCENT/] [0]
29 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler or baby or babies or pediatric or paediatric).mp. [15966]
30 26 or 27 or 28 or 29 [15966]
31 12 and 25 and 30 [64]

EMBASE

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5 vitamin D.mp. [18543]
6 exp Vitamin D/ [30175]
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8 calcium.mp. [192606]
9 Calcium Intake/ [3594]
10 (calcium gluconate or calcium lactate or adcal or cacit or calcichew or calcium-500 or calcium sandoz or sandocal or calcium chloride or ostram or phos-ex or cal-citrate or cal-lac or calphron or citracal or neocalglucon or oyster calcium or phos-ex or phoslo or posture or prelief or super citracal).mp. [15844]
11 (calcium and vitamin D).mp. [9475]
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13 1 or 2 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 [1159122]
14 OSTEOPOROSIS/ [25372]
15 corticosteroid induced osteoporosis.mp. [116]
16 (corticosteroid-induced osteoporosis or glucocorticoid induced osteoporosis or glucocorticosteroid induced osteoporosis).mp. [765]
17 osteoporosis.mp. [30364]
18 (fracture$ adj10 (bone$ or femur$ or vertebra$)).mp. [29770]
19 (bone adj5 mass).mp. [8412]
20 (bone adj5 densit$).mp. [16385]
21 BMD.mp. [7494]
22 Bone Density/ [16199]
23 Fracture/et, pc, dt, ep, th [2831]

24 osteogenesis imperfecta.mp [1937]
25 Osteogenesis Imperfecta/ [1777]
26 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 [68593]
27 exp Child/ [494479]
28 exp Infant/ [137892]
29 exp Adolescent/ [324847]
30 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler$ or baby or babies or pediatric or paediatric).mp. [716027]
31 27 or 28 or 29 or 30 [927737]
32 13 and 26 and 31 [3032]

Cochrane Library

1 (bisphosphonate* or bis-phosphonate* or biphosphonate* or bi-phosphonate* or diphosphonate* or di-phosphonate*)
2 DIPHOSPHONATES explode all trees (MeSH)
3 ((alendronic next acid) or (alendronate next sodium) or alendronate or onclast or fosamax or (clodronic next acid) or (disodium next clodronate) or clodronate or ostac or bonefos or loron or (etidronic next acid) or (disodium next etidronate) or etidronate or didronel or (didronel next pmo) or (pamidronic next acid) or (disodium next pamidronate) or pamidronate or aredia or (risedronic next acid) or risedronate or sodium or risedronate or actonel)
4 (vitamin next d)
5 (calciferol or ergocalciferol or alfacalcidol or one-alpha or calcitriol or rocaltrol or calcijex or colecalciferol or cholecalciferol or dihydrotachysterol or alfarol or onealfa or oxarol or alfad or silkis or tachyrol or calderol or delta-d or dht or hectorol or hytakerol or zemplar)
6 calcium
7 CALCIUM DIETARY single term (MeSH)
8 ((calcium next gluconate) or (calcium next lactate) or adcal or cacit or calcichew or (calcium next sandoz) or sandocal or (calcium next chloride) or ostram or phos-ex or cal-citrate or cal-lac or calphron or citracal or neo-calglucon or (oyster next calcium) or phos-ex or phoslo or posture or prelief or (super next citracal) or calcium*)
9 (calcium and (vitamin next d))
10 (adcal* or caci* or calceos or calcichew* or calfovit* or caltrate or plus or caltrate or (haliborange next calcium next plus next vitamin next d) or osteocare or (porosis next d) or sphp)
11 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
12 OSTEOPOROSIS explode all trees (MeSH)
13 ((corticosteroid-induced next osteoporosis) or (corticosteroid next induced next osteoporosis) or (glucocorticoid next osteoporosis) or (glucocorticosteroid next induced next osteoporosis))
14 osteoporosis
15 (idiopathic next osteoporosis)
16 (osteogenesis next imperfecta)
17 OSTEOGENESIS IMPERFECTA explode all trees (MeSH)
18 (#12 or #13 or #14 or #15 or #16 or #17)
19 CHILD explode all trees (MeSH)
20 ADOLESCENT explode all trees (MeSH)
21 INFANT explode all trees (MeSH)
22 (juvenile* or child or children or infant* or minor* or adolescent* or toddler or baby or babies or pediatric or paediatric)
23 (#19 or #20 or #21 or #22)
24 (#11 and #18 and #23)

ISI Web of Science Conference Proceedings

1 TS=(arthritis SAME juvenile)
2 TS=(bone SAME mineral)
3 TS=osteoporosis
4 #2 OR #3
5 #1 and #4

Appendix 18

Studies excluded from the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D

Study	Reason for exclusion
Acott PD, Crocker JF, Wong JA. Decreased bone mineral density in the pediatric renal transplant population. *Pediatr Transplant* 2003;**7**:358–63	No intervention
Arekat MR, And G, Lemke S, Moses AM. Dramatic improvement of BMD following vitamin D therapy in a bone marrow transplant recipient. *J Clin Densitom* 2002;**5**:267–71	Osteoporosis associated with bone marrow transplant
Aris RM, Lester GE, Renner JB, Winders A, Denene BA, Lark RK, *et al*. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. *Am J Resp Crit Care Med* 2000;**162**:941–6	Osteoporosis associated with cystic fibrosis in adults
Bin-Abbas BS, Al Ashwal AA, Al Zayed ZS, Sakati NA. Radiological features of bisphosphonate therapy in children with osteogenesis imperfecta. *Saudi Med J* 2004; **25**:1772–3	Osteoporosis associated with acute lymphoblastic anaemia
Bourges O, Dorgeret S, Alberti C, Hugot JP, Sebag G, Cezard JP. Low bone mineral density in children with Crohn's disease. *Arch Pediatr* 2004;**11**:800–6	No intervention
Devogelaer JP, Malghem J, Maldague B, Nagant de Deuxchaisenes C. Radiological and absorptiometric manifestations of bisphosphonate treatment with APD in a child suffering from osteogenesis imperfecta. In: Christiansen C, Johansen JS, Riis BJ, editors. *Osteoporosis*. Viborg: Norhaven; 1987. pp. 953–5	Also published as Devogelaer *et al*., 1987[270]
Devogelaer JP, Nagant D. Use of pamidronate in chronic and acute bone loss conditions. *Medicina (Mex)* 1997;**57** Suppl 1:101–8	Also published as Devogelaer *et al*., 1987[270]
Di Leo G, Martelossi S, Berti I, Barbi E, Ventura A. Bone disease in young patients on long-term parenteral nutrition: the role of pamidronate. *Rivista Italiana di Nutrizione Parenterale Ed Enterale* 2002;**20**:S60–3	Osteoporosis associated with total parenteral nutrition
Di Leo G, Neri E, Ventura A. Using pamidronate for osteoporosis. *J Pediatr* 2004; **144**:689–90	Abstract – published as Di Leo, 2002 (see above)
El Husseini AA, El Agroudy AE, El Sayed MF, Sobh MA, Ghoneim MA. Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. *Pediatr Transplant* 2004;**8**:357–61	Osteoporosis associated with renal transplant
Elhusseini A, Elagroudy A, Elsayed M, Sobh M, Ghoneim M. Treatment of bone loss in renal transplant children and adolescents. *World Congress of Nephrology* 2003;T818.	Abstract – published as El Husseini, 2004 (see above)
Geusens P, Menten J, Vosse D, Vanhoof J, van der Linden S. Recovery from severe glucocorticoid-induced osteoporosis in an adolescent boy. *J Clin Densitom* 2001;**4**:389–94	Osteoporosis associated with tumour of mesencephalon
Geusens P, Menten J, Vosse D, Vanhoof J, van der Linden S. Recovery from severe glucocorticoid-induced osteoporosis in an adolescent boy. *J Clini Densitom* 2001;**4**:389–94	Juvenile idiopathic osteoporosis
Glorieux FH, Travers R, Lanoue G. Pamidronate treatment in children with fibrous dysplasia and osteogenesis imperfecta. *Bone* 1995;**17**:611	Abstract – published as Glorieux *et al*., 1998[248]
Hoekman K, Papapoulos SE, Peters AC, Bijvoet OL. Characteristics and bisphosphonate treatment of a patient with juvenile osteoporosis. *J Clin Endocrinol Metab* 1985;**61**:952–6	Juvenile idiopathic osteoporosis
Illum NO. Bisphosphonate treatment of children and adolescents. *Ugeskr Laeger* 2003; **165**:454–6	Review

continued

Study	Reason for exclusion
Lanes R, Toledo T, Obregon O. Calcitonin and calcium therapy in an infant with osteogenesis imperfecta congenita. *J Am Coll Nutr* 1983;**2**:101–6	Intervention with calcitonin
Leroy D, Garabedian M, Guillozo H. The development of serum concentrations of vitamin D metabolites (25-(OH)D, 24,25-(OH)2D3 1,25-(OH)2D) in a case of idiopathic juvenile osteoporosis. *Archives Francaises de Pediatrie* 1981;**38**:165–70	No intervention
Levis S, Gruber HE, Cohn D, Howard GA, Roos BA. Juvenile osteoporosis treated with pamidronate. *Calcif Tissue Int* 1993;**52**:S41	Juvenile idiopathic osteoporosis
Maenpaa H, Savolainen A, Lehto MUK, Belt EA. Multiple stress fractures in a young girl with chronic idiopathic arthritis. Extended case report. *Joint Bone Spine* 2001;**68**:438–42	Intervention with calcitonin
Marder HK, Tsang RC, Hug G, Crawford AC. Calcitriol deficiency in idiopathic juvenile osteoporosis. *Am J Dis Child* 1982;**136**:914–17	Juvenile idiopathic osteoporosis
Marder HK, Tsang RC, Hug G, Crawford AC. Low plasma calcitriol levels and response to calcitriol supplementation in idiopathic juvenile osteoporosis (IJO). *Pediatr Res* (4 II) 1982; 16	Abstract – published as Marder *et al*., 1982 (see above)
Ozaki D, Shirai Y, Nakayama Y, Yoshihara K, Huzita T. Multiple fish vertebra deformity in child with systemic lupus erythematosus: a case report. *J Nippon Med Sch* 2000;**67**:271–4	Intervention with elcatonin
Rosskamp R, Sell G, Emons D, Issa S, Burmeister W. Idiopathic juvenile osteoporosis – report of 2 cases. *Klin Padiatr* 1987;**199**:457–61	Juvenile idiopathic osteoporosis
Saggese G, Bertelloni S, Baroncelli GI, Di Nero G, Perri G. Juvenile idiopathic osteoporosis. Five case reports, evaluation of 1,25-dihydroxyvitamin D3 treatment and review of literature. *Riv Ital Pediatr* 1991;**17**:542–54 (in Italian)	Also published as Saggese *et al*., 1991
Saggese G, Bertelloni S, Baroncelli GI, Perri G, Calderazzi A. Mineral metabolism and calcitriol therapy in idiopathic juvenile osteoporosis. *Am J Dis Child* 1991;**145**:457–62	Juvenile idiopathic osteoporosis
Sambrook PN, Kotowicz M, Nash P, Styles CB, Naganathan V, Henderson-Briffa KN, *et al*. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. *J Bone Miner Res* 2003;**18**:919–24	Corticosteroid-induced osteoporosis in adults
Sbyrakis S, Mengreli C, Cote GB, Morakis A. Vitamin D and related research in osteogenesis imperfecta. *Prog Clin Biol Res* 1982;**104**:367–76	No intervention
Sellers E, Sharma A, Rodd C. The use of pamidronate in three children with renal disease. *Pediatr Nephrol* 1998;**12**:778–81	Osteopenia associated with renal disease
Sellers E, Sharma A, Rodd C. The use of pamidronate in three children with renal disease. *Pediatr Nephrol* 1998;**12**:778–81	Osteoporosis associated with Menkes disease
Smith R. Idiopathic juvenile osteoporosis: experience of twenty-one patients. *Br J Rheumatol* 1995;**34**:68–77	No intervention
Thearle M, Horlick M, Bilezikian JP, Levy J, Gertner JM, Levine LS, *et al*. Osteoporosis: an unusual presentation of childhood Crohn's disease. *J Clin Endocrinol Metab* 2000;**85**:2122–6	Osteoporosis associated with Crohn's disease
Vogelsang H, Ferenci P, Resch H, Kiss A, Gangl A. Prevention of bone mineral loss in patients with Crohn's disease by long-term oral vitamin D supplementation. *Eur J Gastroenterol Hepatol* 1995;**7**:609–14	Osteoporosis associated with Crohn's disease in adults
Williams CJC, Smith RA, Ball RJ, Wilkinson H. Hypercalcaemia in osteogenesis imperfecta treated with pamidronate. *Arch Dis Child* 1997;**76**:169–70	Treatment of hypercalcemia
Zacharin M, Cundy T. Osteoporosis pseudoglioma syndrome: treatment of spinal osteoporosis with intravenous bisphosphonates. *J Pediatr* 2000;**137**:410–15.	Osteoporosis associated with pseudoglioma syndrome

Appendix 19

Studies included in the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D: characteristics

Study	Design	Intervention group	Age and sex	Intervention	Control group	Age and sex	Concomitant treatment(s)	Outcomes	Follow-up
Bisphosphonate studies including children with JIA									
Rudge *et al.*, 2005[229]	RCT	11 children: **JIA (2)**, SLE (6), autoimmune haemolytic anaemia (1), inflammatory bowel disease (1), renal transplantation (1). 10 completed study	Mean 9.9 ± 2.8 years, 6 F, 5 M	Oral alendronate 1–2 mg/kg body weight once weekly	11 children: **JIA (5)**, dermatomyositis (4), inflammatory bowel disease (1), cystic fibrosis (1). 8 completed study. Received placebo	Mean 8.5 ± 4.4 years, 7 F, 4 M	Continued corticosteroid treatment. Calcium supplements not prescribed but subjects with low calcidiol concentrations given supplementary vitamin D	BMD (DXA) lumbar spine and mid femoral shaft at 0, 6 and 12 months, markers of bone turnover monthly, fractures	1 year
Acott *et al.*, 2005[230]	Prospective cohort, controlled	17 children: **JRA (1)**, dermatomyositis (6), polychondritis (1), post-renal transplant (2), rapidly progressive glomerulonephritis (5), nephrotic syndrome (2). All had fractures while on long-term corticosteroid therapy	8 F, 9 M	Pamidronate i.v. 1 mg/kg/dose (max. 90 mg) once every 2 months for 1 ($n = 15$) or 2 years ($n = 2$)	17 children. Matched for disease and corticosteroid exposure. Received standard treatment	Matched for age and sex	Calcium and vitamin D supplementation. All children except those with nephrotic syndrome continued treatment	BMD (DXA) lumbar spine L1–L4, markers of bone turnover at 6, 12, 18, 24 and 36 months after discontinuation of pamidronate, fractures	36 months
Bianchi *et al.*, 2000[231]	Prospective cohort, controlled	38 children: **systemic JIA (7)**, **polyarticular JIA (9)**, SLE (11), dermatomyositis (6), Bechet's syndrome (2), Wegener's granulomatosis (1), undefined connective tissue disease (2)	Mean age 12.8 ± 3.6 years (SD), 26 F, 12 M [Tanner stage 1 (10), 2 (7), 3 (5), 4 (3), 5 (13)] (13 menarche)	Oral alendronate: 5 mg daily for body weight ≤20 kg, 10 mg daily for >20 kg	38 children: **19 JIA**, 13 SLE, 6 dermatomyositis. Less severe disease not requiring corticosteroid therapy, no fractures. Tanner stage 1 (11), 2 (6), 3 (5), 4 (5), 5 (11) (11 menarche). Received standard treatment	Matched for age [12.3 ± 3.9 years (SD)] and sex (26 F, 12 M)	Continued usual treatment including corticosteroids. Dietary calcium intake increased up to recommended daily average but no supplements. No vitamin D deficit noted	BMD (DXA) lumbar spine L2–L4 at baseline, 6 and 12 months, markers of bone turnover, radiographs after 6 months in prepubertal children	1 year

continued

Study	Design	Intervention group	Age and sex	Intervention	Control group	Age and sex	Concomitant treatment(s)	Outcomes	Follow-up
Lepore *et al.*, 1991[232]	Prospective cohort, controlled	**JCA (7)**	Not stated	Clodronate, oral 1200 mg/day	**JCA (6)**. Received standard treatment		Not stated	BMD (CT scan D12, L1, L2, L3) at baseline and after 1 year	1 year
Noguera *et al.*, 2003[233]	Case series	10 children with rheumatic diseases and glucocorticoid-induced osteoporosis: **JIA (8)**, SLE (1), dermatomyositis (1)	Mean 11.1 ± 4.7 years, 8 F, 2 M	Pamidronate, i.v. 2–4 mg/kg body weight, cycle repeated every 6 months	None		No other treatments related to calcium/phosphate metabolism allowed, no diet restrictions	Clinical, radiological, BMD lumbar spine (DXA), markers of bone turnover: follow-up at every treatment cycle	4–12 cycles (2–6 years)
Cimaz *et al.*, 2002[234]	Case series	45 children: **systemic JIA (8)**, **polyarticular JIA (10)**, SLE (14) dermatomyositis (7), other (6)	Mean 12.9 ± 3.8 years (SD), range 5–18, 31 F, 14 M [Tanner stage T1/T2 (20), T3 (6) T4 (4) T5 (15)]	Oral alendronate 5 mg/kg daily for body weight <20 kg and 10 mg/kg for body weight ⩾20 kg	None		Continued with usual treatments including corticosteroids	Markers of bone turnover at baseline, 6 and 12 months. Calcium and phosphate every 3 months. BMD (DXA). Lumbar spine L2–L4 measured every 6 months	1 year
Gandrud *et al.*, 2003[235]	Case series	11 children: **JIA (1)**, corticosteroid-induced osteoporosis (4), OI (6)	Mean 9.9 ± 3.7 years, 7 F, 4 M	Pamidronate infusion, 1 mg/kg once every 3 months (max. 30 mg)	None		Continued with corticosteroid treatment	Spinal L2–L2 BMD, also femoral, neck, hip and whole body (DXA) at baseline, 6, 12, 24 and 305 months, fractures, markers of bone density	3–30 months

continued

Study	Design	Intervention group	Age and sex	Intervention	Control group	Age and sex	Concomitant treatment(s)	Outcomes	Follow-up
Gattinara *et al.*, 2000[236]	Case series	25 children with rheumatic disease and long-term corticosteroid treatment: **systemic JCA (7)**, **polyarticular JCA (11)**, **pauciarticular JCA (4)**, SLE (3)	Mean 15.6 years, (range 7.8–25.0), 6 M, 19 F	Etidronate oral, 150–300 mg/day for 15 days followed by calcium citrate 0.5–1.0 g/day for 75 days on a cyclic course	None		All receiving 25-hydroxycholecalciferol. Continued with corticosteroid treatment	Lumbar spine BMD (DXA)	6–36 months
Brumsen *et al.*, 1997[239]	Case series	12 children: **JRA (1)**, idiopathic juvenile osteoporosis (1), idiopathic osteoporosis (5), OI (4), mitochondrial myopathy (1)	JIA: 10.7 years. (pubertal stage P1M1) F All children: mean 14.1 ± 2.2 years	JIA: i.v. infusion of pamidronate 7.5 mg daily for 18 days, then oral pamidronate 300 mg/day All: oral and/or intravenous pamidronate, range of doses. Oral olpadronate	None			Markers of bone turnover, BMD (DPA until 1990 then DXA), spine L1–L4 and femoral neck, radiology, growth, clinical response, bone histology (6 children)	6 years
Shaw *et al.*, 2000[240]	Case series	5 children: **JIA (1)**, Cushing's syndrome (1), OI (1), liver transplant (1), idiopathic juvenile osteoporosis (1)	JIA: 10 years F All children: 10–15 years, 4 F, 1 M	I.v. infusion of pamidronate, courses every 3 months. Total dose over 1 year range 0.5–12 mg/kg	None		JIA children were receiving oral prednisolone	BMD (DXA) lumbar spine L2–L4 at baseline and after 1 year	1 year

continued

Study	Design	Intervention group	Age and sex	Intervention	Control group	Age and sex	Concomitant treatment(s)	Outcomes	Follow-up
Fernandes *et al.*, 2004[243]	Case series	2 children: **JIA (1)**, SLE (1)	Child 1: 10 years Child 2: 14 years 2 M	Alendronate oral 10 mg/day	None		Not stated	Child 1: X-rays before and 4, 12, 19 and 20 months after starting treatment, densitometry (DXA, spine and whole body) before and 5 months after stopping treatment Child 2: densitometry (DXA spine and whole body) before treatment and at 9 months, X-rays before treatment and at 10 and 21 months	Child 1: 25 months Child 2: 21 months
Bisphosphonate studies in connective tissue disease not including children with JIA									
Bardare *et al.*, 2000[237]	Case series	6 children with corticosteroid induced osteoporosis: SLE (5), dermatomyositis (1)	Mean 15.7 years (range 10.9–18.1), 5 F, 1 M	Alendronate oral 10 mg/day	None		Continued with corticosteroid treatment	Lumbar spine BMD (DXA) L1–L4 every 6 months	2 years
Falcini *et al.*, 1996[238]	Case series	4 children with rheumatic disease or drug-induced osteoporosis: post-streptococcal (1), polyarteritis (1), lupus-like syndrome (1), juvenile dermatomyositis (1)	Mean 10 years 6 months, range 6–13 years, 4 F	Alendronate infusion 3.25 mg/day for 3 consecutive days, second course 3 months later	None		Calcium 1 g/day and vitamin D3 0.5 μg/day. Continued with corticosteroid treatment	BMD (DXA) lumbar spine L2–L4 at baseline and 12-month intervals, markers of bone turnover at baseline, radiology at baseline and after 6 months	1 year

continued

Study	Design	Intervention group	Age and sex	Intervention	Control group	Age and sex	Concomitant treatment(s)	Outcomes	Follow-up
Bayer *et al.*, 2002[241]	Case series	9 children: corticosteroid-induced osteoporosis (3) OI type Ia, Ib, IV (6)	Mean 12.3 ± 1.7 years, 7 M, 2 F	Alendronate oral 5 or 10 mg/day	None		Calcium and vitamin D	BMD, spine and total body	12.9 ± 1.5 months
Chlebna-Sokol *et al.*, 2003[242]	Case series	45 children: secondary osteoporosis (13/15) or osteopenia (2/15), primary osteoporosis (16/30) or osteopenia (2/30)	Range 6.5–18 years, 28 M, 17 F	Bisphosphonates (5)	None		Calcium and vitamin D (all)	BMD (DXA), markers of bone turnover at baseline, 6 and 12 months	6 months to 4 years
Oliveri *et al.*, 1996[244]	Case report	Dermatomyositis (1)	8 years, F	Oral pamidronate 4 mg/day	None		Calcium and vitamin D, diltiazem for calcinosis, azathioprine, methylprednisolone	BMD (DXA, spine and whole body) at baseline and after 21 months, markers of bone turnover, growth	21 months
Calcium and/or vitamin D studies including children with JIA									
Warady *et al.*, 1994[245]	Cohort, controlled, cross-over design	12 children met study criteria, 10 participated: **systemic JRA (4)**, **polyarticular JRA (2)**, SLE (2), mixed connective tissue disease (2)	Mean 13.1 years, (range 10.9–18.0), 7 F, 3 M (6 menarche)	Calcium carbonate 500–1000 mg and vitamin D 400 IU daily	Cross-over design: children received 6 months of supplementation then 6 months of placebo (or vice versa)	As for children receiving intervention	Continued corticosteroid treatment	BMD (DPA for spine L2–L4, SPA for forearm) at baseline, after supplementation and after withdrawal of supplementation, markers of bone turnover, food records, sunshine survey	6 months with supplementation, 6 months without supplementation
Reed *et al.*, 1991[251]	Case series	**Polyarticular JRA (13)**	5–18 years, 12 F, 1 M	25-hydroxyvitamin D 1–2 μg/kg/day	None		7 received corticosteroid treatment	BMD in distal one-third of the non-dominant radius (SPA), calcium, osteocalcin, parathyroid hormone and vitamin D metabolite levels	1 year

Appendix 20

Studies included in the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D: results

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Bisphosphonate studies including children with JIA					
Rudge *et al*., 2005[229]	Mean lumbar spine aBMD was the same in both groups at baseline. Mean lumbar spine BMC increased from 17.5 to 20.9 g ($p = 0.012$) after 12 months in the alendronate group and from 16.2 to 18.3 g ($p = 0.062$) in the placebo group. BMAD increased from 0.266 to 0.307 g/cm^3 ($p = 0.013$) in the alendronate group and from 0.255 to 0.276 g/cm^3 ($p = 0.156$) in the placebo group. Mean femoral shaft BMC increased from 4.06 to 4.24 g ($p = 0.064$) after 12 months in the alendronate group from 3.98 to 4.10 g ($p = 0.220$) in the placebo group. BMAD increased from 1.06 to 1.09 g/cm^3 ($p = 0.434$) in the alendronate group and from 1.03 to 1.04 g/cm^3 ($p = 0.675$) in the placebo group	*N*-telopeptide/creatinine ratio decreased significantly in the alendronate group after 12 months (299 to 148, $p = 0.007$) but not in the placebo group (303 to 301)	One subject in control group sustained a fracture	Well tolerated. No subjects discontinued treatment because of side-effects	
Acott *et al*., 2005[230]	The control group had higher baseline BMD than the pamidronate children. During treatment with pamidronate, lumbar spine *Z*-scores significantly increased from baseline ($F = 11.27$, $p = 0.0057$), pamidronate vs controls mean ± SD: 0–6 months 0.27 ± 0.14 vs –0.82 ± 0.31; 0–12 months 0.63 ± 0.17 vs –0.46 ± 0.27; 0–18 months 0.55–0.32 vs 0.17 ± 0.27; 0–24 months 0.15 ± 0.21 vs –0.23 ± 0.22; 0–30 or 36 months 0.77 ± 0.71 vs –0.68 ± 0.25). Lumbar spine BMD *Z*-score increased in rheumatology and renal children treated with pamidronate but decreased in the control group for up to 36 months after stopping treatment. At 6 months the change was 0.4 for rheumatology ($p < 0.05$) vs 0.3 for renal vs –0.8 for control children; at 12 months, 1.1 ($p < 0.01$) vs 0.6 vs –0.5; at 18 months 0.7 ($p < 0.01$) vs 0.5 vs 0.2; at 24 months 0.6 vs 0.2 vs –0.25; at 36 months 1.25 ($p < 0.01$) vs 0.8 vs –0.7)	BALP (37.7 ± 4.6 mcg/L) and *N*-telopeptide/creatinine ratio (170.3 ± 27.3 μg bone collagen equivalent per mmol creatinine) did not change significantly during treatment	Child with JIA had recurrence of a thoracic compression fracture 1 year after discontinuation of pamidronate	Three children had transient flu-like illness 24 hours after first pamidronate infusion – treated with symptomatic care and did not recur. Two children had persistence of hypercalciuria while treated with pamidronate which was responsive to hydrochlorothiazide therapy	Resolution of skeletal pain in all children within 48 hours of starting pamidronate treatment

continued

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Bianchi *et al.*, 2000[231]	Children: baseline BMD Z-scores –1.6 to –5.3. After 1 year mean increase BMD ± SD = 14.9 ± 9.8%, $p < 0.002$, compared with baseline. 13 children (34%) achieved Z-score >–1 (–0.8 to 0). Disease duration and corticosteroid dose correlated with BMD at baseline and change in BMD after treatment. Controls: mean BMD increase 2.6 ± 5% (ns), 15 children (40%) had a decrease. Results adjusted for body size	In the alendronate group, serum BALP decreased by mean ± SD of 16.5 ± 10.8%, urinary excretion NTX decreased by 27 ± 16.5%. In the control group, ALP increased from 223 ± 180 to 299 ± 157 units/L, NTX was not evaluated	No new fractures in alendronate children. Incidence of fractures in control children not reported	Occasional transient gastrointestinal irritation reported with alendronate. One case of oesophageal erosions, which healed on stopping treatment	Sclerotic lines appeared in metaphyses of the alendronate group. Height increased by mean ± SD 4.3 ± 3.5 cm in the alendronate group. For prepubertal children, the yearly increase was 2.9 ± 1.2 during the study compared with 2.8 ± 1.1 during the year before the study
Lepore *et al.*, 1991[232]	Children: mean BMD increased from 129 to 134 mg/cm^3 (8% increase) Controls: from 123 to 115 mg/cm^3 (7% decrease)	Not evaluated/reported	Not evaluated/reported	One child stopped treatment because of gastrointestinal side-effects. Serum and urinary calcium levels did not change substantially. One child showed a high calcium/creatinine urinary ratio. No haematological abnormalities observed	

continued

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Noguera *et al.*, 2003[233]	Progressive increase in vertebral size. Before treatment *Z*-scores –1.87 to –4.73. After treatment mean *Z*-score for 7 children improved from –3.76 to –1.91 ($p < 0.02$) (range of improvement 2–131%). In 3 children the *Z*-score worsened (–7, –14, –29%)	Levels of serum ALP and OC were normal before treatment, no significant changes during the study	Not evaluated/reported	In all children, hyperthermia occurred in at least one of the infusion cycles, managed with paracetamol. Mild abdominal pain, nausea and vomiting observed in 5 children after first infusion, prevented with ondansetron in subsequent cycles. Mild transient asymptomatic hypolcalcaemia after infusion in some children. No changes in serum electrolytes, haemoglobin levels, liver and renal function tests or urine calcium/creatinine ratio	Progressive subjective reduction in chronic bone pain and disability in daily life, no significant change in linear growth rate
Cimaz *et al.*, 2002[234]	Median change in *Z*-score = 34.08%, $p < 0.001$, mean absolute change 0.87 ± 0.57, $p < 0.001$. Results adjusted for body size	Statistically significant decrease in bone markers after 6 months of treatment, which continued throughout 12 months: median change NTX –40.27% ($p = 0.001$), PYD –29% ($p < 0.001$), BALP –40.77% ($p = 0.011$), OC –38.51% ($p = 0.006$)	Not evaluated/reported	Not reported	

continued

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Gandrud *et al.*, 2003[235]	Baseline BMD range 0.307–0.506 g/cm^2, *Z*-scores –2.6 to –4.46; BMAD 0.054–0.131 g/cm^3, *Z*-scores –1.356 to –4.660. Absolute spinal BMD increased in 8/9 children. Spinal BMD *Z*-scores improved in 5 children with serial *Z*-scores: mean increase 1.260 ± 0.943 (0.287 to 2.430). Mean annual gain in BMAD = 15.1 ± 18.1%. Mean increase in BMAD *Z*-score = 1.403 ± 1.209. BMD at other sites improved: mean annualised gain = 13.6 ± 11.0% at femoral neck, 17.7 ± 17.1% at hip, 5.6 ± 3.8% for whole body	Serum ALP levels fluctuated in several children without a noticeable trend	38 fractures in 10 children during year before treatment (12 in corticosteroid-induced osteoporosis children), 2 fractures in first year of treatment (0 for corticosteroid-induced osteoporosis children)	All 11 children experienced adverse effects after first infusion: fever, muscle aches (6), nausea (4), fatigue (3), bone pain (2). One child hospitalised for vomiting and dehydration. Less frequent and milder symptoms with subsequent infusions. No significant biochemical or haematological abnormalities during treatment	Linear growth velocity and weight normal in all children except one. Increased strength and reduced bone pain
Gattinara *et al.*, 2000[236]	Mean (SD) change in BMD in year before start of treatment was –6.5% (5.0) (range –17.9 to 3.4). After 6 months: 3.4% (4.7) (–7.5 to 10.2) ($p < 0.0001$). After 12 months (20 children): 3.5% (6.1) (–4.4 to 19.2) ($p = 0.005$). After 24 months (14 children): 13.8% (11.8) (–1.2 to 29.6) ($p = 0.004$). After 36 months (11 children): 4.5% (11.8) (–16.1 to 15.5) ($p = 0.05$). A significant difference was seen with expected values in year before treatment but not after 6, 12, 24 and 36 months of treatment	Not evaluated/reported	Not evaluated/reported	Not reported	
Brumsen *et al.*, 1997[239]	JIA (1 child): BMD lumbar spine at baseline *Z*-score = –3.7, increased with treatment to –1.1, increase of 2.6. *T*-score was –1.44 at stopping treatment. For all 12 children BMD increased at all sites: for spine, BMD *Z*-score increased by between 0.5 and 3.0	ALP and urinary HYP secretion decreased progressively in all children; final values were at the upper part of the normal adult range		1 child reported nausea which did not need treatment stopping. Transient flu-like symptoms in 8 children. Transient decrease in lymphocyte count. No long-term changes in any haematological or biochemical parameters	Radiology: skeletal maturation proceeded normally. Bone histology normal. Growth: normal during treatment, catch up growth before puberty. Clinical response: children (except two) who were immobilised were able to walk within a few weeks after starting therapy

continued

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Shaw *et al.*, 2000[240]	JIA (1 child): baseline BMD = 0.444 g/cm^2, SD score (SDS) –3.5. After 1 year, BMD = 0.556 g/cm^2, SDS –3.0, change 26%. All children: baseline BMD 0.246–0.810 g/cm^2, –2.1 to –6.8 SDS. After 1 year 0.378–1.08 g/cm^2, –6.2 to 0.25 SDS, change 26–54%	Not evaluated/reported	No further vertebral fractures	3 children experienced an acute-phase reaction after the first infusion (fever, aches and pains), which settled within 24 hours and was treated symptomatically	
Fernandes *et al.*, 2004[243]	Child 1: no change in *Z*-score at 7, 13 and 25 months. Scores not reported. Child 2: authors stated a substantial improvement in *Z*-score at 9 months but effect size not reported	Not evaluated/reported	Not evaluated/reported	Not reported	Growth rate normal. Children clinically well. Child 1: authors stated metaphyseal bands became progressively wider and denser (size of change not reported). Child 2: authors stated wide dense metaphyseal bands after 10 months, findings secondary to osteoporosis unchanged. At 21 months, there was significant decrease in thickness of metaphyseal bands interwoven with streaks of normal-appearing bone (size of change not reported)
Bisphosphonate studies in connective tissue disease not including children with JIA					
Bardare *et al.*, 2000[237]	After 12 months: mean increase in BMD 19.1% (range 4.9–38%). After 24 months (4 children): mean improvement 6%	Not evaluated/reported	Not evaluated/reported	No relevant side-effects	Dose of corticosteroid could be reduced in 1 child, stable in 4 children, increased in 1 child. BMD fell when alendronate stopped

continued

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Falcini *et al.*, 1996[238]	Mean baseline BMD = 0.654 g/cm^2 (range 0.595–0.722 g/cm^2). After 12 months, mean = 0.764 g/cm^2 (range 0.655–0.860 g/cm^2). Increase was 10% greater than the increase related to growth	Not evaluated/reported	Not evaluated/reported	Well tolerated, no side-effects	Back pain resolved in all children, standing with corset became possible. In 3 children who did not reach puberty, growth velocity was 2.5–4.5 cm/year. Child who did reach puberty grew 6 cm/year. Corticosteroids progressively reduced/withdrawn
Bayer *et al.*, 2002[241]	Baseline *Z*-scores were 4.2 ± 2.2 for spine and –2.3 ± 1.1 for total body. After treatment: spine BMD increased to –3.1 ± 1.6 and total body BMD to –2.0 ± 1.5	Not evaluated/reported	Not evaluated/reported	No side-effects observed	
Chlebna-Sokol *et al.*, 2003[242]	Range total BMD *Z*-score, baseline –3.76 to –1.43; 6 months –3.12 to –0.9; 12 months –2.90 to –0.90. Range spine BMD *Z*-score: baseline –5.09 to –3.00; 6 months –2.85 to –2.00; 12 months –2.50 to –1.18	Decrease in ICTP, OC levels fell in two children but increased in three children, dypyridinoline:creatinine and pyridinoline:creatinine ratios fell in most children	Not evaluated/reported	Not reported	
Oliveri *et al.*, 1996[244]	Total skeleton BMD = 0.790 g/cm^2, *Z*-score = –2.1 at baseline. After 21 months, BMD = 1.047 g/cm^2, *Z*-score = +1.0. Largest increments in pelvis and spine (65 and 70%)	Serum levels of ALP remained within normal range	Not evaluated/reported	Not reported	Grew 13 cm

continued

Study	Densitometry	Markers of bone turnover	Fractures	Adverse event(s) and rates(s)	Comments
Calcium and/or vitamin D studies including children with JIA					
Warady *et al.*, 1994[245]	For all children, mean baseline spine BMD = 0.75 ± 0.05 g/cm^2. After supplementation, 0.83 ± 0.06 g/cm^2 (11% increase). When supplements withdrawn, mean bone density decreased to 0.8 ± 0.05 g/cm^2 ($p < 0.02$ for 3 tests). Mean baseline radius BMD = 0.45 ± 0.04 g/cm^2; during supplementation, 0.47 ± 0.04 g/cm^2; after withdrawal of supplements, 0.45 ± 0.03 g/cm^2	No significant changes in OC or ALP; 7 children had elevated ALP during study	Not evaluated/reported	Well tolerated. No subjects discontinued treatment because of side-effects. Serum calcium and phosphorus were normal in all children. One child was borderline for hypercalciuria at baseline and later developed abdominal pain; supplements were discontinued for 4 months then child was able to complete study	Mean sunshine score of 8.62 out of possible 9.0, indicating homogeneous amount of time in sunlight. No significant differences in dietary intakes
Reed *et al.*, 1991[251]	Mean ± SD score at baseline –2.8 ± 0.5 (13 children); after 6 months –2.3 ± 0.5 (13 children); after 12 months –2.4 ± 0.4 (10 children)	Baseline mean OC low, 3.1 ± 0.7 ng/ml (13 children); after 6 months 5.1 ± 0.9 ($p < 0.05$) (13 children); after 12 months 7.5 ± 1.5 ($p < 0.05$) (7 children)	Not evaluated/reported	Hypercalciuria at baseline but had decreased at 12 months	

Appendix 21

Studies included in the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D: quality assessment

Study	Inclusion bias	Selection bias	Performance bias	Attrition bias	Detection bias	Other points
Bisphosphonate studies including children with JIA						
Rudge *et al.*, 2005[229]	Inclusion criteria: long-term prednisone therapy. Children in the alendronate group were shorter and had been receiving corticosteroid treatment for longer than the placebo group. Distribution of underlying diseases varied between groups	No information	Intervention and control groups continued corticosteroid treatment. No calcium supplementation, but some subjects received vitamin D	1/11 (SLE) children in the alendronate did not complete study. 3/11 children did not finish study in the placebo group (JIA × 2, dermatomyositis × 1)	Use of protocol not stated. Type of software used not stated. Any adjustments for children not stated. Reference data from manufacturer used to calculate *Z*-scores	Method of randomisation not described. Treatment and control group were blinded to treatment. Essentially uncontrolled study as did not compare groups, compared each group with its own baseline
Acott *et al.*, 2005[230]	No inclusion criteria reported but children had fractures, confirmed by radiographic imaging and bone scan, while on long-term corticosteroid therapy. Controls did not have fractures	No information	Both cases and controls continued with corticosteroid treatment. Calcium and vitamin D supplementation	All children completed treatment	Use of protocol not stated. Type of software used not stated. Any adjustments for children not stated. Source of reference data to calculate *Z*-scores not stated	
Bianchi *et al.*, 2000[231]	Inclusion criteria: at least one of the following: (a) spine BMD *Z*-score <–1.5 and history of bone fragility fractures; (b) spine BMD *Z*-score <–1.5 and continuous corticosteroid therapy for at least 6 months. Controls had same diseases but in less severe form that did not require treatment with corticosteroids and without fragility fractures. JIA classified according to criteria of International League of Associations for Rheumatology criteria	Selected from children receiving follow-up care for diffuse connective tissue disease in five paediatric departments	In children, concomitant therapy with calcium, vitamin D supplementation not needed but not discussed for controls	One child with chronic infantile neurological, cutaneous and articular syndrome dropped out because of severe bone pain	Standard protocol used for DXA. All scans for each child performed on same machine (although different machines used at different sites). Type of software used with DXA not stated. Adjustments made to account for size of children. Quality control procedure used. *Z*-score calculated using local reference data. Limited assessment of bone markers	Excluded children with peptic ulcer disease but accepted those with simple dyspepsia. No blinding of control or treatment group. Essentially uncontrolled study as did not compare groups, compared each group with its own baseline

continued

Study	Inclusion bias	Selection bias	Performance bias	Attrition bias	Detection bias	Other points
Lepore *et al.*, 1991[232]	No inclusion criteria reported	No information	No information about other treatments	All 7 children completed treatment	Used CT scan of lumbar spine, which gives true volumetric bone density	No blinding of control or treatment group. Essentially uncontrolled study as did not compare groups, compared each group with its own baseline
Noguera *et al.*, 2003[233]	Severe osteoporosis after long-term systemic corticosteroid treatment	No information	No other treatments related to calcium/phosphate metabolism allowed, no diet restrictions	All 10 children completed treatment	Site of lumbar spine measurement not stated for DXA. Use of protocol not stated. Type of software used with DXA not stated. Any adjustments for children not stated. Source of reference data for *Z*-score not stated. Limited assessment of bone markers – did not state whether ALP was bone specific	
Cimaz *et al.*, 2002[234]	At least one of the following: (a) spine BMD *Z*-score <–1.5 and history of bone fragility fractures; (b) spine BMD *Z*-score <–1.5 and continuous corticosteroid therapy for at least 6 months	Selected from children receiving follow-up care for diffuse connective tissue disease in five paediatric departments	Children continued with usual treatments	All 47 children completed treatment	Described in less detail but appeared to be the same as for the Bianchi study. Adjustments made to account for size of children. *Z*-score calculated using local reference data	

continued

Study	Inclusion bias	Selection bias	Performance bias	Attrition bias	Detection bias	Other points
Gandrud *et al.*, 2003[235]	History of low impact fractures and/or low bone mass	No information	No information about other treatments	Treatment stopped in 1 child after 5 infusions because normal BMD reached and had stopped corticosteroid treatment, 1 child withdrew when transferred to adult care, 1 because of flare of underlying ulcerative colitis after first infusion and 1 after continued slow healing of a pre-existing femur fracture after third infusion	Site of lumbar DXA not stated. Two different machines used although systematic differences were adjusted for. Use of standard protocol not stated. Type of software used with DXA not stated. Any adjustments for children not stated. *Z*-scores calculated using local reference data. Limited assessment of bone markers – did not state whether ALP was bone specific	
Gattinara *et al.*, 2000[236]	No inclusion criteria reported but children had corticosteroid-induced osteoporosis		Concomitant therapy with vitamin D	All 25 children completed 6 months of treatment, 20 completed 12 months, 14 completed 24 months and 11 completed 36 months. Reasons for drop-out not reported	Site of lumbar DXA not stated. Use of standard protocol not stated. Type of software used with DXA not stated. Any adjustments for children not stated	Conference abstract only. Only measured densitometry as outcome
Brumsen *et al.*, 1997[239]	No inclusion criteria reported but children had no current or previous use of corticosteroids			Children completed treatment	DPA used at first then DXA. Use of protocol not stated. Type of software used with DXA not stated. Any adjustments for children not stated. Limited assessment of bone markers – did not state whether ALP was bone specific	All results not reported separately for JIA child

continued

Study	Inclusion bias	Selection bias	Performance bias	Attrition bias	Detection bias	Other points
Shaw *et al.*, 2000[240]	No inclusion criteria reported but children had symptoms and signs of vertebral osteoporosis			Children completed treatment	Use of protocol for DXA not stated. Type of software used with DXA not stated. Any adjustments for children not stated. Reference data from manufacturer used for calculating SDS	
Fernandes *et al.*, 2004[243]	No inclusion criteria reported	No information	Case 1: calcium and vitamin D supplementation Case 2: no supplementation	Both children completed treatment	Site of densitometry measurements not stated. Use of standard protocol for DXA not stated. Type of software used with DXA not stated. Any adjustments for children not stated. No absolute values reported. Source of reference data for *Z*-scores not reported	Only measured densitometry as outcome
Bisphosphonate studies in connective tissue disease not including children with JIA						
Bardare *et al.*, 2000[237]	No inclusion criteria reported but children had corticosteroid-induced osteoporosis	Abstract only, limited information	Abstract only, limited information	2 children stopped treatment after 12 months because of low dose corticosteroid and disease inactivity. Stopped after 24 months in 4 children – reason not stated	Use of standard protocol for DXA not stated. Type of software used with DXA not stated. Any adjustments for children not stated	
Falcini *et al.*, 1996[238]	No inclusion criteria reported but children had prolonged corticosteroid treatment causing multiple vertebral fractures	Abstract only, limited information	Concomitant therapy with calcium and vitamin D	All 4 children completed treatment	Use of protocol for DXA not stated. Type of software used with DXA not stated. Any adjustments for children not stated	

continued

Study	Inclusion bias	Selection bias	Performance bias	Attrition bias	Detection bias	Other points
Bayer *et al.*, 2002[241]	Abstract only, limited information	Abstract only, limited information	Calcium and vitamin D supplementation. Abstract only	Abstract only, limited information	Abstract only, limited information	
Chlebna-Sokol *et al.*, 2003[242]	Abstract only, limited information	Abstract only, limited information	Calcium and vitamin D supplementation in all children. 6 treated with bisphosphonates	Abstract only, limited information	Abstract only, limited information	
Oliveri *et al.*, 1996[244]	No inclusion criteria reported but children had prolonged corticosteroid treatment causing multiple vertebral fractures		Concomitant therapy with calcium and vitamin D	Child completed treatment	Site of lumbar spine measurement not stated. Use of standard protocol for DXA not stated. Any adjustments for children not stated. Source of reference data for *Z*-score not stated. Limited assessment of bone markers – did not state whether ALP was bone specific	
Calcium and/or vitamin D studies including children with JIA						
Warady *et al.*, 1994[245]	Inclusion criteria: (a) treatment with corticosteroids in stable doses for at least 2 consecutive months; (b) bone demineralisation (10%) as determined by DPA; (c) creatinine clearance >75 ml/minute/1.73 m^2; (d) absence of liver disease or gastrointestinal malabsorption	No information	Quantity of supplementation determined by individual dietary intake. Authors comment that calcium intake low for this age group and that they did not use pharmacological doses of vitamin D. Appeared to be no difference in dietary intakes between the two groups. Authors also comment that high protein and sodium diet may have affected calcium metabolism and bone growth. Also exposure to sunlight the same. No washout period between crossover of treatments	12 children met criteria, 10 agreed to participate. All 10 children completed treatment	Used SPA and DPA which are now superseded by DXA. Little information on methodology. Limited assessment of bone markers – did not state whether ALP was bone specific	No blinding of treatment groups

continued

Study	Inclusion bias	Selection bias	Performance bias	Attrition bias	Detection bias	Other points
Reed *et al.*, 1991[251]	JRA had to fulfil American College of Rheumatology criteria. Active disease (assessed using scores), osteopenia	Attending rheumatology clinic in one centre		All 13 children completed 6 months of treatment. Some children appear not to have completed 12 months	Used SPA to measure density, now superseded. BMD reported as SD score with normal values determined from children in a similar geographical area and validated against children in study area with chronic rheumatic disease. Limited assessment of bone markers	

Appendix 22

Studies included in the systematic review of effectiveness of bisphosphonates and calcium and/or vitamin D: concerns about internal and external validity

Study	Internal validity	External validity
Bisphosphonate studies including children with JIA		
Rudge *et al.*, 2005[229]	RCT but method of randomisation not described. Pubertal stage not stated. Children in the alendronate group were shorter and had been receiving corticosteroid treatment for longer than the placebo group. Distribution of underlying diseases varied between groups. Little information on densitometric assessment provided, so quality of methodology uncertain. *Z*-scores calculated for manufacturer's reference data which may not be the most appropriate source of reference data	7 JIA children. Classification of JIA not stated, so do not know how they compare with the general population. Small study
Acott *et al.*, 2005[230]	Ages and pubertal stages not stated. Control group well matched – age, disease, sex, corticosteroid treatment. However, not clear if severities of disease were matched. Control children had higher BMD at baseline compared with intervention groups and had not experienced fractures, but both groups had received similar amounts of corticosteroid treatment. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	Only 1 JIA child and matched control in study. Classification of JIA not stated, so do not know how they compare with general population
Bianchi *et al.*, 2000[231]	Pubertal stage stated. Increased dietary calcium intake but no supplements. Densitometric assessment was thorough and included a quality control procedure. Control group included of similar age but with less severe disease and not requiring corticosteroid treatment, so results in treated and untreated children may not be directly comparable. Not clear if groups were the same at baseline. Groups were not compared with each other, each group compared with its own baseline	All children had rheumatic disease, 16 with JIA. Classification of JIA not stated, so do not know how they compare with the general population
Lepore *et al.*, 1991[232]	No inclusion criteria or baseline details of treated or control children provided. Not stated whether there was concomitant treatment with calcium and vitamin D, so do not know if this was confounding factor. Very little information on general methodology provided, so quality uncertain. Little information on densitometric assessment provided, so quality of methodology uncertain. Groups were not compared with each other, each group compared with its own baseline	13 JIA children (7 treated). Classification of JIA not stated and very little information on children, so do not know how they compare with general population
Noguera *et al.*, 2003[233]	Pubertal stages not stated, affects bone growth and could be confounding factor. No concomitant treatments related to calcium/phosphate metabolism allowed, so did not confound results. No control group. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain. *Z*-scores calculated based on data from age- and sex-matched normal population	10 children with rheumatic diseases, 8 with JIA. Classification of JIA not stated, so do not know how they compare with general population
Cimaz *et al.*, 2002[234]	No comparator group. Pubertal stages stated. Not clear whether children were receiving concomitant therapy with calcium and/or vitamin D, assume same as in Bianchi paper. Little information on densitometric assessment, but assume same methods as in Bianchi paper	All children had rheumatic diseases, 18 with JIA: 8 with systemic JIA, 10 with polyarticular JIA
Gandrud *et al.*, 2003[235]	Minimal inclusion criteria. No comparator group. No information on pubertal stages. Does not state whether children were receiving concomitant therapy with calcium and/or vitamin D and this is a possible confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	Only 4 children had corticosteroid-induced osteoporosis, underlying disease not stated, therefore cannot generalise to overall JIA population

continued

Study	Internal validity	External validity
Gattinara *et al.*, 2000[236]	Little information as study published as conference abstract. Minimal inclusion criteria. No comparator group. No information on pubertal stages. Children were receiving concomitant therapy with vitamin D and this is a possible confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	22 of 25 children had JIA and classification of JIA reported, therefore should be possible to generalise results to overall JIA population on this point
Brumsen *et al.*, 1997[239]	No inclusion criteria and only 1 child had JIA. Little information on pubertal stage, affects bone growth and could be confounding factor. Was dose of bisphosphonate appropriate? Does not state whether child was receiving concomitant therapy with calcium and/or vitamin D, which could have been a confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain. No comparator	Only 1 child with JIA and classification of JIA not stated
Shaw *et al.*, 2000[240]	No inclusion criteria and only 1 child had JIA. No information on pubertal stage, affects bone growth and could be confounding factor. Does not state whether child was receiving concomitant therapy with calcium and/or vitamin D, which could have been a confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain. No comparator	Only 1 child with JIA and classification of JIA not stated
Fernandes *et al.*, 2004[243]	Case series of 2 children. No inclusion criteria and only 1 child had JIA. No comparator group. Very little detail on children and methodology. No information on dose of bisphosphonate. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	One JIA child and classification of JIA not stated, therefore difficult to generalise to overall population of JIA
Bisphosphonate studies in connective tissue disease not including studies in JIA		
Bardare *et al.*, 2000[237]	Little information as study published as conference abstract only. Minimal inclusion criteria. No comparator group. No information on pubertal stages. Does not state whether children were receiving concomitant therapy with calcium and/or vitamin D, which is a possible confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	None of the children had JIA, so cannot generalise to overall JIA population
Falcini *et al.*, 1996[238]	Case series with no comparator. No inclusion criteria and all 4 children had different rheumatic diseases. Pubertal stages not stated: affects bone growth and could be confounding factor. Concomitant treatment with calcium and vitamin D allowed and could have been a confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	Four children with rheumatic diseases, none with JIA, therefore cannot generalise to overall population JIA
Bayer *et al.*, 2002[241]	Only an English abstract is available	Only an English abstract is available at present
Chlebna-Sokol *et al.*, 2003[242]	Only an English abstract is available	Only an English abstract is available at present

continued

Study	Internal validity	External validity
Oliveri *et al*., 1996[244]	Pubertal stage stated. Was dose of bisphosphonate appropriate? Concomitant treatment with calcium and vitamin D allowed and could have been a confounding factor. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	Only 1 child with dermatomyositis
Calcium and/or vitamin D studies including children with JIA		
Warady *et al*., 1994[245]	Pubertal stages not stated, but 6 girls had begun menstruating at start of study. Dietary calcium and vitamin D intake assessed using dietary records; the accuracy of this is uncertain. No washout period between changing treatments. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain	6 children with JIA. Classification of JIA not stated, so not know how they compare with general population
Reed *et al*., 1991[251]	No comparator group. No information on pubertal stages. Little information on densitometric assessment provided, so quality of methodology and reliability of results uncertain. Some children continued corticosteroid treatment. Some did not have corticosteroid treatment	JRA classified according to ACR criteria

Appendix 23

Summary of studies included in systematic review of safety of bisphosphonates and calcium and/or vitamin D for treating children with JIA or osteogenesis imperfecta

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Rauch *et al.*, 2003[277] [a]	165 children with OI (2 weeks–17.9 years)	Pamidronate (i.v.)	<2 years old: 0.25 mg/kg on day 1 of cycle 1, 0.5 mg/kg on days 2 and 3 and 0.5 mg/kg on days 1–3 in subsequent cycles, cycles repeated every 2 months. 2–3 years old: 0.38 mg/kg on day 1 of cycle 1 and 0.75 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg for days 1–3, cycles repeated every 3 months. >3 years old: 0.5 mg/kg on day 1 of cycle 1 and 1 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg daily on days 1–3, cycles repeated every 4 months. Yearly dose of drug was same for all ages. Calcium intake maintained as adequate	4 years	Serum calcium and phosphorus levels decreased markedly during the first treatment cycle. Levels returned to pretreatment results by start of second cycle. No long-term change in calcium levels but phosphorus decreased with time. Bone turnover suppressed to levels lower than in healthy children
Munns *et al.*, 2004[278]	131 children with OI (0–19.9 years)	Pamidronate (i.v.)	<2 years old: 0.25 mg/kg on day 1 of cycle 1, 0.5 mg/kg on days 2 and 3 and 0.5 mg/kg on days 1–3 in subsequent cycles, cycles repeated every 2 months. 2–3 years old: 0.38 mg/kg on day 1 of cycle 1 and 0.75 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg on days 1–3, cycles repeated every 3 months. >3 years old: 0.5 mg/kg on day 1 of cycle 1 and 1 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg daily on days 1–3, cycles repeated every 4 months. Yearly dose of drug was same for all ages. Maintain adequate calcium intake	Unclear	Delayed fracture healing in treated children but not significant when age factors taken into account. After osteotomy, delayed healing was more frequent when pamidronate started before surgery
Zeitlin *et al.*, 2003[279] [a]	125 children with OI (0.04–15.6 years)	Pamidronate (i.v.)	<2 years old: 0.25 mg/kg on day 1 of cycle 1, 0.5 mg/kg on days 2 and 3 and 0.5 mg/kg on days 1–3 in subsequent cycles, cycles repeated every 2 months. 2–3 years old: 0.38 mg/kg on day 1 of cycle 1 and 0.75 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg on days 1–3, cycles repeated every 3 months. >3 years old: 0.5 mg/kg on day 1 of cycle 1, 1.0 mg/kg on days 2 and 3 of cycle 1 and 1.0 mg/kg on days 1–3 of subsequent cycles, cycles repeated every 4 months. Yearly dose of drug was same for all ages. Doses and cycles based on clinical response	116 children, 1 year; 41 children, 4 years	Not reported

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Rauch *et al.*, 2003[280] *a*	56 children with OI (0.2–15.9 years)	Pamidronate (i.v.)	<2 years old: 0.25 mg/kg on day 1 of cycle 1, 0.5 mg/kg on days 2 and 3 and 0.5 mg/kg on days 1–3 in subsequent cycles, cycles repeated every 2 months. 2–3 years old: 0.38 mg/kg on day 1 of cycle 1 and 0.75 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg on days 1–3, cycles repeated every 3 months. >3 years old: 0.5 mg/kg on day 1 of cycle 1 and 1 mg/kg on days 2 and 3. In subsequent cycles the dose was 1 mg/kg daily on days 1–3, cycles repeated every 4 months. Yearly dose of drug was same for all ages. Calcium intake and vitamin intakes maintained as adequate	4 years	Not reported
Rauch *et al.*, 2002[276]	45 children with OI (1.4–17.5 years)	Pamidronate (i.v.)	<2 years old: 0.25 mg/kg on day 1 of cycle 1, 0.5 mg/kg on days 2 and 3 of cycle 1 and 0.5 mg/kg on days 1–3 of subsequent cycles, cycles repeated every 2 months. 2–3 years old: 0.38 mg/kg on day 1 of cycle 1, 0.75 mg/kg on days 2 and 3 of cycle 1, 0.75 mg/kg on days 1–3 of subsequent cycles, cycles repeated every 3 months. >3 years old: 0.5 mg/kg on day 1 of cycle 1, 1.0 mg/kg on days 2 and 3 of cycle 1 and 1.0 mg/kg on days 1–3 of subsequent cycles, cycles repeated every 4 months. Yearly dose of drug was same for all ages. Calcium intake maintained as adequate	Mean 2.4 ± 0.6 years (range 1.0–4.0 years)	Reduction in bone remodelling. No signs of a mineralisation defect
Montpetit *et al.*, 2003[281] *a*	42 children with OI (7.3–15.9 years)	Pamidronate (i.v.)	1 mg/kg for 3 days every 4 months	Minimum 2 years	Not reported
Grissom and Harcke, 2003[282]	32 children: OI (19), cerebral palsy (13) (1–17 years)	Pamidronate (i.v.)	0.5–1.0 mg/kg/day for 3 days every 2–3 months to max. of 35 mg/day	Mean 1 year (range 0.5–1.5 years)	Transient side-effects (pyrexia, nausea, joint pain) experienced by a few children

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Glorieux *et al.*, 1998[248] [a]	30 children with OI (3–16 years)	Pamidronate (i.v.)	1.5–3.0 mg/kg every 3 days. Half the children received the lower dose during the first year then changed to the higher dose. Initial interval between cycles was 6 months, shortened to 4 months. Calcium and vitamin D supplements	Mean 2 years (range 1.3–5.0 years)	Acute-phase reaction (increased temperature, back and limb pain) on second day of cycle 1 in 26 children (87%), controlled with paracetamol and did not recur. Transient decrease in serum calcium and phosphate after each infusion cycle but none of the children had symptomatic hypocalcaemia. Urinary excretion calcium decreased over 3–4-month period. Renal function did not change with treatment
Astrom and Soderhall, 2002[275]	28 children with OI (0.6–18 years)	Pamidronate (i.v.), alendronate (oral)	Pamidronate, once monthly: months 1–3, 10 mg/m^2; months 4–6, 20 mg/m^2; then 30 mg/m^2, increased to 40 mg/m^2 in 5 children. After 2–6 years, 5 adolescents changed to oral alendronate 10 mg daily. Doses chosen based on those used in hypercalcaemia and osteolytic bone metastases in children. Vitamin D supplements	Mean 3.1 years (range 2–9 years)	Fever after first infusion in five children (18%). Four children (14%) had fever after increasing dose. One girl had increased serum calcium concentration and microcalcification of the renal papillae, levels became normal after withdrawing calcium and vitamin D supplements. Microcalcifications are regressing. No adverse effects on fracture healing
Arikoski *et al.*, 2004[283]	26 children with OI (3.2–15.5 years)	Pamidronate (i.v.)	1.0 mg/kg/day for 3 days every 3 months. Calcium and vitamin D supplements	1 year	Flu-like reaction during the first course of treatment. Calcium and phosphate levels decreased slightly then returned to pre-infusion levels

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Robinson *et al.*, 2004[284]	27 children: OI (19), idiopathic juvenile osteoporosis (18) (3–21 years)	Pamidronate (i.v.)	1 mg/kg/dose	Not reported	Pretreatment with paracetamol/ibuprofen reduced occurrence of adverse events ($p = 0.005$). Fewer adverse events with ibuprofen compared with paracetamol: pyrexia ($p = 0.005$), bone pain ($p = 0.027$). No difference for nausea, leucopenia, dizziness
Zacharin and Kanumakala, 2004[286]	18 children with OI (2–15 years)	Pamidronate (i.v.)	1 mg/kg for 1 day every 2 months. Dose was that previously reported in children	2 years	No serious adverse events. Mild fever on first infusion occurred in some children. No ultrasound scan changes to kidney. One child diagnosed with neprocalcinosis at start of the study but no progression occurred. No changes in creatinine or calcium. No clinical signs of hypocalcaemia
Zacharin and Bateman, 2002[285]	14 children with OI (1.4–14.5 years)	Pamidronate (i.v.)	1 mg/kg/day for 3 days every 4 months	2 years	Bone turnover decreased slightly at times during the study but changes were not significant. Renal ultrasound was normal before study and remained normal at end of study
Steelman and Zeitler, 2003[274]	13 children: cystic fibrosis (1), corticosteroid dependent asthma (3), bone marrow transplant (1), chronic lung disease (1), Duchenne muscular dystrophy (2), HIV disease (1), spina bifida (1), cerebral palsy (1), OI (6), idiopathic osteoporosis (1) (6–21 years)	Pamidronate (i.v.)	Single dose every 3 months. <50 kg body weight, 30 mg; ⩾50 kg body weight, 45 mg. Dose based on doses used in adult studies. Vitamin D supplements	6–22 months	In 6 children (44%), a transient fever lasting up to 48 hours after infusion. Body aches and pains in 22%. No other serious adverse events such as electrolyte disturbances, neutropenia or ocular complaints occurred. No short-term evidence of growth impairment

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Bin-Abbas *et al.*, 2004[287]	10 children with OI (2–10 years)	Pamidronate (i.v.)	4-monthly intervals, total annual dose 9 mg/kg/year	2–5 years	All (100%) children had transient self-limited symptoms similar to flu, which resolved with symptomatic treatment
Banerjee *et al.*, 2002[273]	10 children with OI (13–12.7 years)	Pamidronate (i.v.)	1 mg/kg/day for 3 days every 3 months	Mean 1.8 years (range 0.9–3.0 years)	Initial infusion associated with flu-like symptoms, rigors, abdominal pain or vomiting in 6 children (60%). Serum calcium levels were low after treatment in six children and three required treatment with calcium and vitamin D supplements
DiMeglio *et al.*, 2004[288]	9 children with OI (1–35 months)	Pamidronate (i.v.)	<24 months old: total of 0.5 mg/kg/day for 3 days every 6–8 weeks. 24–36 months old: 0.75 mg/kg/day for 3 days every 3 months. >36 months old: 1 mg/kg/day for 3 days every 4 months	Mean 1.5 year (range 1–2.5 years)	Fever after first dose which was managed with paracetamol. No discontinuation of treatment. No missed doses because of difficulties with protocol. Urine calcium/creatinine and NTX/creatinine declined over time. Three children had hypercalcaemia at baseline, serum calcium decreased during study
Plotkin *et al.*, 2000[293]	9 children with OI (<2 years of age) (2.3–20.7 months)	Pamidronate (i.v.)	0.5 mg/kg/day for 3 days every 4 months. Child showed signs of discomfort before next cycle so interval shortened to 6–8 weeks, mean cumulative dose 12.4 mg/kg. Daily intake of calcium and vitamin D was adequate	1 year	No adverse side-effects except acute-phase reaction during first infusion cycle
Van Persijn van Meerten *et al.*, 1992[253]	9 children: OI (3), corticosteroid-induced osteoporosis (2), juvenile chronic arthritis and osteoporosis (1), juvenile osteoporosis (1), Gaucher disease (1), polyostotic fibrous dysplasia (1) (7.5–14.5 years)	Pamidronate (i.v.) or olpadronate (oral)	Pamidronate: 3 children received 0.25 mg/kg for 10–17 days. These and 4 other children then received orally 3–7 mg/kg/day. Olpadronate: 2 children received 0.5 mg/kg/day	Mean 5.3 years (range 1.3–10.7 years)	Band-like metaphyseal sclerosis and concentric epi- and apophyseal sclerosis developed in all children. Sclerosis disappeared on discontinuation of treatment

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Giraud and Meunier, 2002[256]	7 children with OI (1–15 years)	Pamidronate (i.v.)	Every day for 1–3 days. Interval between cycles was 3–12 months. Dosage 0.83–3.77 mg/kg/cycle (mean 1.86 mg/kg). Calcium and vitamin D supplements	1–7 years	Transient flu-like reaction in 2 children (29%) during first cycle. 4 children also had fever after increasing the dose (60%). Serum calcium fell in 18 children after infusion but returned to normal within 7 days, stabilised by administration 1,25-dihydroxycholecalciferol. No abnormal biochemical or haematological values including creatinine and calcium/creatinine ratio
Falk *et al.*, 2003[257]	6 children with OI (22 months–14 years)	Pamidronate (i.v.)	1 mg/kg/day on 3 consecutive days. During day 1 of first cycle, dose was reduced to 0.5 mg/kg/day. Cycle intervals occasionally varied between 3 and 5 months, mean interval 3.8 months. Total annual dose 9 mg/kg. Calcium supplements	Mean 2 years (range 1–3 years)	No clinically significant laboratory abnormalities. Transient flu-like symptoms during first treatment cycle in 5 children (83%). Transient tachycardia in one child who had a concurrent mild upper respiratory tract infection. One child reported transient metallic taste. Peripheral intravenous line infiltration occurred in two children without any adverse effect. Non-union of tibial fracture in one child
Lee *et al.*, 2001[258]	6 children with OI (4.9–13.7 years)	Pamidronate (i.v.)	1.5 mg/kg every 2 months. Dose derived from lytic bone lesions and Paget disease in adults. Calcium supplements	Median 1.6 years (range 1–2 years)	Transient low-grade fever during first infusion. No hypocalcaemia occurred and no symptomatic hypocalcaemia. Renal function and ultrasound remained normal with no evidence of nephrocalcinosis
Bishop *et al.*, 1996[259]	6 children with OI (4–18 years)	Pamidronate (i.v.)	3 mg/kg over 3 days, cycles at 4–6 months	1–3 years	All had fever during first infusion (100%). No change in growth rate or modification of growth plates
Huzjak *et al.*, 2002[254]	6 children with OI (3 months–11 years)	Pamidronate (i.v.)	1–1.5 mg/kg once a month for 6 months, then break for 3 months. Or 1–1.5 mg/kg for 3 days every 4 months. Calcium and vitamin D supplements	1.9–3.5 years	Acute inflammation similar to flu during first infusion cycle. Mild asymptomatic hypocalcaemia in two children. No other laboratory or clinical side-effects

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Fujiwara *et al.*, 1998[291]	5 children with OI (mean 6 years)	Pamidronate (i.v.)	0.6–1.2 mg/kg monthly	0.5–1.5 years	No severe side-effects observed. Transient high fever and slight lowering of serum calcium levels occurred soon after initial treatment in some children. No effect on linear growth
Sumnik *et al.*, 2004[260]	5 children: primary osteoporosis and OI (5.3–14.4 years)	Pamidronate (i.v.)	1 mg/kg/day on 3 consecutive days, repeated every 4 months. Calcium supplements	Mean 1.5 years (range 0.5–3.5 years)	No side-effects reported
Munns *et al.*, 2004[261]	4 infants with OI with pre-existing respiratory compromise	Pamidronate (i.v.)	Child 1: 0.125 mg/kg day 1, 0.25 mg/kg day 2. Only received 2 doses. Child 2: 0.25 mg/kg per day for 3 days. Subsequent cycles. Child 3: 0.23 mg/kg day 1, 0.45 mg/kg day 2. Received 4 cycles. Child 4: 0.5 mg/kg day 1, 1 mg/kg day 2. Received 2 cycles	Unclear	Transient fever in all children (100%). Child 1: increased temperature and respiratory distress after second dose. Serum calcium remained normal. Only received two doses of first course. Subsequent cycles uneventful. Child 2: fever and decreased respiratory rate after third dose of cycle one. Serum calcium remained normal. Subsequent cycles were uneventful. Child 3: respiratory distress after second dose of first cycle. Serum calcium remained normal. Subsequent cycles were uneventful but died after fourth cycle from respiratory failure secondary to an infection. Child 4: developed fever and increased respiratory distress after second dose of cycle 1. Serum calcium remained normal. Died after second cycle from unknown cause
Astrom and Soderhall, 1998[262]	3 children with OI (13, 16 and 20 years)	Pamidronate (i.v.)	10–30 mg/m^2 monthly. Vitamin supplements	2–5.5 years	No clinical complications or pathological changes in laboratory values

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Gonzalez *et al.*, 2001[263]	3 children with OI (9, 9 and 11 years)	Pamidronate (i.v.)	Every 6 months. <30 kg body weight: 30 mg. ≤30 kg body weight: 60 mg (i.e. 2–4 mg/kg/year)	4 years	Generally good but hyperthermia, nausea, vomiting and mild abdominal pain occurred after first dose. Treated with ondansetron. No changes in calcium or phosphorus
Bembi *et al.*, 1997[264]	3 children with OI (8 years 5 months, 8 years 8 months and 4 years)	Pamidronate (i.v.)	Child 1: 15 mg every 20 days, after 1 year increased to 30 mg every 20 days. Child 2: 30 mg every 20 days. Child 3: 15 mg every 20 days, after 5 weeks increased to 15 mg every 10 days. All received calcium and vitamin D supplements	1–2.5 years	All children (100%) developed transient fever during first infusion. No other adverse events noted. Serum calcium and phosphorus remained within normal range
Roldan *et al.*, 1999[265]	2 children with OI (2.5, 7.5 years)	Pamidronate (i.v. and oral)	Child 1: oral 100 mg daily every 4 days. Calcium and vitamin D supplements. Child 2: i.v. 5 mg/day for 4 consecutive days for 5 cycles during first year, then oral 300–400 mg/week	Child1, 7 years; child 2, 3.3 years	Not reported
Munns *et al.*, 2004[266]	2 pregnant young women with OI, received pamidronate before conception	Pamidronate (i.v.)	Not reported. Calcium and vitamin D supplements	Child 1, 7 years; Child 2, 5 years	Child 1: did not receive further pamidronate when pregnant, received calcium and vitamin D throughout pregnancy. Baby has OI. At 24 hours had hypocalcaemia with normal phosphorus and parathyroid hormone but asymptomatic. Serum calcium normal by day 11. Child 2: did not receive further pamidronate when pregnant, received calcium and vitamin D throughout pregnancy. Baby has OI. Calcium not measured but no signs suggesting hypocalcaemia at birth
Guillot *et al.*, 2001[255]	1 child with OI (6 months)	Pamidronate (i.v.)	0.5 mg/kg day 1,1 mg/kg days 2 and 3. Calcium and vitamin D supplements		
Chien *et al.*, 2002[267]	1 child with OI (12 days)	Pamidronate (i.v.)	30 mg/m^2 monthly for first 3 months then every 2 months. Calcium and vitamin D supplements	1 year	Subclinical hypocalcaemia after first and second infusions although receiving calcium and vitamin D supplements

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Devogelaer *et al.*, 1990[268]	1 children with OI (7 years)	Pamidronate (oral)	250–300 mg/day for 3 months alternating with 3 months without treatment	3 years	Opaque bands in metaphyses, older radiopaque bands faded away indicated that dense bone is reabsorbed
Huaux and Lokietek, 1988[269]	1 child with OI (12 years)	Pamidronate (oral)	100 mg daily	6 months	No side-effects observed.
Devogelaer *et al.*, 1987[270]	1 child with OI (12 years)	Pamidronate (oral)	250 mg daily for 2 months alternating with 2 months of no treatment	1 year	Well tolerated clinically and biologically
Maasalu *et al.*, 2003[271]	15 children with OI (8 months–13 years)	Alendronate (oral)	1 mg/kg per week divided into 3–7 doses, 4-week medication break after each 6–8-week cycle. Calcitriol supplementation	Mean 2.5 years (range 1–5 years)	No side-effects observed
Shaw, 1997[289]	1 child with OI (9 years)	Pamidronate (i.v.), etidronate (oral)	Pamidronate i.v. 0.5 mg/kg every 3 months for 6 months then 1 mg/kg/day for 2 days for a further 6 months. Then etidronate oral 600 mg/day (9 mg/kg) for 2 weeks every 3 months for 9 months	1.5 years	No side-effects observed
Sakkers *et al.*, 2004[272]	39 children with OI recruited, 34 randomised (16 to treatment, 18 to placebo) (3–18 years)	Olpadronate (oral)	10 mg/m^2/day. Calcium and vitamin D supplements	2 years	No gastrointestinal discomfort. No impairment of hepatic or renal function. No measurable suppression of urinary C-telopeptides or deoxypyridinolines
Landsmeer-Beker *et al.*, 1997[292]	3 children with OI (1.0, 1.7, 6 years)	Olpadronate (oral)	5 or 10 mg/day. Calcium and vitamin D supplements	5–7 years	Well tolerated with no side-effects observed. No abnormalities in blood count, serum creatinine or liver function tests
Ashford *et al.*, 2003[290]	1 child with OI (13.5 years)	Clodronate (oral)	400 mg/day increasing to 800 mg/day after 5 years	8 years	No side effects observed. Growth not impaired

continued

Study	Children (age range)	Intervention	Dose	Follow-up	Side-effects
Hogler *et al.*, 2004[252]	34 children: corticosteroid-induced osteoporosis and bone pain (3), site-specific avascular necrosis (12), Perthes disease (11), poorly healed fracture site (7), McCune Albright syndrome (1) (2–17 years)	Zoledronic acid (i.v.)	0.02–0.025 mg/kg for the first 2 doses given 6 weeks apart followed by 0.5 mg/kg 12 weeks after the first dose and thereafter every 3 months. Dose chosen based on experience of hypocalcaemia	Minimum of one infusion (14 children received three doses)	Pretreatment calcium, phosphorus, creatinine and urea within normal range. After first infusion, flu-like symptoms and myalgia 85%, fever 68%, hypocalcaemia 74%, hypophosphataemia 82%. No clinical side-effects with subsequent infusions. Decrease in calcium and phosphorus was less after second and third infusions than after first infusion

[a] Overlapping studies.

Appendix 24

Search strategies: systematic review of costs and cost-effectiveness

MEDLINE

1 ECONOMICS/ [23777]
2 exp "costs and cost analysis"/ [113101]
3 "Value of Life"/ [4355]
4 exp Economics, Hospital/ [13107]
5 Economics, Medical/ [5179]
6 Economics, Nursing/ [3631]
7 Economics, Dental/ [1455]
8 Economics, Pharmaceutical/ [1424]
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 [153276]
10 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw. [200282]
11 (expenditure$ not energy).tw. [8683]
12 (value adj1 money).tw. [362]
13 budget$.tw. [8987]
14 10 or 11 or 12 or 13 [209911]
15 9 or 13 [159386]
16 letter.pt. [518555]
17 editorial.pt. [168447]
18 historical article.pt. [214068]
19 16 or 17 or 18 [893053]
20 15 not 19 [146076]
21 animal/ [3663449]
22 human/ [8643661]
23 21 not (21 and 22) [2818175]
24 20 not 23 [144171]
25 (metabolic adj cost).ti,ab,sh. [362]
26 ((energy or oxygen) adj cost).ti,ab,sh. [1626]
27 24 not (25 and 26) [144171]
28 Arthritis, Juvenile Rheumatoid/ [5799]
29 (arthriti$ adj3 (juvenile$ or child$)).mp. [7069]
30 (oligoarticular arthritis or oligoarthritis or polyarticular arthritis or polyarthritis or pauciarticular arthritis or systemic arthritis or psoriatic arthritis or enthesistis-related arthritis or undefined arthritis).mp. [7573]
31 Arthritis, Rheumatoid/ [51822]
32 28 or 29 or 30 or 31 [61749]
33 exp CHILD/ [1028316]
34 exp INFANT/ [631906]
35 exp ADOLESCENT/ [1044324]
36 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler or baby or babies or pediatric or paediatric).mp. [2101460]
37 33 or 34 or 35 or 36 [2101460]
38 27 and 44 and 49 [59]

MEDLINE In-Process & Other Non-Indexed Citations

1 [ECONOMICS/]
2 [exp "costs and cost analysis"/]
3 ["Value of Life"/]
4 [exp Economics, Hospital/]
5 [Economics, Medical/]
6 [Economics, Nursing/]
7 [Economics, Dental/]
8 [Economics, Pharmaceutical/]
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 [0]
10 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw. [7037]
11 (expenditure$ not energy).tw. [250]
12 (value adj1 money).tw. [11]
13 budget$.tw. [317]
14 10 or 11 or 12 or 13 [7363]
15 9 or 13 [317]
16 letter.pt. [8172]
17 editorial.pt. [4610]
18 historical article.pt. [0]
19 16 or 17 or 18 [12782]
20 15 not 19 [314]
21 [animal/]
22 [human/]
23 21 not (21 and 22) [0]
24 20 not 23 [314]
25 (metabolic adj cost).ti,ab,sh. [14]
26 ((energy or oxygen) adj cost).ti,ab,sh. [53]
27 24 not (25 and 26) [314]
28 [Arthritis, Juvenile Rheumatoid/]
29 (arthriti$ adj3 (juvenile$ or child$)).mp. [92]
30 (oligoarticular arthritis or oligoarthritis or polyarticular arthritis or polyarthritis or pauciarticular arthritis or systemic arthritis or psoriatic arthritis or enthesistis-related arthritis or undefined arthritis).mp. [109]
31 [Arthritis, Rheumatoid/]
32 28 or 29 or 30 or 31 [189]
33 [exp CHILD/]
34 [exp INFANT/]
35 [exp ADOLESCENT/]

36 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler or baby or babies or pediatric or paediatric).mp. [17963]
37 33 or 34 or 35 or 36 [17963]
38 27 and 44 and 49 [1]

EMBASE

1 ECONOMICS/ [4551]
2 exp "HOSPITAL COST"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST UTILITY ANALYSIS"/ or exp "DRUG COST"/ or exp "COST BENEFIT ANALYSIS"/ or exp "COST MINIMIZATION ANALYSIS"/ or exp "COST"/ or exp "HEALTH CARE COST"/ or exp "COST OF ILLNESS"/ [125844]
3 ECONOMICS/ [4551]
4 HEALTH ECONOMICS/ [7210]
5 PHARMACOECONOMICS/ [822]
6 1 or 2 or 3 or 4 or 5 [132951]
7 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw. [161889]
8 (expenditure$ not energy).tw. [7025]
9 (value adj1 money).tw. [303]
10 budget$.tw. [6612]
11 7 or 8 or 9 or 10 [168395]
12 6 or 11 [229695]
13 letter.pt. [279868]
14 editorial.pt. [135272]
15 13 or 14 [415140]
16 11 not 15 [165165]
17 ANIMAL/ [15728]
18 Human/ [4796507]
19 17 not (17 and 18 [12768]
20 16 not 19 [165073]
21 (metabolic adj cost).ti,ab,sh. [292]
22 ((energy or oxygen) adj cost).ti,ab,sh. [16257]
23 20 not (21 and 22) [165021]
24 (arthriti$ adj3 (juvenile$ or child$)).mp. [4816]
25 Juvenile Rheumatoid Arthritis/ [4494]
26 (oligoarticular arthritis or oligoarthritis or polyarticular arthritis or polyarthritis or pauciarticular arthritis or systemic arthritis or psoriatic arthritis or enthesistis-related arthritis or undefined arthritis).mp. [7088]
27 Arthritis, Rheumatoid/ [42254]
28 24 or 25 or 26 or 27 [51809]
29 exp Child/ [492040]
30 exp Infant/ [137224]
31 exp Adolescent/ [322915]
32 (juvenile$ or child or children or infant$ or minor$ or adolescent$ or toddler$ or baby or babies or pediatric or paediatric).mp. [712402]
33 29 or 30 or 31 or 32 [922956]
34 23 and 28 and 33 [99]

Cochrane Library

1 MeSH descriptor Economics explode all trees in MeSH products
2 MeSH descriptor Economics, Hospital explode all trees in MeSH products
3 MeSH descriptor Economics, Medical explode all trees in MeSH products
4 MeSH descriptor Economics, Pharmaceutical explode all trees in MeSH products
5 MeSH descriptor Costs and Cost Analysis explode all trees in MeSH products
6 MeSH descriptor Cost of Illness explode all trees in MeSH products
7 MeSH descriptor Cost-Benefit Analysis explode all trees in MeSH products
8 MeSH descriptor Hospital Costs explode all trees in MeSH products
9 MeSH descriptor Health Care Costs explode all trees in MeSH products
10 MeSH descriptor Employer Health Costs explode all trees in MeSH products
11 (econ* or cost or costs or costly or costing or price or pricing or pharmacoeconomic*) in All Fields in all products
12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
13 MeSH descriptor Arthritis, Juvenile Rheumatoid explode all trees in MeSH products
14 (#12 AND #13)

Appendix 25

Studies excluded from the systematic review of costs

Study	Reason for exclusion
Barrett EM, Scott DG, Wiles NJ, Symmons DP. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. *Rheumatology* 2000;**39**:1403–9	Adults with RA
Birnbaum HG, Barton M, Greenberg PE, Sisitsky T, Auerbach R, Wanke LA, *et al*. Direct and indirect costs of rheumatoid arthritis to an employer. *J Occup Environ Med* 2000;**42**:588–96	Adults with RA
Cooper NJ, Mugford M, Scott DG, Barrett EM, Symmons DP. Secondary health service care and second line drug costs of early inflammatory polyarthritis in Norfolk, UK. *J Rheumatol* 2000;**27**:2115–22	Adults with RA
Cooper NJ, Mugford M, Symmons DP, Barrett EM, Scott DG. Total costs and predictors of costs in individuals with early inflammatory polyarthritis: a community-based prospective study. *Rheumatology* 2002;**41**:767–74	Adults with RA
Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. *Rheumatology* 2000;**39**:28–33	Adults with RA
Fautrel B, Guillemin F. Cost of illness studies in rheumatic diseases. *Curr Opin Rheumatol* 2002;**14**:121–6	Adults with RA
Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2310–19	Adults with RA
Packham JC, Hall MA, Pimm TJ. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: predictive factors for mood and pain. *Rheumatology* 2002;**41**:1444–9	No cost data
Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: education and employment. *Rheumatology* 2002;**41**:1436–9	No cost data
Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: social function, relationships and sexual activity. *Rheumatology* 2002;**41**:1440–3	No cost data
Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* 2002;**41**:1428–35	No cost data
Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: a controlled, population-based study. *Arthritis Rheum* 1997;**40**:2235–40	No cost data
Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. *Arthritis Rheum* 2001;**44**:2746–9	Adults with RA
Zak M, Pedersen FK. Juvenile chronic arthritis into adulthood: a long-term follow-up study. *Rheumatology* 2000;**39**:198–204	No cost data

RA, rheumatoid arthritis.

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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