Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review

D Shyangdan, C Clar, N Ghouri, R Henderson,
T Gurung, D Preiss, N Sattar, A Fraser
and N Waugh

**Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk**

HTA

Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review

D Shyangdan,[1] C Clar,[2] N Ghouri,[3] R Henderson,[4] T Gurung,[1] D Preiss,[3] N Sattar,[3] A Fraser[5] and N Waugh[1]*

[1]Warwick Evidence, Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry, UK
[2]Hasenheide 67, Berlin, Germany
[3]University of Glasgow, Glasgow, UK
[4]NHS Highland, Inverness, UK
[5]Aberdeen Royal Infirmary, Aberdeen, UK

*Corresponding author

Declared competing interests of authors: none

This report should be referenced as follows:

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series
Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

Abstract

Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review

D Shyangdan,[1] C Clar,[2] N Ghouri,[3] R Henderson,[4] T Gurung,[1] D Preiss,[3] N Sattar,[3] A Fraser[5] and N Waugh[1]*

[1]Warwick Evidence, Health Sciences Research Unit, Warwick Medical School, University of Warwick, Coventry, UK
[2]Hasenheide 67, Berlin, Germany
[3]University of Glasgow, Glasgow, UK
[4]NHS Highland, Inverness, UK
[5]Aberdeen Royal Infirmary, Aberdeen, UK

*Corresponding author

Background: Non-alcoholic fatty liver disease (NAFLD) is closely linked with obesity and the prevalence of NAFLD is about 17% to 33% in the Western world. There is a strong association of NAFLD with insulin resistance and, hence, insulin sensitisers have been tried. This systematic review examined the clinical effectiveness of insulin sensitisers in patients with NAFLD, to help decide whether or not a trial or trials of the insulin sensitisers was necessary and also to explore whether or not non-invasive alternatives to liver biopsy were available that could be used in a large trial of the insulin sensitisers.

Objective: To review the use of insulin sensitisers in the treatment of NAFLD.

Review methods: A systematic review of the clinical effectiveness of metformin, rosiglitazone and pioglitazone was carried out, including reviews and randomised controlled trials (RCTs). Databases searched were MEDLINE, 1950 to June 2010; EMBASE, 1980 to June 2010; Science Citation Index Expanded, June 2010; Conference Proceedings Citation Index – Science June 2010; The Cochrane Library 2005–10. Abstracts were screened independently by two researchers. A narrative review of diagnostic methods was conducted.

Results: Clinical effectiveness. We identified 15 RCTs (one available as abstract). Four papers explored efficacy of pioglitazone, one rosiglitazone, eight metformin; two compared metformin and rosiglitazone, although one used both metformin and rosiglitazone. The duration of most trials was between 6 and 12 months. Many trials had a small number of participants and the quality of the studies was mixed. Pioglitazone improved all parameters of liver histology. Metformin showed mixed results, with ultrasound changes in two studies showing some improvement in steatosis, whereas there were no changes in the other two. Metformin, however, showed no improvement in non-alcoholic steatohepatitis (NASH) stages. Metformin showed greater reduction in glycosylated haemoglobin (–0.23% to –1.2% vs –0.2% to –0.7%) and fasting plasma glucose (+0.05 to –3.19 mmol/l vs –0.17 to –1.11 mmol/l) compared with pioglitazone. Metformin led to weight reduction (–4.3 to –6.7 kg), whereas participants on pioglitazone gained weight (+2.5 to +4.7 kg). Alanine aminotransferase levels were reduced with both metformin and pioglitazone; however, the reduction in levels with pioglitazone was not different to that caused by vitamin E. Most studies suggested that metformin led to a significant reduction in insulin resistance.

Diagnosis. Non-invasive methods of diagnosing NAFLD without liver biopsy, using combinations of clinical history, laboratory tests and ultrasound, have been explored, but so far liver biopsy is the only proven method of distinguishing simple steatosis from NASH. Transient elastography appears useful, but less so in obese individuals. Magnetic resonance spectroscopy shows promise, but is expensive and not readily available.

Limitations: Mixed quality of trials, with lack of detail as to how some trials were conducted. Many trials had small numbers of patients.

Conclusions: The main need for drug trials is at the NASH stage. However, at present, any trial in the more advanced forms of NAFLD would have to use liver biopsy. The highest priority for research may, therefore, be in the diagnosis of NAFLD, and the differentiation between steatosis and NASH. The newer agents, the glucagon-like peptide-1 analogues such as liraglutide, may be more worthy of a trial.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

AISF	Italian Association for the Study of the Liver
ALD	alcohol-related fatty liver disease
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUROC	area under receiver operating characteristic curve
BAAT	BMI, age, ALT, TG
BAD	BMI, age, T2DM
BARD	BMI, AST/ALT ratio, T2DM
BARG	BMI, age, AST/ALT ratio, HbA_{1c} or glucose
b.i.d.	twice a day
BMI	body mass index
CASP	Critical Appraisal Skills Programme
CK-18	cytokeratin-18
CRN	Clinical Research Network
CT	computerised tomography
DBP	diastolic blood pressure
DCC	Data Coordinating Centre
DURATION	Diabetes therapy Utilization: Researching changes in A_{1c}, weight and other factors Through Intervention with Exenatide ONce weekly
FBC	full blood count
FLD	fatty liver disease
FLIRT	Fatty Liver Improvement with Rosiglitazone Therapy
FPG	fasting plasma glucose
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
HAIR	hypertension, ALT, insulin resistance
HbA_{1c}	glycosylated haemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HOMA–IR	homeostatic model assessment–insulin resistance
HTA	Health Technology Assessment
IQR	interquartile range
ITT	intention to treat
IU	international unit
LDL	low-density lipoprotein
LEAD	Liraglutide Effect and Action in Diabetes
LFT	liver function test
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAFL	non-alcoholic fatty liver
NAFLD	non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	non-alcoholic steatohepatitis
NEFA	non-esterified fatty acid
NFS	NAFLD Fibrosis Score

NGT	normal glucose tolerance
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
PedsQL	Pediatric Quality of Life Inventory
PPAR	peroxisome proliferators-activated receptor
QoL	quality of life
RCT	randomised controlled trial
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
SIGN	Scottish Intercollegiate Guidelines Network
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TE	transient elastography
TG	triglyceride
TONIC	Treatment of Non-alcoholic Fatty Liver Disease in Children
TZD	thiazolidinedione
USG	ultrasonography
UDCA	ursodeoxycholic acid

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 in the notes at the end of the table.

Executive summary

Background

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of disease, ranging from an increased fat content in the liver (steatosis) to inflammatory change (non-alcoholic steatohepatitis – NASH), and potentially to fibrosis and cirrhosis. By definition, it is seen in people whose alcohol intake is not increased (such as < 10 g a day for women, < 20 g a day for men).

Population-based screening studies suggest that the prevalence of NAFLD is in the region of 17–33% in the Western world. The prevalence of NASH is not known because it currently requires a liver biopsy to confirm the diagnosis, but it has been estimated to be around 3% in the total population. We lack good data on the natural history of NAFLD and progression, partly because there are few long-term follow-up studies of well-defined patient cohorts.

The first stage of NAFLD is hepatic steatosis – accumulation of fat in liver cells. NAFLD is strongly linked with insulin resistance and, hence, with obesity and type 2 diabetes. Most people with NAFLD are obese. Because obesity and diabetes have been increasing in the UK, we can expect to see an increase in NAFLD. Steatosis alone does not cause problems. It is the development of NASH, and progression to fibrosis and cirrhosis, which causes the morbidity and mortality in the NAFLD spectrum.

Many treatments have been tried in NAFLD. Because of the link between NAFLD and insulin resistance, two types of drug, which are sometimes called 'insulin sensitisers', have been tried. These are biguanides (metformin) and the glitazones (rosiglitazone and pioglitazone). This review was commissioned by the UK Health Technology Assessment programme to help decide whether or not a trial or trials of the insulin sensitisers was necessary.

Methods

A systematic review of the clinical effectiveness of metformin, rosiglitazone and pioglitazone was carried out. The review included reviews and randomised controlled trials (RCTs). The databases searched were MEDLINE, 1950 to June 2010; EMBASE, 1980 to June 2010; Science Citation Index Expanded, June 2010 (limited to meeting abstracts only); Conference Proceedings Citation Index-Science June 2010; The Cochrane Library 2005–10. No language restriction was applied.

Abstracts retrieved by the searches were screened independently by two researchers for inclusion or exclusion. Data were extracted from the included studies by two researchers with cross-checking. The quality of trials was assessed using seven criteria. Meta-analysis was not considered appropriate.

The original remit for this review did not include a review of diagnostic methods. However, a rapid narrative review of diagnostic methods was carried out, starting with reviewing previous reviews. The aim of this review was to look for non-invasive alternatives to liver biopsy, which could be used in a large trial of the insulin sensitisers.

Results

Clinical effectiveness

A total of 1842 studies were retrieved by the searches, of which 49 were considered possible inclusions. After reading the full texts of these studies, 34 were excluded. The review therefore included 15 RCTs (one available only in abstract form). Four RCTs used pioglitazone, one used rosiglitazone, eight used metformin, two compared metformin and rosiglitazone, and one used both metformin and rosiglitazone. The rosiglitazone results are reported for completeness in the main text. It has been withdrawn from use in Europe.

Five systematic reviews were identified, but none included all of the trials now available.

The quality of the trials was mixed, with a range of scores from '1' to '7' out of a possible seven. The lower scores often reflected a lack of detail as to how the trials were conducted.

Many of the trials had a small number of patients. Four had fewer than 40 recruits. The duration of most trials was between 6 and 12 months.

Pioglitazone

All four pioglitazone studies involved liver biopsies. Pioglitazone was found to improve all parameters of liver histology, was better than placebo, or diet and exercise, or hypocaloric diet, but was no better than vitamin E. It should be noted that the control group on hypocaloric diet lost only 0.5 kg.

Pioglitazone reduced alanine aminotransferase (ALT) levels. In six trials reporting glycosylated haemoglobin (HbA_{1c}), four of which were in patients with diabetes or impaired glucose tolerance, HbA_{1c} level was reduced, by 0.2–0.7%. Weight gain ranging from 2.5 to 4.7 kg was observed with pioglitazone. Results for insulin resistance were mixed, with both increases and decreases reported.

Metformin

Of the eight metformin studies, five involved liver biopsy and three relied on ultrasound. Most showed no clear benefit from the addition of metformin to diet or (in one case) rosiglitazone. Four trials reported ultrasound changes in steatosis, of which two found no difference and two some advantage with metformin. The lack of benefit was in some cases because patients in the control arm improved on diet.

The two trials that compared metformin and rosiglitazone had mixed results. One found significant improvements in histology when the metformin and rosiglitazone groups were combined and then compared with the diet group, but not when the metformin and rosiglitazone groups were considered individually. The other found improvements with rosiglitazone alone, and the combination of rosiglitazone and metformin, but not with metformin alone.

Hence, there is a lack of evidence that metformin improves liver histology at the NASH stage.

Alanine aminotransferase levels improved on metformin. Reductions in HbA_{1c} levels ranged from 0.23% to 1.2% with metformin.

Unlike with pioglitazone, patients on metformin tended to lose weight (by 4.3 kg, based on only one trial). Measures of insulin resistance tended to improve on metformin.

Diagnosis

There is a growing consensus that NAFLD can be diagnosed without liver biopsy, using combinations of clinical history, laboratory tests (full blood count, liver function tests) and ultrasound. A form of ultrasound known as 'transient elastography' may be useful but further research is needed, especially in obese patients. Computerised tomography (CT) scanning may be better than ultrasound, but there are issues around radiation dose and access. Magnetic resonance spectroscopy may be the best of the non-invasive methods, but is expensive and not readily available.

However, distinguishing steatosis from NASH by non-invasive means is proving more difficult, with doubts that this can be done by ultrasound or CT. New methods of magnetic resonance imaging may be more useful, but remain unproven.

Implications for research

The greatest need for drug trials is probably at the NASH stage. However, at present, any trial in the more advanced forms of NAFLD would have to use liver biopsy. The highest priority for research may, therefore, be in the diagnosis of NAFLD and the differentiation between steatosis and NASH.

Further trials of insulin sensitisers may not be the highest priority. Rosiglitazone has now been taken off the market because its cardiovascular safety was less than that of pioglitazone. However, pioglitazone has other adverse effects: weight gain, oedema and fractures. Metformin is safer, but had little effect on liver histology. The newer agents, the glucagon-like peptide-1 analogues, such as liraglutide, may be more worthy of a trial.

One high priority is for research into the ways of preventing people from becoming obese, and into the ways of ensuring weight loss in those who become obese, so that we can reduce the prevalence of NAFLD.

Funding

Chapter 1

Introduction

What is non-alcoholic fatty liver disease?

'Non-alcoholic fatty liver disease' (NAFLD) is a term used for a group of inter-related chronic liver disorders causing a wide spectrum of liver damage associated with increased fat content in the liver in the absence of increased alcohol intake [< 10 g of alcohol per day for women, < 20 g per day for men (around 9–18 units of alcohol per week, respectively)].[1,2] By definition, to have NAFLD, > 5% of the liver weight must be due to accumulation of fat.[2] NAFLD has become recognised as an important problem only recently and was relatively unknown prior to 1980.[3,4] Population-based screening studies suggest that the prevalence of NAFLD is in the region of 17–33% in the Western world.[5] The prevalence of non-alcoholic steatohepatitis (NASH) is not known because it currently requires a liver biopsy to confirm the diagnosis, but it has been estimated to be around 3% in the total population.[5]

The spectrum of potentially progressive liver damage can include:

■ simple (hepatic) steatosis (fatty accumulation in the liver, also known as 'fatty liver')
■ NASH
■ advanced fibrosis
■ cirrhosis
■ hepatocellular carcinoma (HCC), hepatoma, liver cancer.

The term 'NASH' is sometimes used to describe the three subsequent stages after hepatic steatosis,[6] but in this report will be used only for the inflammatory stage that follows simple steatosis.

Non-alcoholic fatty liver disease is the most common cause of abnormal blood tests of liver function.[7] The liver damage seen in NAFLD is similar to the changes seen in alcohol-related liver disease,[3] but, by definition, individuals with NAFLD do not consume increased quantities of alcohol.

Not every individual who develops simple steatosis (which is asymptomatic) progresses to the subsequent stages of liver damage, but some will progress to chronic liver failure (inability of the liver to fulfil its role in detoxifying the blood and synthesising various compounds necessary for the body to function) with potential subsequent acute decompensation. Chronic liver failure is associated with a very poor prognosis.[8] Finally, some individuals can go on to develop HCC after reaching the cirrhotic stage.[9] Data on disease progression are reviewed later in the chapter.

Although more cases of cirrhosis are due to alcohol than to NAFLD,[10] more people have some form of NAFLD than alcohol-related fatty liver disease (ALD).[11] NAFLD is strongly linked to insulin resistance, and thus associated with conditions such as type 2 diabetes mellitus (T2DM) and obesity. Therefore, as the prevalence of these two conditions increases, it is likely that there will be a marked rise in NAFLD, making NAFLD a growing issue for health-care providers. NAFLD is also a risk factor for the development of T2DM.[5]

What causes non-alcoholic fatty liver disease and its progression?

The key feature in NAFLD is the accumulation of fat in the liver. As mentioned above, simple fat deposition occurs at the beginning and is relatively benign; however, this can progress to inflammatory change (steatohepatitis, NASH), with the possible formation of scar tissue (fibrosis) and further structural change associated with the reduction in liver function (cirrhosis).

The accumulation of liver fat

Hepatic steatosis (accumulation of fat within liver cells) is the first stage of NAFLD. There is no single mechanism leading to hepatic steatosis, but rather the combination of a number of pathologies that ultimately disrupt normal lipid [fat-rich products, mainly triglycerides (TGs) – fatty acid molecules] movement through the liver cell and cause lipid accumulation. The fat in the liver can be traced to three sources – dietary intake, de novo synthesis and circulating non-esterified fatty acids (NEFAs) derived from body fat stores.[5] It is known that high-fat diets can lead to hepatic steatosis, but it appears that NEFAs are the main source of liver fat, with 60% in individuals with NAFLD who have a normal fat-containing diet.[12]

The body's resistance to the effects of the hormone insulin (required for the uptake of glucose – the main sugar derived from dietary carbohydrate by liver, fat and muscle cells) is thought to play a key role in increasing levels of NEFAs, particularly the insulin resistance shown by fat and muscle cells (*Figure 1*). Once lipid starts to accumulate in the liver this can, in fact, worsen the body's insulin resistance, reducing the beneficial effects of insulin, leading to a vicious cycle.[13–15]

Inflammation of the fatty liver – non-alcoholic steatohepatitis

McCullough[16] has reviewed the pathophysiology of NASH. Hepatic steatosis is considered to have a benign course in most cases.[17] This may be because of associated counter-regulatory
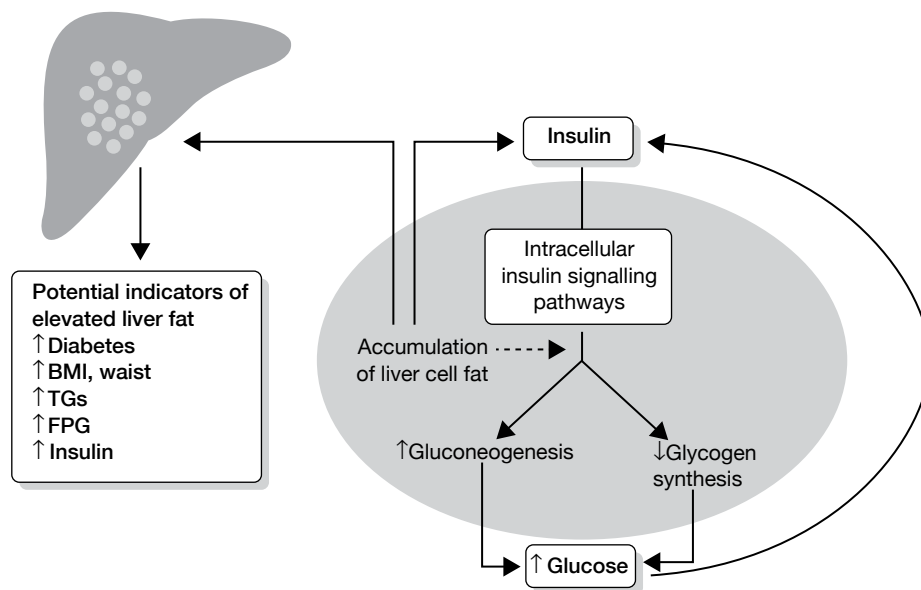
FIGURE 1 The effects and potential clinical indicators of accumulating liver fat. The presence of ectopic fat in the liver cell leads to hepatic insulin resistance following the accumulation of intracellular lipid by-products, which leads to disturbed glucose metabolism. Gluconeogenesis is the production of glucose from protein and fat breakdown, and glycogen is the form of complex carbohydrate that glucose is stored as. BMI, body mass index; FPG, fasting plasma glucose. Adapted from Preiss and Sattar.[5]

protective mechanisms, which means that liver tissue changes (other than steatosis) and liver function may remain normal. NASH represents the stage when the fatty liver starts to show inflammatory change. It is the development of NASH and progression to fibrosis and cirrhosis that is responsible for the liver-specific morbidity and mortality of NAFLD.

It is unclear why only approximately 25–30% of patients with simple steatosis develop NASH.[16] The counter-regulatory processes occurring as a means to maintain liver cell (hepatocyte) health forms the basis of the older 'two-hit' theory in the development of NASH. A newer theory suggests that NASH occurs by liver fat directly causing inflammation.

In the two-hit theory, the first hit refers to the accumulation of liver fat. It has been proposed the hepatocytes act, in addition, as a reservoir of toxic agents and are most susceptible to a 'second hit' – oxidative stress[18,19] – caused by endogenous compounds within liver cells and by environmental toxins.[20,21] The cells in the body constantly react with inhaled oxygen, producing energy – oxidation. As a consequence of this activity, highly reactive molecules (free radicals) are produced. Free radicals interact with other molecules within cells. This can cause damage – oxidative stress – to proteins, membranes and genes. Patients with NASH have increased levels of oxidative stress when compared with patients with steatosis alone.[22,23]

In addition to endogenous toxins, three factors have been proposed as potential causative mechanisms for producing this oxidative stress: increased insulin levels, lipid peroxidation and liver iron content (*Figure 2*).

Insulin may injure the liver both directly and indirectly.[24,25] The indirect effects are related to the hyperinsulinaemic state increasing liver fat accumulation, as described earlier. The direct effect may be due to insulin's ability to generate oxidative stress.[25] It also appears to have direct effects by stimulating scar tissue formation, especially in the presence of increased glucose levels.[26] This may explain the observation that NAFLD patients with T2DM have a particularly poor prognosis.[17,27] Insulin may be directly involved in causing stress on parts of the liver cell that lead to cell death (apoptosis). This, in itself, may exacerbate insulin resistance.[28]

Increased lipid peroxidation (breakdown of NEFAs, causing oxidative stress) has been demonstrated in patients with NAFLD.[22,23,29–31] As previously described, patients with NAFLD have increased breakdown of fat stores and increased delivery of NEFAs to the liver.[22,32] The
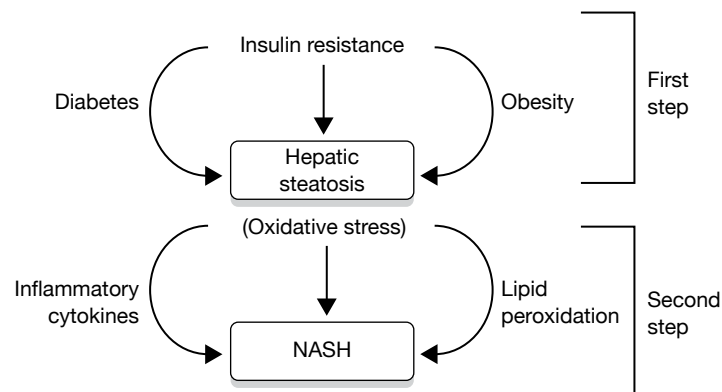
FIGURE 2 The two-hit theory of NASH. This involves insulin resistance, which causes hepatic steatosis, a process enhanced by obesity and/or T2DM. Once developed, hepatic steatosis may remain in a benign state or progress to NASH via the mechanisms discussed. Reproduced with permission from AJ McCullough. Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006;**40**(Suppl. 1):17–29.[16]

products of NEFA oxidation are capable of generating oxidative stress and subsequent lipid peroxidation, setting up a vicious cycle.

In response to oxidative stress, there is usually an increased synthesis of antioxidants. However, NAFLD patients have decreased antioxidants (glutathione).[33] Therefore, patients with NAFLD have an impaired ability to produce sufficient antioxidants. A deficiency in antioxidants is also supported by a preliminary report that demonstrated that betaine (a naturally occurring antioxidant) improved the microscopic images of liver tissue and liver function tests (LFTs) in patients with NAFLD.[34]

The role of iron as a pro-oxidant in NASH is unclear. In McCullough's review,[16] there is mention of patients with NAFLD having increased ferritin levels, and a relationship between hepatic iron and insulin resistance. However, there is acknowledgement that there is no strong evidence associating iron overload with NAFLD. Therefore, for now, iron is likely to be important in only a minority of patients with NASH and more research is required on iron as a pathophysiological factor.

There is also good evidence to support a one-hit theory of liver fat causing chronic inflammation directly, leading to direct NAFLD progression.[5] A key player in steatosis formation appears to be nuclear factor-κB (NF-κB). This is a transcription factor – an intracellular protein required for the transcription of deoxyribonucleic acid to form proteins. In animal models it has been shown that a high-fat diet with resultant hepatic steatosis leads to increased NF-κB signalling in the liver.[35] This then induces the production of chemicals involved with causing inflammation, which may play a role in the progression of NAFLD. The transcription factor also leads to activation of specific cells (Kupffer cells and macrophages) within liver tissue, which are known to cause further damage to liver tissue. In the same study[35] there is evidence that inflammation, in the form of isolated increased NF-κB expression in rat liver, can lead directly to insulin resistance.[35]

Another factor that may be involved in the process is adiponectin, a polypeptide produced in adipocytes (fat cells) and which may be protective via an insulin-sensitising effect in the liver. Polyzos *et al.*[36] reviewed the evidence on the role of adiponectin and noted that it was reduced in NAFLD and NASH, and increased by most interventions which improved NAFLD, including weight loss, bariatric surgery and pioglitazone, but not metformin. However, formal interventions and links to adiponectin genotypes would be required to prove a causal relationship.

The advanced stages – fibrosis and cirrhosis

As NAFLD progresses, more advanced forms can occur – fibrosis and cirrhosis. Liver fibrosis is the formation of excess fibrous tissue in the liver[37] and is a reparative or reactive process, as a result of NASH,[38] or, in a few cases, direct progression from simple steatosis.[39] Liver fibrosis can lead to loss of function.

Cirrhosis of the liver is advanced fibrosis associated with regenerative nodules (an attempt at repair).[40] Cirrhosis is associated with variable and usually irreversible loss of liver function. When liver function is minimally or not significantly compromised clinically, it is often termed 'compensated cirrhosis'; however, when there is clinical evidence that the cirrhotic liver is unable to function properly, it is termed 'decompensated cirrhosis'. Whereas decompensation can be reversible if due to an acute insult (e.g. infection), decompensation is often progressive, resulting in liver failure and death. Hui *et al.*[41] in their prospective cohort study followed up 23 patients with NASH-associated cirrhosis for a mean duration of 84 months (range 5–177 months) and found that 9 out of 23 cases developed liver-related morbidity (eight developed ascites and/or encephalopathy, one developed variceal bleeding). The authors then found that probability

of complication-free survival was 83%, 77% and 48% at 1, 3 and 10 years, respectively, and the cumulative probability of overall survival at 1, 3 and 10 years was 95%, 90% and 84%, respectively.[41]

Other conditions associated with non-alcoholic fatty liver disease

As described above, other diseases and physiological states are associated with the development, severity and progression of NAFLD. The main ones are diabetes mellitus (particularly T2DM[42]), insulin resistance, obesity or overweight, and increased levels of TGs in the blood (hypertriglyceridaemia).[7] Insulin resistance, obesity and hypertriglyceridaemia are key components of the (multiply defined) topical metabolic syndrome,[43] a 'syndrome' associated with increased cardiovascular events.[44] A substantial number of studies have shown the increased prevalence of these three conditions in patients with NAFLD, and some data are summarised in *Table 1*.[45] More data relating to these conditions and NAFLD will be commented on in the next section.

Although all three conditions are associated with the development of NAFLD, it is also likely that NAFLD, associated with elevations in liver enzymes, has a causal role in development of T2DM,[46–49] as previously highlighted in *Figure 1*.

Prevalence and natural history of non-alcoholic fatty liver disease

Estimates of prevalence are variable, because of differences in the method used to diagnose the various stages of NAFLD and the variation in sample selection and size. As the histological (microscopic tissue) features of NAFLD may be indistinguishable from those of alcoholic liver disease, the diagnosis requires the exclusion of known excessive alcohol intake.

International data

As previously mentioned, screening studies using serum liver tests and ultrasonography (USG) suggest that the prevalence of NAFLD ranges from 17% to 33% in the general population of the Western world.[50] Imaging using magnetic resonance spectroscopy (MRS) gives NAFLD a prevalence of 34%.[51] The prevalence of NASH is less well known, as a liver biopsy is required to confirm the diagnosis. Estimates of the prevalence are in the range of approximately 3% in the general population and higher among obese persons.[52] The average age at diagnosis lies between 45 and 55 years,[45] and has a slight female preponderance.[45]

TABLE 1 Type 2 diabetes mellitus, obesity and hypertriglyceridaemia in NAFLD

Author	No. of patients	Diabetes (%)	Obesity (%)	Hypertriglyceridaemia (%)
Ludwig (1980)	20	25	90	67
Diehl (1988)	39	88	71	–
Lee (1989)	49	51	69	4
Powell (1990)	42	36	93	81
Bacon (1990)	33	21	39	21
Matteoni (1999)	132	33	70	92
Angulo (1999)	144	28	60	27

Modified from McCullough.[45]

Natural history

Good long-term data (including UK data) on the natural history of NAFLD from simple steatosis to more advanced stages are lacking, for a number of reasons. NAFLD has only recently been characterised in detail. There are few long-term follow-up studies of well-defined patient cohorts, and follow-up liver biopsies have been performed in only a limited number of patients. The diagnostic method for fatty liver – blood tests ± ultrasound ± liver biopsy (the current gold standard)[50] – is not uniform, and studies using ultrasound to diagnose steatosis will give higher numbers than liver biopsy. Furthermore, it is possible that the long-term complications of NAFLD may be under-recognised and under-reported, as the characteristic features of fatty liver, such as steatosis, may disappear in the late stages of the disease, leading to a picture of 'bland' cirrhosis, frequently described as 'cryptogenic', rather than NAFLD-related cirrhosis, which is now recognised as the most common cause of cryptogenic cirrhosis.[53] Finally, most studies to date that have studied the natural history of NAFLD have been retrospective analyses (e.g. clinical follow-up from cohort studies) or case series in which selected patients with a diagnosis of NASH underwent subsequent liver biopsies.[6]

Despite these limitations, the following diagrams indicate the current thinking on the prevalence and progression of NAFLD (*Figures 3* and *4*).

Hence, it is difficult to determine what proportion of an unselected population will develop NAFLD-related cirrhosis and subsequent HCC. One study estimated that 7% of cases of HCC were related to underlying NAFLD or cryptogenic cirrhosis but such data are, at best, approximates.[9]
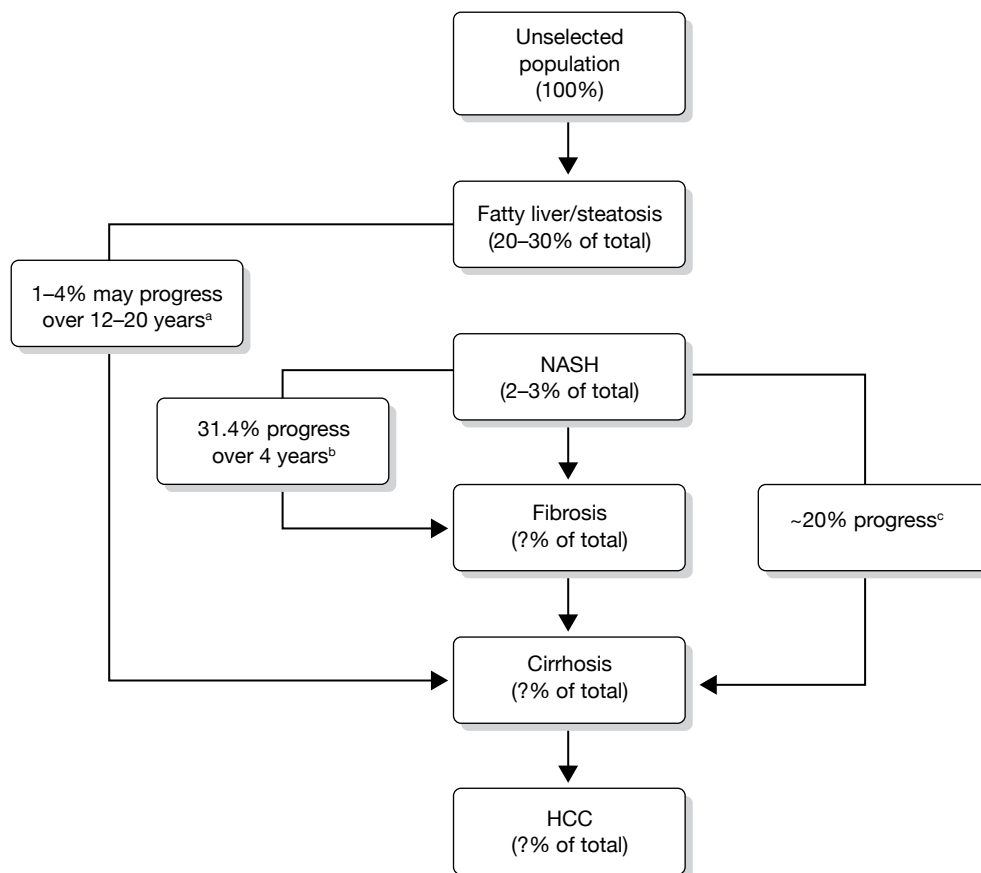
FIGURE 3 The natural history of NAFLD. Adapted from Preiss and Sattar.[5] a, Matteoni *et al.*,[17] Day;[39] b, Fassio *et al.*,[54] McCullough.[16]
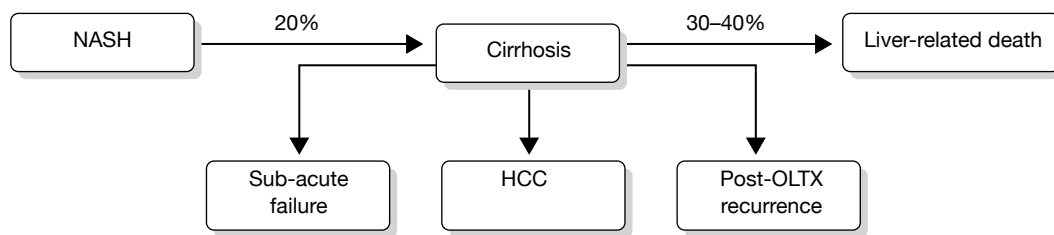
FIGURE 4 The natural history and clinical outcomes of NASH. OLTX, orthotopic liver transplantation. Reproduced with permission from AJ McCullough. Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006;**40**(Suppl. 1):17–29.[16]

UK data

The UK data on NAFLD are limited, with no nationwide data. The incidence of NAFLD in a hepatology catchment area in England of 200,000 residents, based on referrals to a secondary care setting, was calculated at 29 per 100,000 population.[55] This was subdivided into 23.5 per 100,000 population for non-cirrhotic NAFLD and 5.5 per 100,000 population for cirrhotic NAFLD. There are no satisfactory prevalence data.

Associations with type 2 diabetes mellitus and obesity

Numerous studies have reported the increased prevalence of NAFLD in individuals with T2DM,[56] and increased risk and severity of NAFLD in T2DM.[57–59] In 939 randomly selected people with T2DM in Edinburgh, ultrasound-detected steatosis was present in 73.9% of subjects.[60] A recent study in the USA reported the prevalence of ultrasound-determined NAFLD to be 69.5%.[56] The prevalence of NAFLD in obese individuals (ultrasound determined) has been estimated to be high as 80%.[50] One thing is certain – as the incidence and prevalence of obesity and T2DM increase,[61] the incidence and prevalence of fatty liver, and hence NASH and more severe forms of NAFLD, are also likely to increase.

Cardiovascular risk

In addition to the organ-specific related morbidity and mortality of NAFLD, NAFLD has also been linked with increased cardiovascular risk, largely through the components of the metabolic syndrome. A detailed review in 2007 on NAFLD and cardiovascular risk[62] showed that this increased risk was related to the presence of known cardiovascular risk factors, several of which (insulin resistance, obesity and dyslipidaemia/hypertriglyceridaemia) are also well associated with NAFLD.[63]

Similar conclusions were reached in a more recent review by Ghouri *et al.*,[64] who concluded that the presence of NAFLD was an indication for screening for T2DM, but that it did not add useful data on CVD risk compared with traditional risk factors.

Hence, it appears that NAFLD itself is not an independent contributor to CVD risk, but that it is associated with adverse risk factors.

A more recent review by Targher *et al.*[65] also addressed the question of whether or not NAFLD increased the risk of cardiovascular disease, independent from its association with traditional risk factors. They concluded that:

> Although additional research is required to draw a definite conclusion, these observations raise the possibility that NAFLD – especially its necroinflammatory variant, NASH – not only is a marker of cardiovascular disease but may also be involved in its pathogenesis. This process may occur through the systemic release of pro-atherogenic

mediators from the steatotic and inflamed liver or through the contribution of NAFLD itself to insulin resistance and atherogenic dyslipidaemia.

One key issue noted by Targher *et al.*[65] is that cardiovascular disease is a greater threat to people with NAFLD than liver disease.

Associations with type 1 diabetes

A recent study[66] has reported a high prevalence of NAFLD in 202 patients with type 1 diabetes in Italy. NAFLD was diagnosed by history and liver ultrasound. Over half of the group were classed as having NAFLD. Those who did were older, had suffered from diabetes longer and had higher body mass indices (BMIs) than those who did not.

Clinical features of non-alcoholic fatty liver disease

Given that NAFLD is a spectrum of (often progressive) liver damage, the clinical presentation can vary depending on the stage of presentation. Simple hepatic steatosis or fatty liver is often asymptomatic and is picked up only following investigations of abnormal blood LFTs. Symptoms, when present, may include fatigue and right upper quadrant pain and the most commonly reported clinical finding is hepatomegaly (enlarged liver on examination).[67] Often these features are more apparent in individuals with NASH or early cirrhosis. If advanced cirrhosis eventually develops prior to diagnosis, presentation is similar to that of cirrhosis from other causes, with clinical signs including ascites (fluid collecting in the abdomen), variceal haemorrhage (bleeding from large veins in the gastrointestinal tract), splenomegaly (enlarged spleen on examination), bruising and eventual jaundice.

As mentioned above, NAFLD is associated with several other metabolic disorders, and therefore people with NAFLD can exhibit clinical features of these conditions as well. It is beyond the scope of this report to go into this aspect in detail.

Diagnosis of non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease can be reasonably accurately diagnosed from clinical history and ultrasound. However, staging is more difficult, and the current consensus is that NASH can be diagnosed only after liver biopsy. This could be a major hindrance to any trials that need to recruit large number of patients. Liver biopsy can have complications, such as bleeding.

For detecting liver fibrosis, various non-invasive alternatives to liver biopsy have been suggested, including combinations of blood tests ('serum marker panels') and either transient or real-time elastography (a form of ultrasound). For detecting NAFLD, ultrasound and magnetic resonance imaging (MRI)/MRS have been suggested.

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme is commissioning a full review of evidence on non-invasive methods for the assessment and monitoring of liver fibrosis and cirrhosis (HTA no. 09/07),[68] and so this review does not duplicate that. However, we review the diagnosis of lesser degrees of liver damage in *Chapter 3*.

Biochemical picture associated with non-alcoholic fatty liver disease

Table 2 summarises the biochemical pattern in NAFLD, and has been compared with ALD, the other most common cause of liver problems.[5]

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [and sometimes gamma-glutamyl transferase (GGT)] are components of the broader group of liver function blood tests known as the LFTs. It should be noted that the AST concentration can be higher than ALT in cirrhosis, and thus in individuals with known NAFLD a rising AST concentration (and reversal of the ALT/AST ratio) is potentially a bad prognostic sign, suggesting necrosis (liver cell death associated with inflammation).[5]

Predicting non-alcoholic fatty liver disease

There are published algorithms that have attempted to detect individuals with a higher likelihood of NASH.[69,70] Factors such as age (> 50 years), BMI (> 28 kg/m^2), hypertriglyceridaemia and elevated ALT level were risk factors that were independently associated with liver fibrosis. A scoring system combining these factors could reduce the number of patients requiring liver biopsy.[69]

Treatment of non-alcoholic fatty liver disease

There is currently no approved treatment (medical or surgical) for NAFLD. Given that NAFLD is a group of inter-related progressive liver disorders, the aim and type of treatment will depend on the stage at which the diagnosis is made. There is no available prospective evidence showing the outcome of any form of treatment on important long-term outcomes, such as the development of cirrhosis or HCC. Treatment is aimed at reducing future risk of diabetes, or optimising control in patients with diabetes, treating obesity and reducing cardiovascular risk. Interventional studies have tended to use improvements in LFTs and liver histology as surrogate end points, based on the assumption that these will reflect subsequent reductions in morbidity from NAFLD.

TABLE 2 Biochemical profile associated with NAFLD

Feature	NAFLD	ALD
ALT	↑	→
AST	→	↑
ALT/AST ratio	> 1.0	< 1.0
GGT	→↑	↑↑
Mean corpuscular volume	→	↑
FPG	→↑	→
HDL-cholesterol	↓	↑↑
TGs	↑	↑ or ↑↑

FPG, fasting plasma glucose; HDL, high-density lipoprotein.

Lifestyle changes

Reduced calorie intake and increased physical activity are viewed as logical methods to reduce liver fat content. Two studies have shown that a reduction in weight by 10% significantly reduced elevated LFTs compared with subjects with NAFLD who did not lose as much weight.[71,72] Park *et al.*[72] from Republic of Korea reported a marked reduction in liver enzymes (AST and ALT) in those who lost weight, but not in those who did not. Ueno *et al.*[73] from Japan reported that effects of intensive lifestyle modification over a 3-month period in overweight patients with NAFLD produced an improvement in the microscopic changes in liver tissue, but such changes did not attain significance.[73] However, a reduction of three units in BMI normalised previously elevated AST and ALT levels.

Weight loss drugs

Published pilot data on orlistat, a weight loss drug that reduces fat absorption, have shown improvements in LFTs, ultrasound findings and microscopic changes in liver tissue.[74,75] A further small study[76] compared orlistat with another drug – sibutramine, an appetite suppressant – and the results showed an improvement in LFTs and reduced liver fat on ultrasound in both groups.

In a detailed review of the effects of lifestyle modification with and without the use of weight loss drugs in patients with steatosis and NASH, Harrison and Day[77] concluded that a weight loss of 10% of body weight not only improved the biochemical measures seen in NAFLD, but also improved the histological changes seen in NASH. They also concluded that the evidence from a number of studies suggested that physical activity alone, or with only modest (3%) weight loss, was also effective in improving insulin sensitivity.

More recently, a high-quality systematic review by Musso *et al.*[78] reviewed all treatments for NAFLD. The authors also concluded that weight loss improved or reversed NASH, but that it appeared from two randomised controlled trials (RCTs) that weight loss had to be at least 7% or 9% for histological features to measurably improve. Musso *et al.*[78] came to the same conclusion as Harrison and Day[77] (but based on different studies) – that the evidence suggested that physical activity improved NAFLD independently of weight loss. These data, in turn, concur with evidence for an independent association of higher activity levels, albeit assessed by questionnaire, with lower GGT levels in a cohort study of British women.[79]

Drugs that control blood glucose levels

Trials using drugs that improve the body's sensitivity to the effects of insulin have been performed in individuals with NAFLD. Two main drugs – metformin and thiazolidinediones (TZDs) (glitazones) – have been investigated. Metformin reduces glucose production in the liver and improves the uptake of circulating glucose in the blood by fat and muscle, whereas the glitazones improve the uptake of circulating glucose in the blood and are also believed to redistribute fat away from ectopic sources (particularly the liver) to subcutaneous areas, often with an overall increase in weight (substantial in some individuals).[80]

The glitazones have adverse effects, including oedema, higher risk of fracture and in addition the development and worsening of heart failure;[81,82] and rosiglitazone moderately increases cardiovascular risk[83,84] and has recently been suspended in Europe.

The evidence on metformin and the glitazones is reviewed in *Chapter 2*.

Non-alcoholic fatty liver disease and other drugs

Patients with NAFLD are likely to be considered for lipid-lowering statin therapy owing to their elevated lipid levels and increased cardiovascular risk. Statin therapy in NAFLD certainly appears safe and should not be avoided because of mildly abnormal LFTs.[85] There is also some evidence

of improvement in liver histology on statin therapy from a small placebo-controlled study that was recently published.[86] Other drugs studied have included vitamin E and fibrates. Vitamin E therapy has produced variable results[87,88] and fibrate therapy has not shown benefit thus far.[89] In the only placebo-controlled studies so far, combination therapy with the bile component ursodeoxycholic acid (UDCA) with vitamin E for 2 years resulted in a significant reduction in steatosis.[90] UDCA therapy alone did not improve changes in liver tissue, although there was an improvement in LFTs. In two small studies, treatment with the angiotensin II blocker, losartan, also led to improvements in liver histology.[91,92]

A review of all drugs for NAFLD was not in our remit, but we note the findings of the recent review by Musso et al.,[78] who found that:

- There is some evidence of benefit from treatment with polyunsaturated fatty acids. Trials are in progress.
- Fibrates had no effect.
- The evidence on statins was sparse, but there was some evidence of benefit from atorvastatin.
- The lipid-lowering drug probucol lowered ALT, but also high-density lipoprotein (HDL), which might increase cardiovascular risk.
- UDCA had little or no effect.
- There were mixed results with antioxidants.
- Pentoxifylline appeared to be of benefit; two RCTs are under way.
- Telmisartan (an angiotensin receptor blocker) appeared to reduce fibrosis, the only drug to do that. It improved steatosis, ballooning and lobular inflammation. It led to a reduction in insulin resistance, and TG and total cholesterol (TC) levels. It is noteworthy that the effects of valsartan were less despite similar blood pressure effects. The liver effects of telmisartan may be related to its peroxisome proliferators-activated receptor (PPAR) gamma activity.
- There was some evidence of benefit for L-carnitine.
- Orlistat added to diet resulted in little difference – weight loss of 8% instead of 6% on diet alone.

Surgery

Recently, data on surgery for morbid obesity with 18- to 24-month follow-up have been published. There are two main types of surgery for obesity. One procedure, gastric bypass surgery, in essence involves reducing the size of the stomach, by bypassing a large section of the stomach and connecting it to the small intestine, and this can be done laparoscopically (keyhole surgery). The second procedure is adjustable gastric banding, and involves placing an adjustable band over the top part of the stomach, creating a pouch that reduces the size of the stomach, and is also done laparoscopically. Studies have shown improvement of NAFLD staging or even complete disease resolution following surgery. Mummadi et al.[93] carried out a systematic review to explore effectiveness of bariatric surgery in patients with NAFLD and found that the procedure was safe, with resolution of steatosis in 91.6% of patients, improvement of steatohepatitis and fibrosis in 81.3% and 65.5% of patients, respectively, and resolution of NASH in 69.5%.[93]

The effects of bypass surgery and concomitant weight loss (mean loss 50 kg), evaluated by liver biopsy, found considerable improvements in the prevalence of steatosis (90% preoperatively to 2.9% post-operatively), hepatocellular ballooning (swelling of liver cells: 58.9% preoperatively to 0% post-operatively) and fibrosis (50% down to 25%).[94] In a similar study,[95] there were similarly impressive reductions in steatosis, fibrosis and hepatocellular ballooning. In this latter study on a group of 18 patients, NASH resolved in 84% of patients and steatosis in 75%. Laparoscopic adjustable gastric banding with resultant weight loss has also led to promising improvements in liver histology.[96,97] As obesity surgery is relatively novel, long-term outcome data are still limited, but should become more available as more of these procedures are performed.

Musso *et al.*[78] concluded that the RCTs of surgery had insufficient follow-up as yet, noting that liver enzymes fluctuated and did not always correlate with fibrosis and NASH. However, a review of bariatric surgery by Kushner and Noble[98] noted that two studies had shown resolution or improvement in NASH and fibrosis after bariatric surgery.

Conclusion

In summary, NAFLD is a chronic liver condition with a spectrum from simple steatosis to liver failure, associated with metabolic disturbances that result in organ-specific and cardiovascular morbidity and mortality. It appears to be increasing in prevalence. Unless this trend is reversed, this is likely to lead to increased demands on NHS resources in the years to come.

Decision problems

The HTA commissioning brief for this review identified the main issues as being the clinical effectiveness and cost-effectiveness of the insulin sensitisers in NAFLD, with the expectation that a trial might be required.

The first aim of this review is therefore to assess the current evidence base, with possible outcomes as follows:

- There may be enough evidence to show that these drugs are effective, and that a further trial is not necessary. Alternatively, there may be sufficient evidence to show that, though effective, the effect size is too small to make them worth pursuing as a therapy for NAFLD.
- There may be insufficient evidence for use in therapy, but enough to justify a large trial.

If there were to be a large trial, one problem would be how to identify eligible patients. It would be impractical to carry out liver biopsies on large numbers of people, so we would need a non-invasive screening test. Possible options are reviewed in *Chapter 3*.

Another consideration, which is outwith the scope of this review, is whether or not other drugs might be better options. The number of drugs that have been used suggests that none has been strikingly effective. Chekhov's comment may be relevant: 'When a lot of remedies are suggested for a disease, that means it can't be cured'.[99]

However, the evidence suggests that NAFLD can be cured by sufficient weight loss. Unfortunately, adherence to lifestyle change is frequently poor.

Chapter 2

Clinical effectiveness

Methodology

Criteria for considering studies for this review

Types of studies

Systematic reviews and RCTs. There was no size restriction on the number of patients in trials, as those with inadequate numbers, and hence power, might be useful when combined in a meta-analysis. Observational studies were considered for data on safety.

Types of participants

Participants of any age, sex or ethnic origin with NAFLD proven by liver biopsy.

Types of interventions

Metformin, pioglitazone or rosiglitazone given at any dose or any duration, given separately or in combination versus no intervention, placebo or other pharmacological interventions.

Types of outcome measures

Measures of disease progression such as:

- fibrosis and cirrhosis
- other hepatic-related morbidity, such as variceal bleeding or liver failure
- cardiovascular events
- quality of life (QoL)
- new diabetes
- adverse events.

Search strategy

Comprehensive systematic searches of electronic databases were performed in order to retrieve relevant papers.

Searches were conducted in the following sources to identify both published studies and meeting abstracts:

- MEDLINE, 1950 to June 2010; EMBASE, 1980 to June 2010; Science Citation Index – Expanded, June 2010 (limited to meeting abstracts only); Conference Proceedings Citation Index – Science, June 2010; The Cochrane Library, 2005–2010; and authors' reference lists. Websites such as 'ClinicalTrials.gov' were systematically searched to find any ongoing trials.

The following MEDLINE search strategy (Ovid) was adapted for use with the other databases:

1. fatty liver/
2. liver.tw.
3. (non-alcoholic or non alcoholic or nonalcoholic).tw.
4. (fatty or steato*).tw.
5. (NAFLD or NAFLD or NASH).tw.

6. 4 and 3 and 2
7. 6 or 1 or 5
8. exp Metformin/
9. exp Thiazolidinediones/
10. (insulin sensit* or metformin or pioglitazone or rosiglitazone or thiazolidinedione* or glitazone*).tw.
11. 18 or 9 or 10
12. 7 and 11.

All of the relevant systematic reviews were searched for additional studies. No attempt was made to find unpublished studies. No language restriction was applied to the search strategy.

Details of the electronic search strategies used for the review of clinical effectiveness are given in *Appendix 1*.

Identification of studies

Abstracts and titles retrieved by the search strategy were assessed independently by two researchers and screened for inclusion and exclusion. Full texts of studies considered possible inclusions were obtained and each was examined by two reviewers independently. Any discrepancies between the two were resolved by discussions and with involvement of a third reviewer when necessary. The papers that did not meet the inclusion criteria were excluded.

Data extraction strategy

Two reviewers independently extracted data in a specially designed form, and data regarding study design and characteristics, details of the intervention and patient characteristics and outcomes were recorded in the form for each study. Differences in data extraction were resolved by discussion, referring back to the original papers and with involvement of a third reviewer when necessary.

Quality assessment strategy

To assess the quality of the RCTs, the following criteria were used: (1) method and description of randomisation; (2) allocation concealment; (3) blinding; (4) intention-to-treat (ITT) analysis; (5) percentage who completed the trial; (6) power calculation; and (7) similarity of group participants at baseline.

Best practice for each of the criteria would be as follows:

- *randomisation* random assignment generated by computer
- *concealment of allocation* those at point of implementing random allocation to treatment do not know to what the next patient will be allocated
- *blinding* those assessing outcomes (e.g. the pathologist looking at biopsies) should not know which treatment patients were on
- *intention to treat* patients remained on their allocated treatments throughout with no crossover
- *loss to follow-up* all patients completed the trial with no losses to follow-up
- *baseline matching* randomisation ensured that prognostically important variables were equally distributed across the arms.

Studies meeting most of these criteria were regarded as high-to-moderate quality.

Analysis

Meta-analyses of the outcomes were not possible, as outcomes were reported incompletely and in a variety of ways. Hence, all of the results are presented in text and tables.

Results

Result of the searches

A total number of 1842 titles and abstracts were retrieved by the searches (*Figure 5*). The titles and abstracts were screened for inclusion and exclusion; 49 were considered possible inclusions and full texts of these were obtained. Out of these, 34 papers were excluded because of not meeting the inclusion criteria, not reporting outcomes of interest or not being RCTs. Details of the reasons for exclusion are given in *Figure 5*.
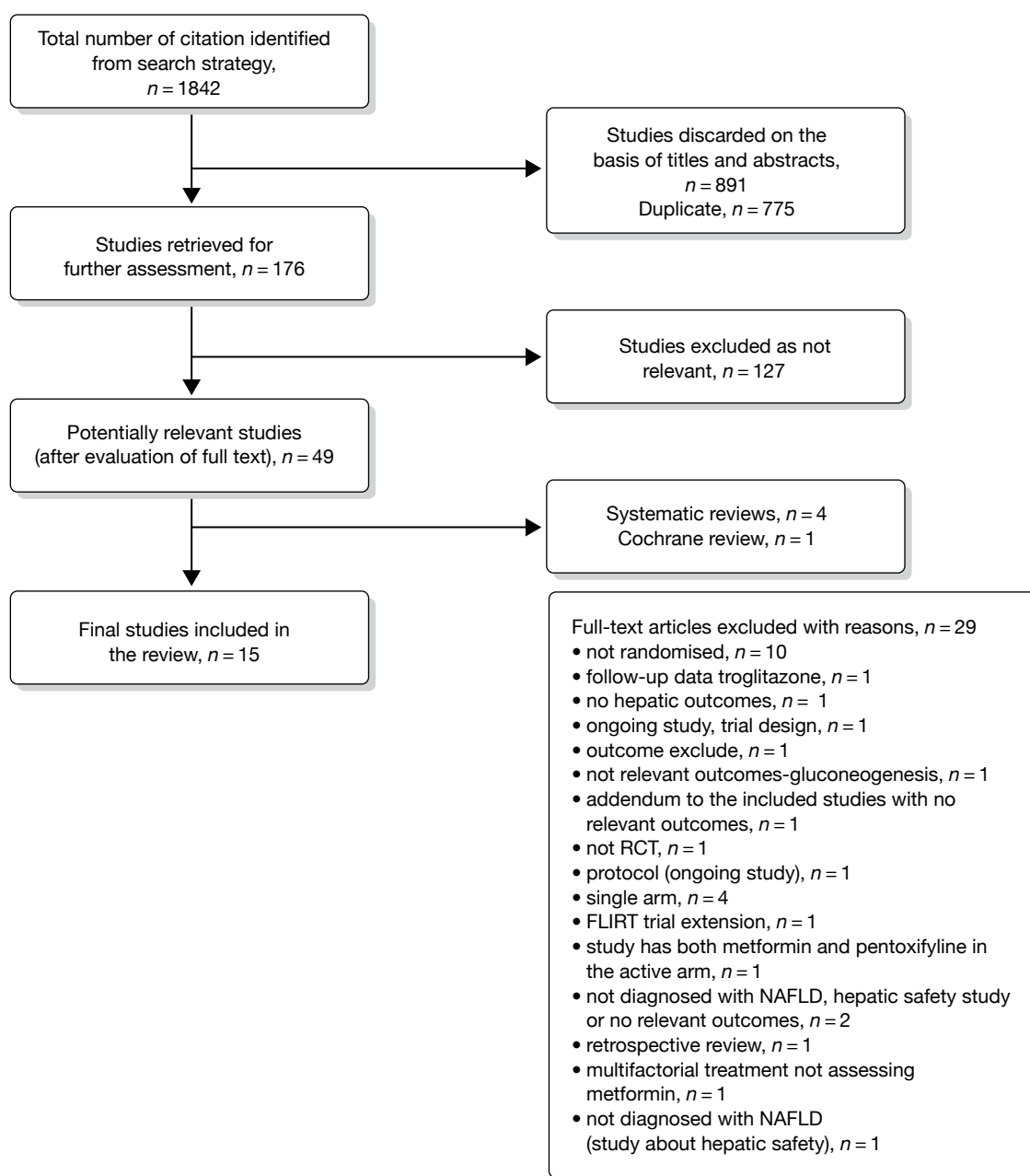
FIGURE 5 Flow chart of search results.

A total of 15 RCTs (14 full texts and one abstract[100]) fulfilled the inclusion criteria and were included in the review. Of the 15 studies included, four examined pioglitazone,[101–104] eight metformin,[87,100,105–110] one rosiglitazone[111] and two trials compared the effects of metformin and rosiglitazone.[112,113]

A search for ongoing trials or reviews was carried out. An out-of-date Cochrane review on insulin sensitisers by Angelico *et al.*,[114] in Rome, was found. It excluded people with T2DM, and included only three trials: two of metformin and one of pioglitazone. Four systematic reviews were also found but none included all of the trials now available. A systematic review by Musso *et al.*[78] also included fully published trials and abstracts that had explored the efficacy of non-pharmacological interventions, UDCA, lipid-lowering drugs, antioxidants, anti-tumour necrosis factor alpha agents (pentoxifylline), anti-hypertensive drugs, endocannabinoid receptor antagonists, L-carnitine and bariatric surgery among patients with NASH/NAFLD.

Descriptions of included studies

The included trials (identified by first author and year) are reviewed in this section. Further details of these can be found in the data extraction tables in *Appendix 2*. *Table 3* gives a summary of all of the included studies.

Pioglitazone

Aithal (2008)[101] conducted a randomised, double-blind, placebo-controlled trial in 74 non-diabetic patients, aged 18–70 years, diagnosed with NASH, confirmed by liver biopsy and ultrasound. The participants were randomised into two groups, one receiving pioglitazone 30 mg/day, whereas the second group had placebo tablets. Both of these groups also received advice on diet and exercise. Mean BMI at baseline was 29.8 kg/m^2 [standard deviation (SD) 3.0 kg/m^2] in the pioglitazone group and 30.8 kg/m^2 (SD 4.1 kg/m^2) in the control group. The treatment was carried out for 1 year. The primary aim of the study was to measure changes in liver histology by assessing liver biopsy specimens using staging and grading criteria proposed by Brunt *et al.*[115]

Belfort (2006)[102] conducted a randomised, double-blind, placebo-controlled trial, to explore the effects of pioglitazone plus a calorie-restricted diet in patients with NASH. The treatment group received 30 mg of pioglitazone per day for the first 2 months, which was increased to 45 mg/day and remained unchanged until end of the study, whereas the control group received placebo pills. These interventions were combined with dietary advice in all the participants. They were advised to reduce their calorie intake by 500 kcal per day. Mean BMI at baseline was 33.5 kg/m^2 (SD 4.9 kg/m^2) in the treatment group and 32.9 kg/m^2 (SD 4.4 kg/m^2) in the control group. The primary outcome measure was histological changes in liver assessed by the NASH histological scoring system proposed by Kleiner *et al.*[116]

Sanyal (2004),[103] in a pilot study, compared the effects of pioglitazone along with an antioxidant (vitamin E) in 20 participants with NASH. In this prospective RCT, the first group took pioglitazone 30 mg/day in combination with vitamin E 400 international units (IU)/day, whereas the other group were on vitamin E only. The treatment was given for 6 months. Mean BMI at baseline was 32.5 kg/m^2 (SD 4.3 kg/m^2) in the pioglitazone group and 30.7 kg/m^2 (SD 4.7 kg/m^2) in the control group. The primary aim of the study was to explore the changes in liver histology using modified Brunt score.

Sanyal (2010)[104] conducted a multicentre, randomised, double-blind, placebo-controlled trial to compare vitamin E and pioglitazone with placebo in NASH. A total of 247 participants were randomised into three groups, i.e. pioglitazone, vitamin E and placebo. Pioglitazone was given in a dose of 30 mg/day, vitamin E 400 (IU)/day, and placebo resembling either pioglitazone or

TABLE 3 Summary of included studies

Study ID	Sample size (completed/ randomised)	Interventions	Comparators	Comparisons	Duration of trial	Country (settings)	Diabetes
Pioglitazone							
Pioglitazone vs placebo							
Aithal *et al.* 2008[101]	*n* Pio: 31/37 *n* Pbo: 30/37	Pioglitazone + diet/exercise	Placebo + diet/exercise	Pio vs Pbo	1-year run-in period; 3 months before randomisation; treatment period, 12 months	UK (Queens Medical Centre in Nottingham and Derby City General Hospital)	People with NASH and without diabetes
Belfort *et al.* 2006[102]	*n* Pio: 18/26 *n* Pbo: 22/26	Pioglitazone + hypocaloric diet	Placebo + hypocaloric diet	Pio vs Pbo	6 months: October 2002 to November 2004; run-in period, 4 weeks; treatment, 6 months	USA, TX	55 with impaired glucose tolerance test or diabetes
Sanyal *et al.* 2004[103]	*n* Pio: 8/10 *n* Pbo: 10/10	Pioglitazone + vitamin E	Vitamin E	Pio vs Pbo	6 months; follow-up before randomisation, 3 months; treatment, 6 months	USA (NAFLD clinic within the general clinical research centre at the Virginia University)	People with NASH and without diabetes
Sanyal *et al.* 2010[104]	*n* Pio: 80 *n* Pbo: 83	Pioglitazone	Placebo	Pio vs Pbo	96 weeks; 24 weeks' follow-up	USA, multiple centres	People with NASH and without diabetes
Pioglitazone vs vitamin E							
Sanyal *et al.* 2010[104]	*n* Pio: 80 *n* Vitamin E: 84	Pioglitazone	Vitamin E	Pio vs Vit E	96 weeks; 24 weeks' follow-up	USA, multiple centres	People with NASH and without diabetes
Metformin							
Metformin vs placebo							
Garinis *et al.* 2010[105]	*n* Met: 15/20 *n* Pbo: 25/25	Metformin + hypocaloric diet	Hypocaloric diet	Met vs Pbo	6 months	Italy (Endocrine Unit of University Magna Graecia of Cantanzora)	People with NAFLD and without diabetes
Haukeland *et al.* 2009[106]	*n* Met: 20/24 *n* Pbo: 24/24	Metformin + advice on healthy lifestyle	Placebo + advice on healthy lifestyle	Met vs Pbo	6 months	Norway (four university hospitals)	Impaired glucose tolerance or T2DM

continued

TABLE 3 Summary of included studies (continued)

Study ID	Sample size (completed/randomised)	Interventions	Comparators	Comparisons	Duration of trial	Country (settings)	Diabetes
Idilman et al. 2008[112]	n Met: 24/24 n C: 25/25	Metformin + diet and exercise	Diet and exercise only	Met vs Pbo	48 weeks: December 2004 to October 2005; treatment, 48 weeks; follow-up, 6 months	Turkey, (Ankara, outpatient clinic)	People with NASH and without diabetes
Nadeau et al. 2009[107]	n Met: 28/37 n Pbo: 10/13	Metformin + lifestyle modifications	Placebo + lifestyle modifications	Met vs Pbo	6 months; treatment, 6 months	USA	People without diabetes
Nar and Gedik 2009[108]	n Met: 19/19 n Pbo: 15/15	Metformin + diet and exercise	Diet and exercise only	Met vs Pbo	6 months	Turkey, Ankara	34 patients with newly diagnosed diabetes with NAFLD without anti-diabetic medication
Shields et al. 2009[109]	n Met: 9/9 n Pbo: 7/10	Metformin + diet and exercise	Placebo + diet and exercise	Met vs Pbo	1 year	USA (Gastroenterology clinics at the Naval Medical Centre, San Diego, CA)	People with NASH and without diabetes
Uygun et al. 2004[110]	n Met: 15/17 n Pbo: 17/17	Metformin + diet	Diet alone	Met vs Pbo	6 months: August 1999 to June 2001	Turkey, Ankara	People with NASH and without diabetes
Metformin vs diet							
Bugianesi et al. 2005[87]	n Met: 55/55 n C: prescriptive diet 27/27	Metformin	Prescriptive diet only	Met vs prescriptive diet	1-year treatment; 12 months	Italy (two units, Bologna and Turin)	People with NAFLD and without diabetes
Metformin vs vitamin E							
Bugianesi et al. 2005[87]	110: n Met: 55/55 n Pbo: vitamin E 28/28	Metformin	Vitamin E	Met vs Vit E	1 year	Italy (two units: Bologna and Turin)	People with NAFLD and without diabetes
Metformin vs rosiglitazone + metformin							
Omer et al. 2010[113]	n Met: 19/22; n Met + Rosi: 22/22	Metformin	Metformin + rosiglitazone	Met vs Met + Rosi	12 months	Turkey (outpatient clinics)	Impaired glucose tolerance or T2DM with NAFLD

Rosiglitazone

Rosiglitazone vs placebo

Study ID	Sample size (completed/randomised)	Interventions	Comparators	Comparisons	Duration of trial	Country (settings)	Diabetes
Idilman et al. 2008[112]	n Rosi: 24/25; n C: 25/25	Rosiglitazone + diet and exercise	Diet and exercise only	Rosi vs Pbo	48 weeks	Turkey (Ankara, outpatient clinic)	People with NASH and without diabetes
Ratziu et al. 2008, FLIRT[111]	n Rosi: 32/32; n Pbo: 31/31	Rosiglitazone	Placebo	Rosi vs Pbo	1 year; January 2003 to November 2004; treatment, 12 months; follow-up, 4 months	France	People with NASH and without diabetes

Rosiglitazone vs metformin + rosiglitazone

Study ID	Sample size (completed/randomised)	Interventions	Comparators	Comparisons	Duration of trial	Country (settings)	Diabetes
Omer et al. 2010[113]	n Rosi: 20/20; n Met + Rosi: 22/22	Rosiglitazone	Rosiglitazone + metformin	Rosi vs Rosi + Met	12 months	Turkey (outpatient clinics)	Impaired glucose tolerance or T2DM with NAFLD
Torres et al. 2009[100] (abstract)	108 randomised (till date); 49 completed; n Rosi: 15; n Met + Rosi: 16; n Rosi + Los: 18 (excluded)	Rosiglitazone	Rosiglitazone + metformin	Rosi vs Rosi + Met	1 year	NR (presumably USA – San Antonio, TX); Centre: NR	People with NASH, diabetes not reported

Rosiglitazone vs metformin

Study ID	Sample size (completed/randomised)	Interventions	Comparators	Comparisons	Duration of trial	Country (settings)	Diabetes
Omer 2010 et al.[113]	n Rosi: 20/20; n Met: 19/22	Rosiglitazone	Metformin	Rosi vs Met	12 months	Turkey (outpatient clinics)	Impaired glucose tolerance or T2DM with NAFLD

C, control; Los, losartan; Met, metformin; NR, not reported; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; Vit E, vitamin E.

vitamin E. The treatment was given for 96 weeks, with an additional 24 weeks' follow-up. Mean BMI at baseline was 34.0 kg/m^2, 34.0 kg/m^2 and 35.0 kg/m^2 in pioglitazone, vitamin E and placebo group, respectively. The primary aim of the study was to explore the changes in liver histology.

Metformin

Bugianesi (2005)[87] recruited 110 participants with NAFLD confirmed by liver biopsy. This was an open-label trial conducted in two units in Italy and the participants were followed up for 12 months. At one centre, metformin was compared with vitamin E and in the other it was compared against a prescriptive diet. One group of participants received metformin, with a maximum dose of 2000 mg/day, the second group either received vitamin E 400 IU twice a day (b.i.d.)/day or a weight-reducing prescriptive diet to determine a caloric deficit of 500 kcal per day. In addition, all of the participants were encouraged to walk or to jog at least 30 minutes a day. Mean BMI at baseline in metformin group was 28.7 kg/m^2 (SD 3.6 kg/m^2) (in both centres), 29.1 kg/m^2 (SD 2.7 kg/m^2) in the vitamin E group and 28.2 kg/m^2 (SD 3.6 kg/m^2) in the prescriptive diet group. The primary aim of this study was to compare the effects of metformin against vitamin E or prescriptive weight-reducing diet in terms of ALT normalisation, histological changes in liver, changes in liver enzymes and insulin resistance.

Garinis (2010)[105] recruited 50 participants in an open-label trial and randomised them into two groups; one group ($n = 25$) received metformin plus hypocaloric diet (1300 kcal/day) and the second received hypocaloric diet only. Mean age of the participants in the metformin and placebo groups was 40.8 and 45.8 years, respectively. Mean BMI at baseline was 36.5 kg/m^2 in the metformin group and 34.7 kg/m^2 in the second. The participants were followed up for 6 months to explore the changes in liver steatosis confirmed by USG.

Haukeland (2009)[106] recruited 48 participants with NAFLD in a double-blind RCT. The mean ages of the participants in the placebo and metformin group was 49.9 years and 44.3 years, respectively. All of the participants received general advice about a healthy lifestyle that included taking 30 minutes of physical activity a day, and a diet low in fat, especially saturated fat, and refined carbohydrates. Mean BMI at baseline in the placebo and metformin groups was 31.4 kg/m^2 and 30.3 kg/m^2, respectively. The intervention was given for 6 months. Changes in steatosis, confirmed by liver biopsy, were measured.

Nadeau (2009)[107] conducted a double-blind RCT and recruited 55 participants with fatty liver and elevated liver-associated enzymes. The participants were adolescents aged between 12 and 18 years and received either metformin or placebo capsules. Mean age of the participants was 15.1 years. Both groups underwent a dietary assessment and watched a standardised video about healthy eating habits. The participants were treated for 6 months and the progression or regression of the fatty liver was measured by liver ultrasound and other biochemical examination. Mean BMI at baseline was 39.6 kg/m^2 [standard error (SE) 0.98 kg/m^2)] and 40.2 kg/m^2 (SE 1.8 kg/m^2) in the metformin and placebo groups, respectively.

Nar (2009)[108] recruited 34 participants with newly diagnosed T2DM and NAFLD (diagnosed by ultrasound) to explore the effect of metformin on plasma leptin levels. The participants on metformin were given the maximum dose of 1700 mg of metformin per day, whereas the other group was only on diet and exercise. Dietary advice was given by a dietician and the recommended exercise was walking for a minimum of 30 minutes at least 3 days a week. The progression of liver disease was measured by liver ultrasound and biochemical examinations. Mean BMI at baseline was 31.0 kg/m^2 (SE 4.0 kg/m^2) in the metformin group and 33.7 kg/m^2 (SE 6.0 kg/m^2) in the control group.

Shields (2009)[109] conducted a pilot study of a prospective, randomised, placebo-controlled trial conducted in 19 participants with insulin resistance and NASH. The intervention group received 500 mg of metformin daily titrated to 1000 mg, and dietary counselling with recommendation to lose weight and take 30 minutes of aerobic exercise four times a week. The control group received the same diet and exercise advice. The primary aim of the study was to assess the histological changes in liver using criteria proposed by Brunt *et al.*[115] Mean BMI at baseline in the treatment group was 32.2 kg/m^2 (SD 4.9 kg/m^2) and 32.8 kg/m^2 (SD 4.9 kg/m^2) in the control group. The participants were treated for 1 year.

Torres (2009)[100] conducted an open-label, randomised trial (reported as an abstract only) and recruited 108 participants with NASH to compare the effects of rosiglitazone against rosiglitazone and metformin in combination. Details given are scarce and the abstract gives results for the first 49 (of 108) participants who have completed the trial to date. The third group of participants receiving rosiglitazone and losartan was not considered in the present review. Mean age of the participants was 48.9 years. Mean BMI at baseline was 33.3 kg/m^2.

Uygun (2004)[110] conducted an RCT of metformin in 36 participants with NASH, insulin resistance and elevated liver enzyme concentrations. The treatment group received metformin in the dose of 850 mg twice daily plus dietary treatment, whereas the control group received only dietary treatment. In addition, all obese participants were advised to lose weight with a restriction of calorie intake to 1600–1800 calories per day. The interventions were given for 6 months and the groups were followed up for another 6 months. The primary aim of the study was to compare the effects of these interventions on liver histology and insulin resistance. Mean BMI of the treatment and control groups at baseline was 30.1 kg/m^2 (SD 3.4 kg/m^2) and 28.4 kg/m^2 (SD 3.9 kg/m^2), respectively.

Rosiglitazone

Ratziu [Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) trial] (2008)[111] recruited 64 participants with NASH to a double-blind, placebo-controlled RCT. The treatment group received rosiglitazone 4 mg daily for the first month, and then 8 mg daily until end of the trial. Both groups were instructed to lose weight, to follow a healthy diet and to exercise at least twice a week, if they were obese or overweight. No specialised nutritional counselling was implemented. The primary aim of the study was to assess if there had been a > 30% reduction or even a complete disappearance of hepatic steatosis at end of the study compared with the baseline findings. The progression of the liver histology was assessed using the Brunt scoring system. Mean BMI at baseline in the rosiglitazone group was 31.5 kg/m^2 (SD 6 kg/m^2), whereas it was 30.5 kg/m^2 (SD 4.4 kg/m^2) in the placebo group.

Metformin and rosiglitazone

Idilman (2008)[112] recruited participants over 18 years with newly diagnosed NASH to compare the effect of metformin and rosiglitazone. The participants were randomised into three groups: one received diet and exercise plus metformin 850 mg b.i.d., the second group diet and exercise plus rosiglitazone 8 mg per day, and the third group was on diet and exercise alone. The intervention was carried out for 48 weeks with 6 months of post-intervention follow-up. The primary aim of the study was unclear; however, the authors compared the effects of these interventions in terms of metabolic, biochemical and histological parameters. The progression or regression of the liver disease was assessed by liver biopsy using criteria proposed by Brunt *et al.*[115] and a NAFLD activity score (NAS) by Kleiner *et al.*[116] Mean BMI at baseline was 31.2 kg/m^2 (SD 3.6 kg/m^2) in the insulin sensitisers group and 32.2 kg/m^2 (SD 5.1 kg/m^2) in the diet and exercise group.

Omer (2010)[113] conducted an open-label, single-centre RCT and recruited 64 participants with NAFLD and T2DM or impaired glucose metabolism. The participants were randomised into three different groups and received metformin or rosiglitazone or both. All the groups also received dietary counselling from an endocrinologist and dieticians, and were also encouraged to do regular exercise 12 weeks prior to the intervention and also during the study period. The intervention was given for 12 months and at the end histological changes were assessed using Kleiner *et al.*'s grading system.[116] The mean age of the participants receiving metformin or rosiglitazone or both was 48 years, 49.3 years and 49.6 years, respectively. Mean BMI at baseline was 30.8 kg/m² in the metformin group, 28.4 kg/m² in the rosiglitazone group and 32.5 kg/m² in the metformin and rosiglitazone group.

Quality of included studies

A summary of the quality of the studies is given in *Table 4*. Full details are given in *Appendix 3*.

Internal validity
Randomisation

The majority of the studies described the randomisation procedure. In some[100,105,107,108,112,113] the descriptions were unclear or not given. Aithal (2008),[101] Sanyal (2004)[103] and Ratziu (2008)[111] used block randomisation. Belfort (2006),[102] Haukeland (2009)[106] and Shields (2009)[109] used computerised allocation. Bugianesi (2005)[87] used random sequence and the randomisation was centralised in one centre. Sanyal (2010)[104] randomised participants centrally by the Data Coordinating Centre (DCC) and the participants were assigned in permuted blocks of treatments.

The methods of allocation concealment were reported in only four studies;[87,104,106,111] in the remaining papers the method of allocation concealment was either not clear or not reported.

Sample size

Descriptions of study power were given in only four studies.[101,104,111,117] The remaining studies did not report if the power was calculated. Two of the 15 trials[103,109] were pilot studies.

Similarity of groups at baseline

In the majority of the studies, patients in the arms were similar to each other at baseline. Aithal (2008)[101] reported that all other parameters were similar between groups except that the pioglitazone group had lower alkaline phosphatase and fasting insulin levels than the placebo group. Sanyal (2010)[104] reported that all three groups were similar in demographic, clinical, laboratory results, and the NASH scores. However, about 17%, 18% and 28% in the placebo, vitamin E and pioglitazone groups, respectively, did not have hepatocellular ballooning on assessment of their initial biopsy specimen. Shields (2009)[109] stated that the treatment group was older and predominantly male. Haukeland (2009)[106] reported that the participants on metformin were younger, less often treated for hypertension and slightly more obese. Omer (2010)[113] reported that all groups were similar at baseline, except that baseline serum insulin was significantly higher in the metformin group and in the group that was on a combination of metformin and rosiglitazone than in the rosiglitazone group.

Intention-to-treat analysis

Only three studies[87,104,109] conducted an ITT analysis. Haukeland (2009)[106] had done per-protocol analysis. The descriptions of completion rate, loss to follow-up and withdrawals were given in all the studies except those by Nar (2009)[108] and Torres (2009).[100] Torres (2009) has published results only for the first 49 participants that have completed the trial and in addition reported that a total of 108 participants have been randomised to date. Three studies[87,111,112] had no dropouts.

TABLE 4 Quality of included studies

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation	Total score
Pioglitazone									
Aithal 2008[101]	✓	×	✓	×	✓	✓	×	×	4
Belfort 2006[102]	✓	×	✓	×	✓	×	✓	✓	5
Sanyal 2004[103]	✓	×	×	×	✓	×	✓	✓	4
Sanyal 2010[104]	✓	✓	✓	✓	✓	✓	✓	✓	8
Metformin									
Bugianesi 2005[87]	✓	✓	×	✓	✓	×	×	×	4
Garinis 2010[105]	×	×	×	×	✓	×	✓	×	2
Haukeland 2009[106]	✓	✓	✓	×	✓	✓	✓	✓	7
Nadeau 2009[107]	×	×	✓	×	✓	×	✓	✓	4
Nar 2009[108]	×	×	×	×	✓	×	✓	×	2
Shields 2009[109]	✓	×	×	✓	✓	×	✓	✓	5
Torres 2009[100]	×	×	×	×	✓	×	×	×	1
Uygun 2004[110]	✓	×	×	×	✓	×	✓	×	3
Rosiglitazone									
Ratziu 2008 (FLIRT trial)[111]	✓	✓	✓	×	✓	✓	✓	✓	7
Idilman 2008[112]	×	×	×	×	✓	×	✓	✓	3
Omer 2010[113]	×	×	×	×	✓	×	✓	×	2

Detection bias

Out of 15 trials, only six[101,102,104,106,107,111] were double-blind, placebo-controlled trials.
The remaining trials were unblinded. In the unblinded trials, the pathologists reviewing
liver biopsies[100,103,106,107,109,111,112] and radiologists conducting ultrasound[108] were blinded to
treatment arms.

External validity

The trials were conducted in the UK, France, Italy, Turkey, Norway and the USA, with none of
them in Asian or African countries.

Main results

The following outcomes are summarised in this section:

1. liver histology
2. glycosylated haemoglobin (HbA_{1c})
3. fasting plasma glucose (FPG)
4. weight/BMI
5. blood pressure
6. lipid parameters
7. liver biochemistry
8. insulin sensitivity/resistance
9. QoL
10. conversion to diabetes/impaired glucose tolerance/metabolic syndrome.

Details of all outcomes are given in the tables below (see *Tables 5–12*).

Liver histology
Pioglitazone

All four studies[101–104] collected liver biopsy specimens at baseline and at the end of the study. The
studies used different grading and staging methods to report the progression or regression of
liver histology. Aithal (2008)[101] used a NASH histological grading system developed by Brunt
et al.,[115] Sanyal (2004)[103] used modified Brunt scores, whereas Belfort (2006)[102] followed criteria
proposed by Kleiner *et al.*[116] to report on histological changes of liver with pioglitazone. Sanyal
(2010)[104] used a grading system proposed by Brunt *et al.*[115] and Kleiner *et al.*[116]

Aithal (2008)[101] followed up participants for 12 months and at the end of the study found that
steatosis, hepatocellular injury, lobular inflammation, Mallory bodies and fibrosis were all
improved with pioglitazone 30 mg/day. There was some improvement with placebo, but this was
limited to hepatic steatosis, whereas all other parameters worsened during the study period.
The reduction in hepatocellular injury, Mallory bodies and fibrosis was statistically significant
with pioglitazone compared with placebo (*Table 5*). Belfort (2006)[102] reported that at 6-months'
follow-up, the only improvement seen in the placebo group was a reduction in inflammation,
whereas with pioglitazone there were improvements in all parameters and the differences were
statistically significant compared with placebo (see *Table 5*). Sanyal (2004)[103] found that there
were significant histological changes from baseline to end with both vitamin E and pioglitazone
(see *Table 5*). However, there were no significant improvements in inflammation and fibrosis
with vitamin E. The changes in cytological ballooning, Mallory's hyaline and inflammation were
statistically significant with pioglitazone compared with vitamin E (see *Table 5*). Sanyal (2010)[104]
found significant changes in most histological parameters with both vitamin E and pioglitazone
compared with placebo; however, the difference between vitamin E and pioglitazone was not
significant for any of the parameters.

TABLE 5 Liver histology (pioglitazone studies)

Study	Outcome	Change from baseline	p-value (from baseline to end)	p-value (between groups)
Pioglitazone				
Aithal 2008[101] (Brunt *et al.*[115]): *n* (%)	Steatosis	Decrease: *Pio*: 15/31 (48%); *Pbo*: 11/30 (37)	Not given	*p* = 0.19
		Increase: *Pio*: 1/31 (3.2%); *Pbo*: 3/30 (10)		
	Hepatocellular injury	Decrease: *Pio*: 10/31 (32); *Pbo*: 3/30 (10)		*p* = 0.005
		Increase: *Pio*: 4/31 (13); *Pbo*: 12/30 (40)		
	Lobular inflammation	Decrease: *Pio*: 14/31 (45); *Pbo*: 8/30 (27%)		*p* = 0.25
		Increase: *Pio*: 4/31 (13); *Pbo*: 3/30 (10)		
	Portal inflammation	Decrease: *Pio*: 8/31 (26); *Pbo*: 7/30 (23)		*p* = 0.67
		Increase: *Pio*: 8/31 (26); *Pbo*: 11/30 (37%)		
	Mallory bodies	Decrease: *Pio*: 8/31 (26); *Pbo*: 1/30 (3)		*p* = 0.004
		Increase: *Pio*: 0/31 (0); *Pbo*: 3/30 (10)		
	Fibrosis	Decrease: *Pio*: 9/31 (29); *Pbo*: 6/30 (20)		*p* = 0.05
		Increase: *Pio*: 0/31 (0); *Pbo*: 6/30 (20)		
Belfort 2006[102] (Kleiner *et al.*[116])	Steatosis	Improvement: *Pio*: 65%; *Pbo*: 38%	Not given	Improvement: *p* = 0.003; reduction in score of ≥ 2: *p* = 0.004
		Reduction in score of ≥ 2: *Pio*: 9/21 (43%); *Pbo*: 0/14 (0%)		
	Ballooning necrosis	Improvement: *Pio*: 54%; *Pbo*: 24%		*p* = 0.02
	Lobular inflammation	Improvement: *Pio*: 65%; *Pbo*: 29%		*p* = 0.008
	Combined necroinflammation	Improvement: *Pio*: 85%; *Pbo*: 38%		Improvement: *p* = 0.001; reduction in score of ≥ 2: *p* = 0.02
		Patients with reduction in score of ≥2: *Pio*: 11/24 (46); *Pbo*: 3/21 (14)		
	Fibrosis	Improvement: *Pio*: 46%; *Pbo*: 33%		Improvement:0.08; reduction in score of ≥ 2: *p* = 0.31
		Reduction in score: *Pio*: 5/12 (42%); *Pbo*: 1/6 (17%)		
Sanyal 2004[103] (modified Brunt score)	Steatosis grade	*Pio*: −1.4; *Vit E*: −0.8	*Pio*: *p* = 0.002; *Vit E*: *p* = 0.02	*p* = NS
	Cytological ballooning	*Pio*: −1; *Vit E*: −0.7	*Pio*: *p* = 0.01; *Vit E*: *p* = 0.055	*p* = 0.002
	Mallory's hyaline	*Pio*: −0.7; *Vit E*: −0.2	*Pio*: *p* = 0.02; *Vit E*: *p* = 0.055	*p* = 0.03
	Pericellular fibrosis	*Pio*: −0.7; *Vit E*: −0.3	*Pio*: *p* = 0.03; *Vit E*: NS	*p* = NS
	Inflammation	Not given	Not given	*p* = 0.001
	Portal fibrosis	*Pio*: −0.2; *Vit E*: −0.1	*Pio*: NS; *Vit E*: NS	*p* = NS

TABLE 5 Liver histology (pioglitazone studies) *(continued)*

Study	Outcome	Change from baseline	*p*-value (from baseline to end)	*p*-value (between groups)
Sanyal 2010[104] (Brunt *et al.*[115]/ Kleiner *et al.*[116])	Fibrosis (%)	*Pio*: −0.4; *Vit E*: −0.3; *Pbo*: −0.1	Not given	*Pio* vs *Pbo*: *p* = 0.10; *Vit E* vs *Pbo*: *p* = 0.19; *Vit E* vs *Pio*: *p* = 0.78
	Steatosis (%)	*Pio*: −0.8; *Vit E*: −0.7; *Pbo*: −0.1		*Pio* vs *Pbo*: *p* < 0.0001; *Vit E* vs *Pbo*: *p* < 0.0001; *Vit E* vs *Pio*: *p* = 0.41
	Amount (foci) of lobular inflammation (%)	*Pio*: −0.7; *Vit E*: −0.6; *Pbo*: −0.2		*Pio* vs *Pbo*: *p* = 0.0009; *Vit E* vs *Pbo*: *p* = 0.008; *Vit E* vs *Pio*: *p* = 0.59
	Portal, chronic inflammation (%)	Not given		Not given
	Ballooning degeneration (%)	*Pio*: −0.4; *Vit E*: −0.5; *Pbo*: −0.2		*Pio* vs *Pbo*: *p* = 0.01; *Vit E* vs *Pbo*: *p* = 0.03; *Vit E* vs *Pio*: *p* = 0.59
Metformin				
Bugianesi 2005[87] (modified Brunt score): *n* (%)	Fat	*Met*: −20	*Met*: *p* = 0.004	Not given
	Necroinflammation	*Met*: −0.65	*Met*: *p* = 0.012	
	Fibrosis	*Met*: −0.7	*Met*: *p* = 0.012	
	NASH index	*Met*: −2.06	*Met*: *p* < 0.0001	
Garinis 2010[105] (liver ultrasound)	Liver steatosis	Improved/disappeared: *Met*: 5/20 (25%); *Pbo*: 6/25 (24%)	*Met*: *p* < 0.0001; *Pbo*: *p* = 0.029	Not given
		Moderate to mild: *Met*: 2/20 (10%); *Pbo*: 5/25 (20%)		
		Disappeared: *Met*: 3/20 (15%); *Pbo*: 1/25 (4%)		
Haukeland 2009[106] (Kleiner score)	Steatosis	Proportion with improvement: *Met*: 25%; *Pbo*: 38%	*Met*: *p* = 0.10; *Pbo*: *p* = 0.033	*p* = 0.52
	Ballooning necrosis	Proportion with improvement: *Met*: 5%; *Pbo*: 13%	*Met*: *p* = 0.058; *Pbo*: *p* = 1.0	*p* = 0.61
	Lobular inflammation	Proportion with improvement: *Met*: 15%; *Pbo*: 33%	*Met*: *p* = 0.21; *Pbo*: *p* = 0.59	*p* = 0.29
	Fibrosis	Proportion with improvement: *Met*: 5%; *Pbo*: 17%	*Met*: *p* = 1.0; *Pbo*: *p* = 0.56	*p* = 0.066
	Steatosis as % of hepatocytes with fat, (mean)	*Met*: −8; *Pbo*: −7	*Met*: *p* = 0.024; *Pbo*: *p* = 0.052	*p* = 0.09
	NAS	*Met*: 0.3; *Pbo*: −0.42	*Met*: *p* = 0.23; *Pbo*: *p* = 0.12	*p* = 0.066; proportion with improvement (*p* = 0.060)
		Proportion with improvement: *Met*: 20%; *Pbo*: 50%		
Nadeau 2009[107] (liver ultrasound)	Fatty liver by ultrasound (*n*,%)	*Met*: −4 (13%); *Pbo*: 2 (15%)	*Met*: *p* < 0.04	*p* < 0.04
Nar 2009[108] (liver ultrasound)	Grade of hepatic steatosis	Results unclear – report decreases in liver echogenicity, but table suggests increase?	*Met*: *p* = NS; *Pbo*: *p* = NS	*p* = 0.043

TABLE 5 Liver histology (pioglitazone studies) *(continued)*

Study	Outcome	Change from baseline	*p*-value (from baseline to end)	*p*-value (between groups)
Shields 2009[109] (Brunt scores)	Grade	*Met*: −0.11; *Pbo*: −0.35	Not given	*p* = 0.67
	Steatosis	*Met*: −0.09; *Pbo*: −0.65		*p* = 0.23
	Ballooning	*Met*: −0.22; *Pbo*: −0.28		*p* = 0.967
	Intra-acinar inflammation	*Met*: 0.11; *Pbo*: −0.12		*p* = 0.478
	Portal tract inflammation	*Met*: −0.22; *Pbo*: −0.08		*p* = 0.523
	Fibrosis	*Met*: −0.05; *Pbo*: 0.2		*p* = 0.447
	NAS	*Met*: −0.9; *Pbo*: −1.2		*p* = 0.108
Torres 2009[100]	Steatosis	*Met + Rosi*: −23.1%; *Rosi*: −24.5%	Not given	Not given
	Inflammation grade	*Met + Rosi*: −8.7%; *Rosi*: −12.5%		
	Fibrosis grade	*Met + Rosi*: −45.6%; *Rosi*: −15%		
Uygun 2004[110] (Brunt scores)	Necroinflammatory score	*Met*: −0.26; *Pbo*: −0.11	*Met*: *p* = 0.31; *Pbo*: *p* = 0.62	Not given
	Fibrosis	*Met*: −0.02; *Pbo*: 0.07	*Met*: *p* = 0.96; *Pbo*: *p* = 0.91	
	Steatosis (USG abdomen)	*Met*: −0.64; *Pbo*: −0.25	*Met*: *p* = 0.038; *Pbo*: *p* = 0.17	
Rosiglitazone				
Ratziu 2008[111] (Brunt scores)	Steatosis grade	Reduction, mean (%): *Rosi*: −20 (26%); *Pbo*: −5 (23%)	Not given	*p* = 0.02
	Hepatocyte ballooning	*Rosi*: 0.13, SD 0.71; *Pbo*: 0.23, SD 0.8		*p* = 0.61
	Lobular necrosis and inflammation	*Rosi*: −0.09, SD 0.73; *Pbo*: −0.13, SD 0.81		*p* = 0.86
	Mallory bodies	Not given		Not given
	Perisinusoidal fibrosis	*Rosi*: −0.03, SD 0.54; *Pbo*: −0.06, SD 0.63		*p* = 0.83
	Fibrosis (stage)	*Rosi*: 0.03, SD 0.95; *Pbo*: −0.18, SD 1.14		*p* = 0.43
	NAS score, median (IQR)	Not given		*p* = 0.60

Metformin

Eight studies examined the effect of metformin on liver histology.[87,100,105–110] Five studies[87,100,106,109,110] carried out liver biopsy at baseline and at the end of the study to report histological changes of the liver while three[105,107,108] used liver ultrasound.

Out of the five[87,100,109,110,115] that used liver biopsy, three studies[87,109,110] used the scoring system proposed by Brunt *et al.*[115] and the other[106] used criteria proposed by Kleiner *et al.*[116] One study[100] did not mention which grading system was used to assess liver histology.

Bugianesi (2005)[87] carried out a second liver biopsy only in participants treated with metformin, but not in the control groups because of 'ethical issues'. Metformin significantly reduced the

TABLE 5 Liver histology (pioglitazone studies) *(continued)*

Study	Outcome	Change from baseline	*p*-value (from baseline to end)	*p*-value (between groups)
Metformin vs rosiglitazone				
Idilman 2008[112] (Brunt *et al.*[115])	Steatosis	*Met*: −1; *Rosi*: −1; *Pbo*: −0.5	*Met*: *p* = NS; *Rosi*: *p* < 0.05; *Pbo*: *p* = NS	Not given; *p* < 0.05 insulin sensitisers vs baseline
	Lobular inflammation	*Met*: 0; *Rosi*: 0; *Pbo*: 0	*Met*: *p* = NS; *Rosi*: *p* = NS; *Pbo*: *p* = NS	
	Ballooning	*Met*: 0; *Rosi*: −1; *Pbo*: 0	*Met*: *p* = NS; *Rosi*: *p* = NS; *Pbo*: *p* = NS	Not given; *p* < 0.05 insulin sensitisers vs baseline
	Portal inflammation	*Met*: 0.5; *Rosi*: 1; *Pbo*: −1	*Met*: *p* = NS; *Rosi*: *p* = NS; *Pbo*: *p* = NS	Not given
	Fibrosis	*Met*: 0; *Rosi*: 1; *Pbo*: 0	*Met*: *p* = NS; *Rosi*: *p* = NS; *Pbo*: *p* = NS	
	NAS	*Met*: −1; *Rosi*: −2; *Pbo*: 1	*Met*: *p* = NS, *Rosi*: *p* = NS; *Pbo*: *p* = NS	NR; *p* < 0.05 insulin sensitisers vs baseline
	Brunt's grade	*Met*: −0.5; *Rosi*: −1; *Pbo*: 0	*Met*: *p* = NS; *Rosi*: *p* = NS; *Pbo*: *p* = NS	Not given
Omer 2010[113] (Kleiner *et al.*[116])	NAS	Not given	*Met*: *p* = 0.726; *Rosi*: *p* = 0.012; *Met + Rosi*: *p* = 0.026	Not given

IQR, interquartile range; Met, metformin; NR, not reported; NS, not significant; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone.
The *p*-values that are given in the paper as NS, were also reported in this table as NS.

percentage of fat in liver and also reduced necroinflammation, fibrosis and the NASH index (see *Table 5*). Haukeland (2009)[106] found a slight reduction in all the parameters of liver histology with both metformin and placebo, but no significant difference between arms (see *Table 5*). Shields (2009)[109] compared the efficacy of metformin and diet and exercise in participants with NASH, and found no statistically significant differences between the groups in regards to NAS, individual components of NAS or fibrosis. However, the authors reported that both the interventions had caused improvements in steatosis and NAS.

Uygun (2004)[110] compared metformin against dietary treatment alone and found no significant differences between the groups in terms of NAS and fibrosis. There was slight decrease in the necroinflammatory activity with metformin, whereas no changes were seen with dietary treatment. The frequency of participants achieving improvements was significantly greater with metformin (46% vs 10%) than with diet alone and the difference between the two was reported to be statistically not significant (*p* = 0.17). In addition to liver biopsy, Uygun (2004)[110] had carried out liver ultrasound to explore the changes in liver steatosis with the two treatments and found the changes from baseline to end was significant (*p* = 0.038) with metformin than with diet alone.

Three trials[105,107,108] used only liver ultrasound to report the progression or regression of NAFLD. Garinis (2010)[105] reported that the proportions of participants in whom liver steatosis improved or disappeared were not different between the two groups, i.e. one taking metformin plus hypocaloric diet and the second only on dietary treatment (25% vs 24%). In some, the liver steatosis disappeared completely, and this was more common in the metformin group than in the control group (15% vs 4% – *p*-value not given). Nadeau (2009)[107] quantified the severity of fatty liver using a scoring system of 0, 1, 2 and 3, where '0' meant absence of fatty liver and '1', '2' and '3' represented mild, moderate or severe fatty liver, respectively. There was some improvement in fatty liver with metformin (74% in baseline vs 61% at the end; *p* < 0.04) and in some (three participants) it completely resolved, whereas the participants on placebo had no improvements.

The difference between the two groups was significant ($p < 0.04$). Nar (2009)[108] reported that both groups, i.e. metformin with lifestyle interventions versus diet and exercise alone, had significant improvements ($p < 0.05$) in grades of liver echogenicity at end of the study, but the difference between the two groups was not significant.

In Torres (2009),[100] the combination of metformin and rosiglitazone had no greater effect than rosiglitazone alone in terms of steatosis (–23.1% with combination, –24.5% with rosiglitazone) and inflammation (–8.7% with combination, –12.5% with rosiglitazone), but more effect on fibrosis (–45.6% with combination vs –15% with rosiglitazone, *p*-value not reported).

Rosiglitazone
One trial[111] compared rosiglitazone with placebo. The Brunt scoring system[115] was used to assess liver histology, and the modified Kleiner *et al.*[116] criteria for steatosis.

Ratziu (2008)[111] found a significantly greater reduction (> 30%) in hepatic steatosis (47% vs 16%; $p = 0.014$) with rosiglitazone than with placebo. There were some improvements in ballooning, inflammation and fibrosis, but the changes were not significantly different between treatments. The authors found no significant difference in the mean variation of the composite NAS, but the ranked assessment of pretreatment and end-of-treatment liver biopsy specimens showed a significantly greater effect with rosiglitazone than with placebo. The proportion of participants progressing to hepatocyte ballooning, portal inflammation and overall fibrosis was lower with rosiglitazone than with placebo ($p < 0.05$).

Metformin vs rosiglitazone
Two trials[112,113] compared the effects of metformin and rosiglitazone. Idilman (2008)[112] assessed liver histology by the Brunt *et al.*[115] scoring system and Omer (2010)[113] by Kleiner *et al.*[116] Idilman (2008)[112] also assessed NAS by using the criteria proposed by Kleiner *et al.*[116] (see *Table 5*). Idilman (2008)[112] performed a second biopsy at the end of the study in 29 participants with NASH (eight in the diet and exercise group and 21 in the treatment group) and found greater improvements in hepatic steatosis, ballooning and NAS score in the treatment groups than in the diet and exercise group. Omer (2010)[113] found that the NAFLD score significantly decreased in the groups that were on combination treatment ($p = 0.026$) and rosiglitazone ($p = 0.012$), whereas no significant changes were observed in the metformin group. None of the treatments had a significant effect on fibrosis.

Glycosylated haemoglobin
Out of 15 trials, only six[101,102,106,108,111,113] reported changes in HbA$_{1c}$ levels (*Table 6*). The reduction in HbA$_{1c}$ levels was greater with insulin sensitisers than with placebo. The changes ranged from –0.2% to –0.7% with pioglitazone, –0.23% to –1.2% with metformin, –0.18% to –1.2% with rosiglitazone and from +0.17% to –0.6% with placebo. The reductions with pioglitazone[101,102] and metformin[106,108] were significantly greater than with placebo. Rosiglitazone[111,113] led to a greater reduction in HbA$_{1c}$ levels than metformin in one head-to-head trial.[113]

Fasting plasma glucose
Eleven trials[87,101,102,104,106–108,110–113] reported FPG changes (*Table 7*). In most trials, the reduction in FPG levels with insulin sensitisers was significantly greater than with placebo. In the placebo group, FPG levels increased in most trials. The changes ranged from –0.17 to –1.11 mmol/l with pioglitazone, from +0.05 to –3.19 mmol/l with metformin and from –0.78 to –0.93 mmol/l with rosiglitazone. Omer (2010)[113] found a greater reduction in FPG with rosiglitazone (–0.78 mmol/l) than with a combination of rosiglitazone and metformin (–0.42 mmol/l), whereas there was an increment in FPG with metformin (+0.05 mmol/l). In Idilman (2008),[112] there was reduction in FPG with rosiglitazone (–0.7 mmol/l) and metformin (–0.26 mmol/l), whereas there was an

TABLE 6 Changes in HbA$_{1c}$ levels with insulin sensitisers

Study	HbA$_{1c}$ levels (%)		Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
	Baseline	End of study			
Pioglitazone					
Althal 2008[101]	Pio (31) 5.8, SD 0.6 Pbo (30) 5.9, SD 1.0	Pio (31) 5.6, SD 0.4 Pbo (30) 6.0, SD 1.2	*Pio:* −0.2; *Pbo:* +0.1	*Pio: p*=0.06; *Pbo: p*=0.04	*p*=0.01
Belfort 2006[102]	Pio (26) 6.2, SD 1.5 Pbo (21) 6.2, SD 1.1	Pio (26) 5.5, SD 0.8 Pbo (21) 6.1, SD 0.9	*Pio:* −0.7; *Pbo:* −0.1	*Pio: p*<0.001; *Pbo: p*=0.73	*p*=0.008
Metformin					
Haukeland 2009[106]	Met (24) 5.7, SD 0.6 Pbo (24) 5.8, SD 0.4	Met (24) 5.5, SD 0.4 Pbo (24) 5.9, SD 0.6	*Met:* −0.23, SD 0.36; *Pbo:* 0.1	*Met: p*=0.020; *Pbo: p*=0.017	*p*=0.001
Nar 2009[108]	Met (19) 6.9, SE 1.4 Pbo (15) 6.1, SE 1.1	Met (19) 5.7, SD 1.1 Pbo (15) 5.5, SD 0.3	*Met:* −1.2; *Pbo:* −0.6	*Met: p*=0.001; *Pbo: p*=0.010	*p*=NS
Rosiglitazone					
Ratziu 2008[111]	Rosi (32) 5.6, IQR 1.03 Pbo (31) 5.6, IQR 0.9	Rosi (32) Not given Pbo (31) Not given	*Rosi:* −0.18, SD 0.98; *Pbo:* 0.17, SD 0.53	Not given	*p*=0.078
Metformin vs rosiglitazone					
Omer 2010[113]	Met (22) 5.8, SD 1.3 Rosi (20) 6.0, SD 0.7 Met + Rosi (22) 6.9, SD 2.1	Met (22) 5.8, SD 0.7 Rosi (20) 5.8, SD 0.6 Met + Rosi (22) 6.9, SD 1.9	*Met:* 0; *Rosi:* −0.2; *Met + Rosi:* 0	*Met:* NS; *Rosi: p*=NS; *Met + Rosi: p*=NS	*p*=NS

IQR, interquartile range; Met, metformin; NS, not significant; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone.
The *p*-values that are given in the paper as NS, were also reported in this table as NS.

TABLE 7 Changes in FPG (mmol/l) with insulin sensitisers

Study	FPG (mmol/l)		End of study		p-value (from baseline to end)	Change from baseline/end minus baseline	p-value between groups
	Baseline						
Pioglitazone							
Aithal 2008[101]	**Pio (31)** 5.7, SD 1.6	**Pbo (30)** 5.6, SD 0.9	**Pio (31)** 5.3, SD 0.6	**Pbo (30)** 6.0, SD 1.3	Pio: p=0.78; Pbo: p=0.002	Pio: −0.4; Pbo: +0.4	p=0.02
Belfort 2006[102]	**Pio (26)** 6.61, SD 1.94	**Pbo (21)** 6.38, SD 1.55	**Pio (26)** 5.5, SD 0.88	**Pbo (21)** 6.44, SD 1.72	Pio: p=0.004; Pbo: p=0.75	Pio: −1.11; Pbo: +0.06	p=0.011
Sanyal 2010[104]	**Pio (80)** Vit E: 5.28 Pbo: 5.28	**C (84/83)**	**Pio (80)** Not given	**C (84/83))** Not given	Not given	Pio: −0.17; Vit E: 0.10; Pbo: 0.10	Pio vs Pbo: p=0.006; Vit E vs Pbo: p=0.81
	5.11						
Metformin							
Bugianesi 2005[87]	**Met (55)** BU: 5.61, SD 2.33 TU: 5.89, SD 1.94	**C (28/27)** Vit E: 5.17, SD 0.67 Diet: 5.56, SD 2.22	**Met (55)** Not given	**C (28/27)** Not given	Not given	Met: −0.56; C: −0.28	p=0.125
Haukeland 2009[106]	**Met (24)** 5.5, SD 0.8	**Pbo (24)** 5.7, SD 1.0	**Met (24)** 5.2, SD 0.6	**Pbo (24)** 5.8, SD 0.9	Met: p=0.051; Pbo: p=0.30	Met: −0.34, SD 0.70; Pbo: +0.1	p=0.032
Nadeau 2009[107]	**Met (37)** 5.06, SE 0.12	**Pbo (13)** 4.93, SE 0.14	**Met (37)** 4.91, SE 0.09	**Pbo (13)** 5.12, SE 0.21	Not given	Met: −0.15; Pbo: +0.19	p=NS
Nar 2009[08]	**Met (19)** 9.58, SD 3.35	**Pbo (15)** 8.02, SD 1.54	**Met (19)** 6.39, SD 1.59	**Pbo (15)** 6.22, SD 0.42	Met: p=0.001; Pbo: p=0.002	Met: −3.19; Pbo: −1.8	Not given
Uygun 2004[110]	**Met (17)** 4.83, SD 0.79	**Pbo (17)** 5.36, SD 1.07	**Met (17)** 4.48, SD 0.37	**Pbo (17)** 5.15, SD 0.87	Met: p=0.033 Pbo: p=0.04	Met: −0.35, SD 0.62 (7.2%); Pbo: −0.21, SD 0.39 (3.8%)	p=0.38

TABLE 7 Changes in FPG (mmol/l) with insulin sensitisers *(continued)*

Study	FPG (mmol/l)		Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
	Baseline	End of study			
Rosiglitazone					
Ratziu 2008[111]	Rosi (32) 5.3, IQR 1.9; Pbo (31) 5.4, IQR 2.2	Rosi (32) Not given; Pbo (31) Not given	*Rosi: −0.93, SD 1.72; Pbo: 0.55, SD 1.74*	Not given	*p* = 0.001
Metformin vs rosiglitazone					
Idilman 2008[112]	Met (10) 5.86, SD 1.09; Rosi (11) 5.83, SD 1.06; Pbo (8) 5.53, SD 0.86	Met (10) 5.26, SD 0.72; Rosi (11) 5.13, SD 0.77; Pbo (8) 5.68, SD 3.07	*Met: −0.26; Rosi: −0.7; Pbo: +0.15*	*Met: p = 0.005; Rosi: p < 0.001; Pbo: p > 0.05*	Not given
Omer 2010[113]	Met (22) 6.56, SD 1.29; Rosi (20) 6.46, SD 1.49; Met + Rosi (22) 7.81, SD 2.71	Met (22) 6.61, SD 1.07; Rosi (20) 5.68, SD 1.13; Met + Rosi (22) 7.39, SD 3.23	*Met: +0.05; Rosi: −0.78; Met + Rosi: −0.42*	*Met: p = NS; Rosi: p = 0.029; Met + Rosi: p = NS*	Not given

BU, Bologna unit; C, control; IQR, interquartile range; Met, metformin; NS, not significant; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; SD, standard deviation; TU, Turin unit; Vit E, vitamin E.
The *p*-values that are given in the paper as NS, were also reported in this table as NS.

increment with diet and exercise (+0.15 mmol/l). Similarly, in Ratziu (2008),[111] rosiglitazone led to a significantly greater reduction in FPG levels than placebo (–0.93 mmol/l, SD 1.72, vs +0.55 mmol/l, SD 1.74).

Weight-related outcomes

Three pioglitazone trials[101,102,104] reported this outcome (*Table 8*). In all three trials, participants taking pioglitazone gained weight (+2.5 to +4.7 kg), whereas those on placebo lost weight (–0.5 to –3.5 kg); however, in one trial[104] the participants in the control group also gained weight. In the latter trial, the participants in the control group were taking either vitamin E or placebo. Two trials[105,106] reported changes with metformin. Participants lost between 4.3 and 6.7 kg with metformin, whereas those in the placebo arm gained 0.3 kg in one trial[106] and those on a hypocaloric diet in the other trial lost 5.2 kg.[105] Two trials[100,111] reported changes with rosiglitazone and the results varied between the two. In Torres (2009),[100] weight was reduced in the rosiglitazone-only group (–1.3%); however, there was no significant difference to the reduction in the combined metformin and rosiglitazone group (–3.3%). In contrast, participants on rosiglitazone in the trial by Ratziu (2008)[111] gained weight (+1.5 kg, SD 5.2 kg), whereas those on placebo lost weight (–1 kg, SD 0.5 kg).

With pioglitazone, BMI increased with changes ranging between +0.7 to +1.8 kg/m^2, whereas with metformin and rosiglitazone BMI was reduced and the changes ranged between –0.4 and –3.2 kg/m^2 and between –0.3 and –0.6 kg/m^2, respectively. The reduction also occurred in the participants taking a combination of rosiglitazone and metformin (–1.3 kg/m^2)[113] and the change was greater than with rosiglitazone. In all of the pioglitazone trials, except Belfort (2006),[102] the BMI of the participants in the control group increased. All of the participants in Belfort (2006)[102] were also on a hypocaloric diet, whereas the participants in Aithal (2008)[101] received diet and exercise advice. In the remaining pioglitazone trials none of the participants received any other interventions. In most of the metformin trials, reduction in BMI also occurred in the control group and the changes ranged between +1.5 and –2.5 kg/m^2. In two head-to-head trials,[112,113] reduction in BMI was greater with metformin (–1.8 to –3.2 kg/m^2), followed by those taking a combination of metformin and rosiglitazone (–1.3 kg/m^2) and finally those only on rosiglitazone (–0.3 to –0.6 kg/m^2). The changes with metformin and a combination of metformin and rosiglitazone were significant from baseline to end, but were not significant with rosiglitazone alone.

Some studies used other parameters such as waist–hip ratio, waist or hip circumference and body fat content. Only two pioglitazone[101,103] and one metformin[108] study reported waist–hip ratio. The change in waist–hip ratio with pioglitazone was very small (0 to +0.02 with pioglitazone vs 0 to –0.01 with placebo). There was reduction in waist–hip ratio with metformin, but not greater than the reduction in the control group (–0.02 to –0.04 in metformin group vs –0.05 in control group; p = not significant).[105,108] The change in body fat content with pioglitazone was inconclusive. One trial[103] found a reduction in both the pioglitazone and control groups (vitamin E) (greater reduction in the control group; –4.4% vs –2.9%), but there were increases with pioglitazone in the other two trials.[102,104] Only one head-to-head trial[112] reported this outcome and it found that the reduction in body fat was higher in the participants on diet and exercise (–2%), followed by metformin (–1.9%) and rosiglitazone (–0.9%). In the same trial, it was found that the reduction in waist circumference was greater with metformin (–6.6 cm) than with rosiglitazone (–2.5 cm) or diet and exercise (–2.4), and the findings were not different for hip circumference (–1.6 cm with metformin, –1 cm with rosiglitazone and –0.8 cm with a combination of metformin and rosiglitazone). Another head-to-head trial[113] reported that the reduction in waist circumference was greater with metformin (–4.2 cm) than with rosiglitazone (–1 cm) or a combination of metformin and rosiglitazone (–2.9 cm).

TABLE 8 Changes in weight (kg), BMI (kg/m²), waist–hip ratio, waist–hip circumference (cm) and body fat content (%) with insulin sensitisers

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Pioglitazone					
Weight (kg)					
Athal 2008[101]	**Pio (31)** 88.6, SD 10.7 **Pbo (30)** 92.8, SD 21.1	**Pio (31)** 91.2, SD 12.6 **Pbo (30)** 89.3, SD 18.6	*Pio:* 2.6; *Pbo:* –3.5	*Pio: p* = 0.005; *Pbo: p* = 0.69	*p* = 0.02
Belfort 2006[102]	**Pio (26)** 93.7, SD 18.1 **Pbo (21)** 90.2, SD 15.4	**Pio (26)** 96.2, SD 19.6 **Pbo (21)** 89.7, SD 14.8	*Pio:* 2.5; *Pbo:* –0.5	*Pio: p* < 0.001; *Pbo: p* = 0.53	*p* = 0.003
Sanyal 2010[104]	**Pio (80)** 97 **C (84/83)** *Vit E:* 94 *Pbo:* 99	**Pio (80)** **C (84/83)** Only baseline values reported	*Pio:* 4.7; *Vit E:* 0.4; *Pbo:* 0.7	Not given	*Pio* vs *Pbo: p* < 0.0001 *Vit E* vs *Pbo: p* = 0.65
Metformin					
Weight (kg)					
Garinis 2010[105]	**Met (20)** 85.5, SD 13.4 **C (25)** 83.7, SD 10.5	**Met (20)** 78.8, SD 15 **C (25)** 78.5, SD 10.9	*Met:* –6.70; *C:* –5.20,	*Met: p* = 0.0001; *C: p* = 0.0001	Not given
Haukeland 2009[106]	**Met (24)** 97.1, SD 17.6 **Pbo (24)** 91.5, SD 12.1	**Met (24)** 92.8, SD 17.3 **Pbo (24)** 91.8, SD 13.0	*Met:* –4.3, SD 4.3; *Pbo:* +0.3, SD 2.2	*Met: p* < 0.001; *Pbo: p* = 0.45S	*p* < 0.001
Torres 2009[100]	**Met + Rosi (16)** Not given **Rosi (15)** Not given	**Met + Rosi (16)** Not given **Rosi (15)** Not given	*Met + Rosi:* –3.3%; *Rosi:* –1.3%	Not given	Not given
Rosiglitazone					
Weight (kg)					
Ratziu 2008[111]	**Rosi (32)** Not given **Pbo (31)** Not given	**Rosi (31)** Not given **Pbo (31)** Not given	*Rosi:* +1.5, SD 5.2; *Pbo:* –1, SD 0.5	Not given	*p* = 0.03

Pioglitazone

BMI (kg/m²)

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Aithal 2008[101]	Pio (31) 29.8, SD 3.0; Pbo (30) 30.8, SD 4.1	Pio (31) 30.5, SD 3.9; Pbo (30) 30.8, SD 4.5	Pio: 0.7; Pbo: 0	Pio: $p=0.31$; Pbo: $p=0.90$	$p=0.45$
Belfort 2006[102]	Pio (10) 33.5, SD 4.9; Pbo (10) 32.9, SD 4.4	Pio (10) 34.6, SD 5.7; Pbo (10) 32.7, SD 4.5	Pio: 1.1; Pbo: –0.2	Pio: $p<0.001$; Pbo: $p=0.62$	$p=0.005$
Sanyal 2004[103]	Pio (80) 32.5, SD 4.3; Pbo (10) 30.7, SD 4.7	Pio (80) 32.5, SD 7; Pbo (10) 31.2, SD 3.6	Pio: 0; Pbo: 0.5	Not given	$p=$NS
Sanyal 2010[104]	C (84/83); Vit E: 34; Pbo: 35	Not given	Pio: 1.8; Vit E: 0.1; Pbo: 0.4	Not given	Pio vs Pbo: $p=0.0001$; Vit E vs Pbo: $p=0.50$

Waist–hip ratio

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Aithal 2008[101]	Pio (31) 0.95, SD 0.06; Pbo (30) 0.97, SD 0.13	Pio (31) 0.95, SD 0.07; Pbo (30) 0.96, SD 0.07	Pio: 0; Pbo: –0.01	Pio: $p=0.84$; Pbo: $p=0.12$	$p=0.23$
Sanyal 2004[103]	Pio (10) 0.92, SD 0.08; Pbo (10) 0.94, SD 0.08	Pio (10) 0.94, SD 0.1; Pbo (10) 0.94, SD 0.08	Pio: 0.02; Pbo: 0	Not given	$p=$NS

Fat (%)

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Belfort 2006[102]	Pio (26) 33.7, SD 5.6; Pbo (21) 35.7, SD 8.8	Pio (26) 35.2, SD 6.1; Pbo (21) 34.9, SD 8.8	Pio: 1.5; Pbo: –0.8	Not given	$p=0.005$
Sanyal 2004[103]	Pio (10) 36.5, SD 9; Pbo (10) 34.7, SD 9	Pio (10) 33.6, SD 14; Pbo (10) 30.3, SD 7	Pio: –2.9; Pbo: –4.4	Not given	$p=$NS
Sanyal 2010[104]	Pio (80) 40; C (84/83); Vit E: 39; C: 40	Not given	Pio: 2.7; Vit E: 0.4; Pbo: 0.0	Not given	Pio vs Pbo: $p<0.0001$; Vit E vs Pbo: $p=0.50$

continued

TABLE 8 Changes in weight (kg), BMI (kg/m²), waist–hip ratio, waist–hip circumference (cm) and body fat content (%) with insulin sensitisers (continued)

Study	Baseline		End of study		Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Metformin							
BMI (kg/m²)							
Bugianesi 2005[87]	**Met (55)** 28.7, SD 3.5	**C (28/27)** C (Vit E/Pbo): 28.8, SD 3.2	**Met (55)** 27.4, SD 3.4	**C (28/27)** C (Vit E/Pbo): 27.8, SD 2.9	*Met:* −1.3; *C:* −1	*Met: p<0.0001; C: p=0.0003*	*Met vs. C: p=0.113*
Garinis 2010[105]	**Met (20)** 36.5, SD 4.9	**C (25)** 34.7, SD 3.5	**Met (20)** 33.3, SD 5.4	**C (25)** 32.9, SD 3.6	*Met:* −3.20; *C:* −1.80	*Met: p=0.0001; C: p=0.0001*	Not given
Haukeland 2009[106]	**Met (24)** 31.4, SD 3.9	**Pbo (24)** 30.3, SD 3.3	**Met (24)** 30.1, SD 4.2	**Pbo (24)** 30.4, SD 3.4	*Met:* −1.3; *Pbo:* 0.1	*Met: p<0.001 Pbo: p=0.59*	*p<0.001*
Nadeau 2009[107]	**Met (37)** 39.6, SE 0.98	**Pbo (13)** 40.2, SE 1.8	**Met (37)** 39.2, SE 1.3	**Pbo (13)** 41.7, SE 3.1	*Met:* −0.4; *Pbo:* +1.5	Not given	*p=NS*
Nar 2009[108]	**Met (19)** 31.0, SD 4.0	**Pbo (15)** 33.7, SD 6.0	**Met (19)** 28.8, SD 3.85	**Pbo (15)** 31.2, SD 5.75	*Met:* −2.2; *Pbo:* −2.5	*Met: p=0.001 Pbo: p=0.001*	*p=NS*
Shields 2009[109]	**Met (9)** 32.2, SD 4.9	**Pbo (10)** 32.8, SD 4.9	**Met (9)** Not given	**Pbo (10)** Not given	*Met:* −0.9; *Pbo:* −1.7	Not given	*p=0.514*
Uygun 2004[110]	**Met (17)** 30.1, SD 3.4	**Pbo (17)** 28.4, SD 3.9	**Met (17)** 27.7, SD 2.5	**Pbo (17)** 26.5, SD 3.7	*Met:* −2.4, SD 1.9 (7.9%); *Pbo:* −1.9, SD 2.1 (6.7%);	*Met: p=0.001; Pbo: p=0.01*	*p=0.01*
Waist–hip ratio							
Garinis 2010[105]	**Met (20)** 0.86, SD 0.05	**C (25)** 0.88, SD 0.05	**Met (20)** 0.82, SD 0.02	**C (25)** 0.85, SD 0.07	*Met:* −0.04; *C:* −0.0	*Met: p=0.33; C: p=0.11*	Not given
Nar 2009[108]	**Met (19)** 0.90, SD 0.07	**Pbo (15)** 0.89, SD 0.09	**Met (19)** 0.88, SD 0.07	**Pbo (15)** 0.84, SD 0.07	*Met:* −0.02; *Pbo:* −0.05	*Met: p=0.035 Pbo: p=0.019*	*p=NS*

Waist circumference (cm)

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Garinis 2010[105]	**Met (20)** 108.4, SD 12.5　**C (25)** 102.8, SD 8.8	**Met (20)** 101.4, SD 12.7　**C (25)** 95.6, SD 8.5	*Met: −7.00; C: −7.20*	*Met: p=0.0009; C: p=0.0001*	Not given

Metformin vs rosiglitazone

BMI (kg/m²)

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Idilman 2008[112]	**Met (10)** 30.8, SD 3.9　**Rosi (11)** 31.5, SD 3.4　**Pbo (8)** 32.2, SD 5.1	**Met (10)** 29.0, SD 3.5　**Rosi (11)** 30.9, SD 3.2　**Pbo (8)** 31.5, SD 5.3	*Met: −1.8; Rosi: −0.6; Pbo: −0.7*	*Met: p<0.001; Rosi: p=0.09; Pbo: p=0.002; no significant change in either group during the 6-month follow-up*	Not given
Omer 2010[113]	**Met (22)** 30.8, SD 6.6　**Rosi (20)** 28.4, SD 4.1　**Met + Rosi (22)** 32.5, SD 7.0	**Met (22)** 27.6, SD 2.8　**Rosi (20)** 28.1, SD 3.8　**Met + Rosi (22)** 31.2, SD 6.7	*Met: −3.2; Rosi: −0.3; Met + Rosi: −1.3*	*Met: p=0.002 Rosi: p=NS Met + Rosi: p=0.006*	Not given

Waist circumference (cm)

Study	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Idilman 2008[112]	**Met (10)** 101.9, SD 9.7　**Rosi (11)** 102.7, SD 7.3　**Pbo (8)** 104.3, SD 8.5	**Met (10)** 95.3, SD 8.9　**Rosi (11)** 100.2, SD 7.7　**Pbo (8)** 101.9, SD 9.2	*Met: −6.6; Rosi: −2.5; Pbo: −2.4*	*Met: p<0.001; Rosi: p=0.061; Pbo: p=0.023; no significant change in either group during the 6-month follow-up*	Not given
Omer 2010[113]	**Met (22)** 99.6, SD 11.6　**Rosi (20)** 97.9, SD 9.0　**Met + Rosi (22)** 106.4, SD 12.1	**Met (22)** 95.4, SD 6.8　**Rosi (20)** 96.0, SD 8.7　**Met + Rosi (22)** 103.5, SD 11.8	*Met: −4.2; Rosi: −1.9; Met + Rosi: −2.9*	*Met: p=0.022 Rosi: p=NS Met + Rosi: p=0.031*	Not given

TABLE 8 Changes in weight (kg), BMI (kg/m^2), waist–hip ratio, waist–hip circumference (cm) and body fat content (%) with insulin sensitisers (continued)

Study	Baseline			End of study			Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
	Met (10)	Rosi (11)	Pbo (8)	Met (10)	Rosi (11)	Pbo (8)			
Hip circumference (cm)									
Idilman 2008[112]	100.9, SD 5.9	103.1, SD 6.8	105.1, SD 10.2	99.3, SD 7.4	102.1, SD 6.2	104.3, SD 10.1	*Met:* −1.6; *Rosi:* −1; *Pbo:* −0.8 (end minus baseline)	*Met:* p=0.040; *Rosi:* p=0.067; *Pbo:* p=0.003; no significant change in either group during a 6-month follow-up	Not given
Body fat content (%)									
Idilman 2008[112]	31.4, SD 6.2	34.0, SD 6.6	33.4, SD 7.5	29.5, SD 6.9	33.1, SD 6.7	31.4, SD 8.3	*Met:* −1.9; *Rosi:* −0.9; *Pbo:* −2	*Met:* p=0.017; *Rosi:* p=0.205; *Pbo:* p=0.019; no significant change in either group during a 6-month follow-up	Not given

C, control; Met, metformin; NS, not significant; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone.
The p-values that are given in the paper as NS, were also reported in this table as NS.

Blood pressure

Only Aithal (2008),[101] and none of the metformin trials, reported this outcome (*Table 9*). Pioglitazone led to reductions in both systolic blood pressure (SBP) and diastolic blood pressure (DBP), but changes also occurred in the placebo group with no significant difference between the groups.

Lipid profiles

Eleven of the 15 trials reported the changes in lipid profiles (*Table 10*).[87,101,102,104–108,110–112] The changes with pioglitazone were not significant for any of the parameters when compared with control except for TG levels ($p = 0.003$) in Belfort (2006).[102] In Sanyal (2010),[104] vitamin E led to greater reduction in most lipid parameters than pioglitazone and placebo; however, the difference was significant only for low-density lipoprotein (LDL) cholesterol. There was a reduction in some of the lipid parameters with metformin, but the changes were significant only in Haukeland (2009).[106] The participants in this trial were on either metformin or placebo, and all of the participants received advice on healthy lifestyle. The reduction in TC levels and LDL levels were significantly greater with metformin than with placebo. With rosiglitazone, the findings were mixed. Idilman (2008)[112] (where all the participants were also on diet and exercise) found a greater reduction in TC and TGs with metformin than with rosiglitazone (–0.24 vs –0.16 mmol/l for TC, –0.42 vs –0.28 mmol/l for TG), but the reduction in TC, but not TGs, was greater with diet and exercise alone (–0.52 mmol/l for TC and –0.16 mmol/l for TG). In contrast to these findings, Ratziu (2008)[111] (where none of the participants was on any form of diet or exercise regime) found an increment in all parameters of the lipid profile with rosiglitazone, whereas there was a reduction in TC and LDL cholesterol (–0.24 vs +0.45 mmol/l for TC, –0.32 vs +0.41 mmol/l for LDL) with placebo, and the changes were significant between the groups.

Alanine aminotransferase

There was a significantly greater reduction in ALT levels with pioglitazone in all the trials except in the trial by Sanyal (2004)[103] (*Table 11*). In Sanyal (2004),[103] the reduction was greater in the control group (vitamin E) than the pioglitazone group [–75 unit/litre (U/l) vs –65 U/l; p = not significant (NS)]. In contrast to this finding, in Sanyal 2010,[104] the reduction with vitamin E was not greater than the reduction seen with pioglitazone (–40.8 U/l with pioglitazone, –37 U/l with vitamin E and -20.1 U/l with placebo). The changes in ALT levels with pioglitazone ranged between –37.7 and –65 U/l, –37.0 U/l and –75 U/l with vitamin E, and –6.9 and –21 U/l with placebo. The changes were significantly different between the groups.

In all of the trials, a significant reduction from baseline to end occurred with metformin (see *Table 11*). The reductions ranged between –15 and –37.1 U/l in the metformin group and between –6.8 and –40.7 U/l in the control group. The change in ALT with rosiglitazone was not different to those caused by a combination of metformin and rosiglitazone (Torres 2009[100]) (–46.3% vs –46.5%). Metformin led to a greater reduction in ALT levels than rosiglitazone.[112]

Insulin sensitivity

Most trials reporting insulin sensitivity used homeostatic model assessment–insulin resistance (HOMA–IR) (*Table 12*). Pioglitazone showed varying results, with Aithal (2008)[101] reporting an increase in insulin resistance with pioglitazone and Sanyal (2010)[104] reporting a reduction with pioglitazone and an increase with vitamin E or placebo. Aithal (2008)[101] argued that the increment in insulin resistance with pioglitazone could have occurred because all of the participants were non-diabetic and a relatively low dose of pioglitazone was used.[101] In most trials, metformin led to a significant reduction in insulin resistance from baseline to end, but there was no significant difference with placebo. In one trial (Haukeland 2009[106]), both metformin and placebo (+0.58% with metformin and +0.63% with placebo) led to an increase in insulin resistance. However, the difference between the two was not statistically significant

TABLE 9 Changes in blood pressure with insulin sensitisers

Study	Outcome	Baseline		End of study		Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
		Pio (31)	Pbo (30)	Pio (31)	Pbo (30)			
Pioglitazone								
Aithal 2008[101]	SBP (mmHg)	144.6, SD 17.6	141, SD 18.7	139.4, SD 15.8	139, SD 20.4	*Piα: –5.2; Pbα: –2*	*Piα: p=0.32; Pbα: p=0.74*	*p=0.70*
		Pio (31)	Pbo (30)	Pio (31)	Pbo (30)			
Aithal 2008[101]	DBP (mmHg)	93.3, SD 9.0	89.1, SD 10.4	85.3, SD 9.3	78.7, SD 11.1	*Piα: –8; Pbα: –10.4*	Significant reduction in both groups from baseline *Piα: p=0.008; Pbα: p<0.001*	*p=0.36*

NS, not significant; Pbo, placebo; Pio, pioglitazone.

TABLE 10 Changes in lipid profiles with insulin sensitisers

Study	Outcome	Baseline		End of study		Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
		Pio (31)	Pbo (30)	Pio (31)	Pbo (30)			
Pioglitazone								
Aithal 2008[101]	TC (mmol/l)	5.6, SD 1.2	5.6, SD 1.3	5.5, SD 1.4	5.4, SD 1.3	*Piα: –0.1; Pbα: –0.2*	*Piα: p=0.26; Pbα: p=0.17*	*p=0.88*
	LDL cholesterol (mmol/l)	3.3, SD 1.0	3.4, SD 1.1	3.2, SD 1.2	3.2, SD 1.1	*Piα: –0.1; Pbα: –0.2*	*Piα: p=0.04; Pbα: p=0.44*	*p=0.17*
	HDL cholesterol (mmol/l)	1.3, SD 0.3	1.3, SD 0.3	1.3, SD 0.3	1.3, SD 0.4	*Piα: 0; Pbα: 0*	*Piα: p=0.77; Pbα: p=0.93*	*p=0.99*
	TGs (mmol/l)	2.4, SD 2.1	2.1, SD 1.2	2.2, SD 1.2	1.8, SD 0.9	*Piα: –0.2; Pbα: –0.3*	*Piα: p=0.79; Pbα: p=0.19*	*p=0.35*
		Pio (26)	Pbo (21)	Pio (26)	Pbo (21)			
Belfort 2006[102]	TC (mmol/l)	4.86, SD 0.85	4.89, SD 1.06	4.99, SD 0.93	4.94, SD 1.06	*Piα: 0.13; Pbα: 0.05*	*Piα: p=0.48; Pbα: p=0.62*	*p=0.79*
	LDL cholesterol (mmol/l)	3.05, SD 0.80	3.03, SD 0.96	3.10, SD 0.91	2.97, SD 0.93	*Piα: 0.05; Pbα: –0.06*	*Piα: p=0.68; Pbα: p=0.65*	*p=0.58*
	HDL cholesterol (mmol/l)	1.03, SD 0.23	0.96, SD 0.23	1.11, SD 0.23	1.01, SD 0.23	*Piα: 0.08; Pbα: 0.05*	*Piα: p=0.004; Pbα: p=0.22*	*p=0.31*
	TGs (mmol/l)	1.76, SD 0.98	1.95, SD 1.60	1.49, SD 0.95	2.34, SD 1.78	*Piα: –0.27; Pbα: 0.39*	*Piα: p=0.17; Pbα: p=0.001*	*p=0.003*

Study	Outcome	Baseline		End of study		Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Sanyal 2010[104]		Pio (80)	C (84/83)	Pio (80)	C (84/83)			
	TC (mmol/l)	5.04	Vit E: 5.04 Pbo: 5.15	Not given	Not given	Piα: −0.29; Vit E: −0.35; Pbo: −0.25	Not given	Pio vs Pbo: p=0.50 Vit E vs Pbo: p=0.25
	LDL cholesterol (mmol/l)	3.10	Vit E: 3.08 Pbo: 3.23	Not given	Not given	Piα: −0.21; Vit E: −0.31; Pbo: −0.15	Not given	Pio vs Pbo: p=0.26 Vit E vs Pbo: p=0.07
	HDL cholesterol (mmol/l)	1.16	Vit E: 1.14 Pbo: 1.11	Not given	Not given	Piα: 0.03; Vit E: −0.02; Pbo: −0.05	Not given	Pio vs Pbo: p=0.008 Vit E vs Pbo: p=0.51
	TGs (mmol/l)	1.83	Vit E: 1.87 Pbo: 1.86	Not given	Not given	Piα: −0.22; Vit E: −0.01; Pbo: −0.08	Not given	Pio vs Pbo: p=0.16 Vit E vs Pbo: p=0.45
Metformin								
Bugianesi 2005[87]		Met (55)	C (28/27)	Met (55)	C (28/27)			
	HDL cholesterol (mmol/l)	BU: 1.14, SD 0.28; TU: 1.24, SD 0.28	Vit E: 1.09, SD 0.31; Diet: 1.14, SD 0.21			Not given	Not given	p=NS
	TGs (mmol/l)	BU: 2.00, SD 1.06; TU: 1.61, SD 0.98	Vit E: 2.62, SD 1.40; Diet: 1.61, SD 0.78			Not given	Not given	p=NS
Garinis 2010[105]		Met (20)	C (25)	Met (20)	C (25)			
	TC (mmol/l)	5.03, SD 1.0	5.45, SD 0.88	5.06, SD 1.01	5.22, SD 0.95	Met: 0.03, C: −0.23,	Met: p=0.35; C: p=0.21	Not given
	LDL cholesterol (mmol/l)	3.34, SD 0.87	3.61, SD 0.90	3.30, SD 0.75	3.43, SD 0.99	Met: −0.04; C: −0.18	Met: p=0.70; C: p=0.81	Not given
	HDL cholesterol (mmol/l)	1.35, SD 0.39	1.51, SD 0.35	1.50, SD 0.38	1.46, SD 0.36	Met: 0.15; C: −0.05,	Met: p=0.63; C: p=0.95	Not given
	TGs (mmol/l)	1.09, SD 0.4	1.28, SD 0.87	1.06, SD 0.48	1.15, SD 0.38	Met: −0.03; C: −0.13,	Met: p=0.99; C: p=0.53	Not given

TABLE 10 Changes in lipid profiles with insulin sensitisers *(continued)*

Study	Outcome	Baseline Met	Baseline Pbo	End of study Met	End of study Pbo	Change from baseline/end minus baseline	*p*-value (from baseline to end)	*p*-value between groups
Haukeland 2009[106]		**Met (24)**	**Pbo (24)**	**Met (24)**	**Pbo (24)**			
	TC (mmol/l)	5.9, SD 1.0	5.4, SD 1.3	5.4, SD 1.3	5.4, SD 1.2	*Met:* −0.57, SD 0.86; *Pbo:* −0.02, SD 0.47	*Met:* p=0.008; *Pbo:* p=0.64	p=0.004
	LDL cholesterol (mmol/l)	3.9, SD 0.9	3.3, SD 0.9	3.2, SD 1.1	3.2, SD 1.0	*Met:* −0.73, SD 0.82; *Pbo:* −0.07, SD 0.34	*Met:* p=0.001; *Pbo:* p=0.34	p<0.001
	HDL cholesterol (mmol/l)	1.25, SD 0.35	1.23, SD 0.26	1.24, SD 0.32	1.21, SD 0.26	*Met:* −0.01; *Pbo:* −0.02	*Met:* 0.92; *Pbo:* p=0.43	p=0.80
	TGs (mmol/l)	1.8, SD 0.8	2.0, SD 1.5	2.2, SD 1.0	2.4, SD 2.4	*Met:* 0.4; *Pbo:* 0.4	*Met:* p=0.007; *Pbo:* p=0.42	p=0.27
Nadeau 2009[107]		**Met (37)**	**Pbo (13)**	**Met (37)**	**Pbo (13)**			
	TC (mmol/l)	4.39, SE 0.13	4.17, SE 0.23	4.19, SE 0.12	4.16, SE 0.29	*Met:* −0.2; *Pbo:* −0.01	Not given	p=NS
	LDL cholesterol (mmol/l)	2.58, SE 0.11	2.41, SE 0.21	2.57, SE 0.14	2.45, SE 0.23	*Met:* −0.01; *Pbo:* 0.04	Not given	p=NS
	HDL cholesterol (mmol/l)	1.02, SE 0.04	1.12, SE 0.04	1.02, SE 0.04	1.07, SE 0.07	*Met:* 0; *Pbo:* −0.05	Not given	p=NS
	TGs (mmol/l)	1.75, SE 0.11	1.45, SE 0.31	1.45, SE 0.08	1.42, SE 0.33	*Met:* −0.3; *Pbo:* −0.03	*Met:* p=0.03; *Pbo:* Not given	p=NS
Nar 2009[108]		**Met (19)**	**Pbo (15)**	**Met (19)**	**Pbo (15)**			
	TC (mmol/l)	5.68, SD 0.95	4.88, SD 1.01	5.18, SD 0.61	4.67, SD 0.31	*Met:* −0.5; *Pbo:* −0.21	*Met:* p=0.085; *Pbo:* p=0.412	p=NS
	LDL cholesterol (mmol/l)	3.55, SD 0.77	2.90, SD 0.74	2.95, SD 0.59	2.76, SD 0.26	*Met:* −0.6; *Pbo:* −0.14	*Met:* p=0.002; *Pbo:* p=0.470	Unclear
	HDL cholesterol (mmol/l)	1.17, SD 0.19	1.16, SD 0.20	1.26, SD 0.22	1.15, SD 0.06	*Met:* 0.09; *Pbo:* −0.01	*Met:* p=0.035; *Pbo:* p=0.257	Unclear
	TGs (mmol/l)	2.05, SD 0.91	1.94, SD 0.93	2.03, SD 1.39	1.69, SD 1.15	*Met:* −0.02; *Pbo:* −0.25	*Met:* p=0.851; *Pbo:* p=0.053	p=NS
Uygun 2004[110]		**Met (17)**	**Pbo (17)**	**Met (17)**	**Pbo (17)**			
	TC (mmol/l)	4.89, SD 1.01	5.12, SD 1.03	4.42, SD 1.29	4.48, SD 0.82	*Met:* 0.48, SD 0.97 (9.7%); *Pbo:* 0.63, SD 1.06 (12.3%)	*Met:* p=0.05; *Pbo:* p=0.01	p=0.9
	TGs (mmol/l)	2.01, SD 0.80	2.29, SD 0.77	1.94, SD 0.74	2.09, SD 0.58	*Met:* 0.07, SD 0.55 (3.5%); *Pbo:* 0.20, SD 0.44 (8.7%)	*Met:* p=NS; *Pbo:* p=NS	p=0.8

Study	Outcome	Baseline			End of study			Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups

Rosiglitazone

		Rosi (32)	Pbo (31)		Rosi (32)	Pbo (31)				
Ratziu 2008[111]	TC (mmol/l)	Not given	Not given		Not given	Not given		*Rosi:* 0.45, SD 0.67; *Pbo:* −0.24, SD 0.75	Not given	*p* = 0.0013
	LDL cholesterol (mmol/l)	Not given	Not given		Not given	Not given		*Rosi:* 0.41, SD 0.79; *Pbo:* −0.32, SD 0.87	Not given	*p* = 0.0014
	HDL cholesterol (mmol/l), median (IQR)	1.22, IQR 0.42	1.27, IQR 0.49		Not given	Not given		*Rosi:* 0.05, SD 0.27; *Pbo:* 0.01, SD 0.27	Not given	*p* = 0.72
	TGs (mmol/l), median (IQR)	1.34, IQR 0.9	1.65, IQR 1.21		Not given	Not given		*Rosi:* 0.21, SD 1; *Pbo:* 0.2, SD 1.26	Not given	*p* = 0.94

Metformin vs rosiglitazone

		Met (10)	Rosi (11)	Pbo (8)	Met (10)	Rosi (11)	Pbo (8)			
Idilman 2008[112]	Cholesterol (mmol/l)	5.93, SD 1.35	5.25, SD 1.30	5.57, SD 0.80	5.69, SD 1.43	4.89, SD 1.09	5.05, SD 1.10	*Met:* −0.24; *Rosi:* −0.16; *Pbo:* −0.52	*Met:* *p* = 0.287; *Rosi:* *p* = 0.171; *Pbo:* *p* = 0.001	*p* = NS
	TGs (mmol/l)	2.66, SD 1.21	1.91, SD 0.83	1.87, SD 0.72	2.24, SD 1.06	1.63, SD 0.76	1.71, SD 0.74	*Met:* −0.42; *Rosi:* −0.28; *Pbo:* −0.16	*Met:* *p* = 0.120; *Pbo:* *p* = NS	Not given

BU, Bologna unit; C, control; IQR, interquartile range; LDL, low-density lipoprotein; Met, metformin; NS, not significant; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; TU, Turin unit.
The *p*-values that are given in the paper as NS, were also reported in this table as NS.

TABLE 11 Changes in liver biochemistry with insulin sensitisers

Study	Outcome	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Pioglitazone						
Athal 2008[101]	ALT (U/l)	**Pio (31)** 93.6, SD 61.3; **Pbo (30)** 84.1, SD 37.7	**Pio (31)** 55.9, SD 25.7; **Pbo (30)** 77.2, SD 43.0	Pio: −37.7; Pbo: −6.9	Pio: p<0.001; Pbo: p=0.02	p=0.009
Belfort 2006[102]	ALT (U/l)	**Pio (26)** 67, SD 26; **Pbo (21)** 61, SD 33	**Pio (26)** 28, SD 12; **Pbo (21)** 40, SD 17	Pio: −39; Pbo: −21	Pio: p<0.001; Pbo: p=0.033	p<0.001
Sanyal 2004[103]	ALT (U/l)	**Pio (10)** 121, SD 76; **Pbo (10)** 111, SD 45	**Pio (10)** 56, SD 67; **Pbo (10)** 36, SD 15	Pio: −65; Pbo: −75	Not given	p=NS
Sanyal 2010[104]	ALT (U/l)	**Pio (80)** 82; **C (84/83)** Vit E: 86 Pbo: 81	**Pio (80)** Not given; **C (84/83)** Not given	Pio: −40.8; Vit E: −37.0; Pbo: −20.1	Not given	Pio vs Pbo: p<0.0001; Vit E vs Pbo: p=0.001
Metformin						
Bugianesi 2005[87]	ALT (U/l)	**Met (55)** BU: 99, SD 52; TU: 91, SD 52; **C (28/27)** Vit E: 83, SD 29; Diet: 90, SD 47	**Met (55)** 45.5, SE 5 (estimated from graph); **C (28/27)** Vit E: 70.3, SE 8; Diet: 59.5, SE 10 (estimated from graph)	Vit E: −12.7; Diet: −30.5	Not given	p<0.0001
	ALT within normal range (<40 U/l)		n=31; n=12			p=0.0006
Garinis 2010[105]	ALT (U/l)	**Met (20)** 26.1, SD 12.1; **C (25)** 23.0, SD 10.1	**Met (20)** 24.0, SD 17.5; **C (25)** 18.9, SD 5.9	Met: −2.10, C: −4.10	Met: p=0.75; C: p=0.29	Not given
Haukeland 2009[106]	ALT (U/l)	**Met (24)** Not given; **Pbo (24)** Not given	**Met (24)** Not given; **Pbo (24)** Not given	Met: median reduction −15 U/l; Pbo: median reduction −22 U/l	Met: p=0.025; Pbo: p=0.025	Not given

Study	Outcome	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Nadeau 2009[107]	ALT (IU/l)	Met (37) 61.5, SE 4; Pbo (13) 52.9, SE 8.2	Met (37) 46, SE 3; Pbo (13) 36.8, SE 2.8	Met: −15.5; Pbo: −16.1	Met: p<0.006; Pbo: Not given	p=NS
Nar 2009[108]	ALT (U/l)	Met (19) 37.4, SD 17.7; Pbo (15) 32.3, SD 11.0	Met (19) 21.4, SD 8.9; Pbo (15) 25.5, SD 13.4	Met: −16; Pbo: −6.8	Met: p=0.015; Pbo: p=0.047	p=NS
Shields 2009[109]	ALT (IU/l)	Met (9) 79.4, SD 26.1; Pbo (10) 97.5, SD 45.6	Met (9) Not given; Pbo (10) Not given	Met: −21.5; Pbo: −40.7	Overall change: p=0.014	p=NS
Torres 2009[100]	ALT (U/l)	Met + Rosi (16) Not given; Rosi (15) Not given	Met + Rosi (16) Not given; Rosi (15) Not given	Met + Rosi: −46.5%; Rosi: −46.3%	Not given	Not given
Uygun 2004[110]	ALT (U/l)	Met (17) 83.5, SD 24.6; Pbo (17) 72.8, SD 31.2	Met (17) 46.4, SD 23.3; Pbo (17) 55.4, SD 16.3	Met: −37.1, SD 22.2 (44%); Pbo: −17.4, SD 14.1 (24%);	Met: p=0.0001; Pbo: p=0.001	p=0.003
Rosiglitazone						
Ratziu 2008[111]	ALT (U/l)	Rosi (32) 69, SD 40; Pbo (31) 84, SD 38	Rosi (32) Not given; Pbo (31) Not given	Normal ALT level: Rosi: 12 (38%); Pbo: 2 (7%),	Not given	p=0.005
Metformin vs rosiglitazone						
Idilman 2008[112]	ALT (U/l)	Met (10) 82.9, SD 52.9; Rosi (11) 73.6, SD 39.3; Pbo (8) 66.9, SD 28.9	Met (10) 50.0, SD 37.1; Rosi (11) 44.6, SD 32.7; Pbo (8) 42.0, SD 16.2	Met: −32.9; Rosi: −29; Pbo −24.9	Met: p=0.017; Rosi: p=0.001; Pbo: p<0.001; no significant change in either group during a 6-month follow-up	p=NS for insulin sensitisers vs control
Omer 2010[113]	ALT (U/l)	Met (22) 63.1, SD 24.2; Rosi (20) 64.9, SD 23.5; Met + Rosi (22) 72.6, SD 31.9	Met (22) 46.4, SD 28.5; Rosi (13) 28.7, SD 18.2; Met + Rosi (12) 49.9, SD 28.1	Met: −16.7; Rosi: −36.2; Met + Rosi: −22.7	Met: p=NS; Rosi: p<0.0001; Met + Rosi: p=0.017	Not given

BU, Bologna unit; Met, metformin; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; TU, Turin unit; Vit E, vitamin E.
The p-values that are given in the paper as NS, were also reported in this table as NS.

TABLE 12 Changes in insulin sensitivity with insulin sensitisers

Study	Outcome	Baseline	End of study	Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Pioglitazone						
Aithal 2008[101]	HOMA–IR	**Pio (31)** 4.3, SD 3.4; **Pbo (30)** 5.2, SD 2.8	**Pio (31)** 4.8, SD 4.6; **Pbo (30)** 5.1, SD 2.9	*Pio: 0.5; Pbo: –0.1*	*Pio: p=0.87; Pbo: p=0.09*	*p=0.26*
Sanyal 2010[104]	HOMA–IR	**Pio (80)** 5.0; **C (84/83)** Vit E: 5.2 Pbo: 5.5	**Pio (80)** **C (84/83)** Not given	*Pio: –0.7; Vit E: 0.4; Pbo: 0.4*	Not given	*Pio vs Pbo: p=0.03 Vit E vs Pbo: p=0.80*
Metformin						
Bugianesi 2005[37]	HOMA (%)	**Met (55)** BU: 3.5, SD 1.3 TU: 5.0, SD 2.4; **C (28/27)** Vit E: 3.6, SD 1.9 Diet: 3.9, SD 2.8	**Met (55)** **C (28/27)** Not given	*Met: –1.5%; C: –0.5%*	Not given	*p=0.002*
Garinis 2010[105]	HOMA–IR	**Met (20)** 3.3, SD 1.6; **C (25)** 3.2, SD 1.6	**Met (20)** 2.4, SD 1.2; **C (25)** 2.8, SD 1.1	*Met: –0.90; C: –0.40*	*Met: p=0.003; C: p=0.15*	Not given
Haukeland 2009[106]	HOMA–IR	**Met (24)** 1.88, SD 0.88; **Pbo (24)** 2.18, SD 1.24	**Met (24)** 2.41, SD 1.96; **Pbo (24)** 2.81, SD 2.17	*Met: 0.53; Pbo: 0.63*	*Met: p=NS; Pbo: p=0.067*	*p=0.71*
Nar 2009[108]	HOMA–IR	**Met (19)** 3.1, SD 2.0; **Pbo (15)** 3.2, SD 1.8	**Met (19)** 2.6, SD 1.1; **Pbo (15)** 2.7, SD 1.1	*Met: –0.5; Pbo: –0.5*	*Met: p=0.038; Pbo: p=0.035*	*p=NS*
Shields 2009[109]	HOMA–IR	**Met (9)** 6.14, SD 4.5; **Pbo (10)** 4.02, SD 3.99	**Met (9)** **Pbo (10)** Not given	*Met: –1.58; Pbo: –1.14*	*Overall change: p=0.002*	*p=0.886*
Torres 2009[100]	HOMA–IR	**Met+Rosi (16)** **Rosi (15)** Not given	**Met+Rosi (16)** **Rosi (15)** Not given	Met+Rosi: –51.8%; Rosi: –50.2%	Not given	Not given

Study	Outcome	Baseline			End of study			Change from baseline/end minus baseline	p-value (from baseline to end)	p-value between groups
Uygun 2004[110]	HOMA (%)	Met (17) 2.53, SD 0.98	Pbo (17) 1.83, SD 0.74		Met (17) 1.38, SD 0.71	Pbo (17) 1.81, SD 0.67		Met: −1.15; Pbo: −0.02	Met: p=0.0001; Pbo: p=0.18	p=0.001
Ratziu 2008[111]	HOMA, median (IQR)	Rosi (32) 4.57, IQR 4.66	Pbo (31) 4.21, IQR 4.32		Rosi(32) Not given	Pbo (31) Not given		Rosi: −1.4, IQR 2.6; Pbo: 0.61, IQR 5.5	Not given	p<0.001
Metformin vs rosiglitazone										
Idliman 2008[112]	HOMA–IR	Met (10) 4.9, SD 3.9	Rosi (11) 5.7, SD 3.8	Pbo (8) 3.8, SD 3.1	Met (10) 2.8, SD 2.9	Rosi (11) 2.8, SD 1.8	Pbo (8) 3.9, SD 2.0	Met: −2.1; Rosi: −2.9; Pbo: 0.1	Met: p=0.002; Rosi: p=0.001; Pbo: p=NS; No significant change in either group during 6-month follow-up	Not given
Omer 2010[113]	HOMA–IR	Met (22) 4.4, SD 2.5	Rosi (20) 2.9, SD 1.9	Met + Rosi (22) 5.7, SD 4.3	Met (22) 3.6, SD 3.8	Rosi (13) 1.8, SD 0.9	Met + Rosi (12) 4.1, SD 3.8	Met: −0.8; Rosi: −1.1; Met + Rosi: −1.6	Met: p=NS; Rosi: p=0.003; Met + Rosi: p=NS	p=NS

BU, Bologna unit; C, control; Met, metformin; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; TU, Turin unit; Vit E, vitamin E.
The p-values that are given in the paper as NS, were also reported in this table as NS.

($p = 0.71$). In Idilman (2008)[112] (–2.9 HOMA–IR score with rosiglitazone, –2.1 score with metformin and +0.1 score with placebo) and Omer (2010)[113] (–1.1 score with rosiglitazone, –0.8 score with metformin), rosiglitazone led to a greater reduction in insulin resistance than metformin. In Ratziu (2008),[111] there was a reduction with rosiglitazone and an increase in the placebo group [–1.41 interquartile range (IQR) vs +0.61 IQR]. Two trials (Omer 2010[113] and Torres 2009[100]) reported that the changes in insulin resistance were greater with a combination of metformin and rosiglitazone than with either rosiglitazone or metformin alone (–1.6 with combination in Omer;[113] in Torres[100] –51.8% with a combination vs –50.2% with rosiglitazone).

Quality of life

Only Sanyal (2010)[104] reported health-related QoL, assessed using the Short Form questionnaire-36 items (SF-36). There was reduction in both the physical and mental components with pioglitazone (reduction by a mean of –0.9 in the physical component of SF-36 and a reduction by a mean of –1.9 in the mental component of SF-36), but only in the physical component with placebo (mean score of –0.3 physical component and mean score of +0.4 mental component), and only in the mental component (mean score of –0.5 mental component and mean score of +0.4 physical component) with vitamin E. However, the changes were not significantly different between the groups.

Conversion to diabetes/impaired glucose tolerance/metabolic syndrome

Two studies (Idilman 2008[112] and Sanyal 2010[104]) reported frequency of new-onset diabetes at the end of the study, and one study (Garinis 2010[105]) compared the total number of participants with impaired glucose tolerance at baseline and end of the study. In Sanyal (2010),[104] two participants in the vitamin E group and none in the placebo or pioglitazone group developed new-onset diabetes. Idilman (2008)[112] reported that two participants in the group on diet and exercise alone and a total of six (combined number for both rosiglitazone and metformin) in the remaining groups developed diabetes by the end of the study. Garinis (2010)[105] found that the number of participants who had impaired glucose tolerance at baseline reduced at the end of the study in the group taking metformin (three at baseline and two at end), whereas the number remained unchanged in the control group (three at baseline and three at end). The numbers in some of these groups are quite small.

Discussion

Summary

Fifteen RCTs were included in this review. Four trials examined the effects of pioglitazone, seven examined metformin, one rosiglitazone and three compared metformin against rosiglitazone. The duration of most trials ranged between 6 months and 1 year, and only one trial[104] lasted 96 weeks with a 24-week follow-up. The total number of participants analysed in this review was 881 (751 excluding participants who received rosiglitazone in combination with other drugs or rosiglitazone on its own). In all of the pioglitazone trials, the dose of pioglitazone was 30 mg once a day. The dose of metformin varied between 1 and 2.5 or 3 g/day, with most trials using 1.7 g/day. The dose of rosiglitazone ranged between 4 and 8 mg/day. In most trials, the participants in the control group as well as in the intervention group also received other measures including counselling on diet and exercise, use of a hypocaloric diet and lifestyle modifications.

Pioglitazone was found to improve all parameters of liver histology, was better than placebo or diet and exercise or a hypocaloric diet, but no better than vitamin E.

Results with metformin were mixed. In comparison with placebo or diet and exercise, some studies suggested that metformin led to some improvements in steatosis and necroinflammation, but not in fibrosis. However, in most studies the changes seen with metformin were not significantly different from those in the control arms. The Bugianesi trial[87] reported clear improvements in histology with metformin, but no biopsies were done in the control arm. The ultrasound trials suggest that metformin led to improved liver echogenicity compared with diet and exercise. Uygun *et al.*[110] found significant differences with ultrasound ($p = 0.038$), but not with biopsy.

Rosiglitazone showed significant improvement in hepatic steatosis and very little improvement in any of the other parameters. In head-to-head trials comparing metformin and rosiglitazone, the results varied. Idilman (2008)[112] found greater improvements in hepatic steatosis, ballooning and fibrosis with metformin than diet and exercise alone. 'Rosiglitazone only' led to a reduction in hepatic steatosis. The overall improvement in NAFLD score from baseline to end was better with either metformin or rosiglitazone than with diet and exercise (Idilman 2008[112]). Omer (2010)[113] found significant improvement in NAFLD score with rosiglitazone and a combination of rosiglitazone and metformin and no significant changes occurred with metformin alone.

Pioglitazone was better than any control groups (placebo, diet or exercise) in terms of improvement of ALT, insulin sensitivity, and FPG, but led to weight gains of 2.5–4.7 kg, and increases in BMI of 0.7–4.7 kg/m^2. The changes in waist–hip ratio, waist or hip circumference and body fat with pioglitazone were not significant. Metformin led to greater reduction in weight, BMI and waist or hip circumference than rosiglitazone or a combination of the two. Although there were reductions in lipid parameters, ALT and insulin resistance with metformin, the changes were similar to those with placebo or lifestyle modifications or rosiglitazone.

Rosiglitazone was better than metformin in terms of HbA$_{1c}$ levels, FPG and insulin sensitivity, but the changes in weight were inconclusive, with one trial (Ratziu 2008[111]) showing better results with rosiglitazone and the other with a combination of rosiglitazone and metformin (Torres 2009[100]). The reductions in BMI, body fat and waist or hip circumference were not greater with rosiglitazone. The changes in lipid profiles with rosiglitazone were inconclusive. A combination of metformin and rosiglitazone was found to be similar to rosiglitazone alone in terms of ALT reduction and insulin resistance (Torres 2009[100]).

Strengths and limitations

Strengths

We carried out an up-to-date systematic search to identify all trials that explored the effectiveness of insulin sensitisers in patients with NAFLD. We included only RCTs either published in full or as an abstract. There were no language restrictions.

Limitations

There were only two head-to-head trials comparing the effects of different insulin sensitisers against each other and, therefore, no firm conclusions can be made about their relative effectiveness. Given recent evidence, pioglitazone would have been a more useful comparator than rosiglitazone because of its better cardiovascular risk profile. There are also doubts about comparisons of pioglitazone and metformin against vitamin E. Although Sanyal (2010)[104] found that effect of vitamin E was similar to pioglitazone in terms of histological changes to the liver, no firm conclusions can be made that vitamin E would be as effective as insulin sensitisers.

The trials were not long enough to make firm conclusions that insulin sensitisers would be effective for long periods of time. Only one trial lasted 96 weeks, and the comparison was against vitamin E, whose effect on NAFLD is not proven.

Because the data were inadequately reported, meta-analyses could not be done. Therefore, our results are reported only as texts and tables. Out of 15 studies, only three[87,104,109] had carried out an ITT analysis. We made no attempts to find unpublished studies.

There are also doubts about some of the findings. Bugianesi (2005)[87] conducted a follow-up biopsy only in the participants who were on metformin, but not in the control groups, because the physicians taking care of the participants in the control group did not support a second one. The findings showed a marked improvement in liver steatosis with metformin, but without a control biopsy the findings are inconclusive. It is noteworthy that Haukeland (2009),[106] with a much larger sample size, found improvements also in the placebo group. Torres (2009)[100] reported findings of only the first 49 participants who completed a trial that is still ongoing. The preliminary findings, however, suggest that rosiglitazone alone was as effective as when combined with metformin.

There are also doubts about the generalisability of the findings. Three of the trials were conducted in Turkey, one each in the UK and Italy, and the rest in the USA. The total number of participants in most trials was small, i.e. < 50, and, in addition, the methodological quality of some trials was low. We did not explore the safety and tolerability of these drugs as these are well documented. In some trials there were concerns about loss to follow-up. In three trials[107,109,110] one or more arms had loss to follow-up of > 20%, raising the risk of bias and generalisability of the results.[118]

Other systematic reviews[114,119,120] on the effectiveness of insulin sensitisers in patients with NAFLD were identified, but they differed from this review. Angelico *et al.*[114] included only three RCTs. Chavez-Tapia *et al.*[119] included non-RCTs and Socha *et al.*[120] also included trials that compared efficacy of non-insulin sensitisers in patients with NAFLD. A systematic review by Musso *et al.*[78] included trials that compared the efficacy of non-pharmacological interventions and all drugs in patients with NASH/NAFLD. The findings from these reviews were inconclusive regarding the effectiveness of insulin sensitisers and suggested that more trials were needed. Our findings showed improvements in some outcomes with insulin sensitisers. There is need for more head-to-head trials with relevant comparators and a bigger sample size with participants followed up for longer durations of time.

Conclusions

There were some improvements in liver histology and other parameters with pioglitazone, but there was a lack of evidence that metformin improved liver histology, compared with placebo or diet and exercise, in mainly short-term trials. There were only two head-to-head trials comparing rosiglitazone with metformin.

Chapter 3

Diagnosis of non-alcoholic fatty liver disease and its stages

Introduction

This chapter examines the ways in which NAFLD is diagnosed and the differentiation of simple steatosis from NASH. The main interest is in doing this in a non-invasive manner.

Liver biopsy has traditionally been viewed as being necessary for accurately diagnosing and staging NAFLD.[121–123] However, there has been much interest in alternative means of diagnosing the condition for the following reasons:

- *Prevalence of NAFLD* It is believed that NAFLD affects approximately 25–30% of adults in Western countries.[123–126] Performing liver biopsies on such a large number of people is not feasible.[127]
- *Risks of liver biopsy* Biopsy is an invasive procedure and is associated with complications including haemorrhage and death, although the risk of these complications is very low (mortality risk about 0.1%).[123,126] After a review of the literature, Gaidos *et al.*[128] estimated the risk of death after liver biopsy to be around 0.01%.
- *Costs of biopsy* Biopsy is not an inexpensive test. Therefore, its use in a large number of trial people is not feasible.[126]
- *Accuracy of biopsy* 'Biopsy-only' samples a small amount of hepatic tissue. It is recognised, however, that pathological changes in chronic liver disease may not be evenly distributed throughout the liver. Therefore, sampling a relatively small area of tissue could give rise to false-negative results.[121,123,125,126,129]

If there is to be a large trial to provide better evidence on the effectiveness of insulin sensitisers, it will need to be based on a diagnostic method other than liver biopsy, especially if patients are to be recruited from the more advanced stages than simple steatosis. Ultrasound at baseline, combined with alcohol history, could establish a diagnosis of NAFLD but not the stage, such as differentiating steatosis from NASH.

Methods

A systematic search was undertaken on electronic bibliographic databases, MEDLINE (1950 to June 2010) and EMBASE (1980 to June 2010). Searches were developed by using relevant medical subject heading (MESH) terms with explosion of the MESH terms when necessary.

The following search strategy was used:

1. Liver.tw
2. (non-alcoholic or non alcoholic or nonalcoholic).tw
3. (fatty or steato*).tw.
4. (NAFL or NAFLD or NASH).tw

5. exp *Diagnosis/
6. diagnos*.tw.
7. Fatty Liver/di [Diagnosis].

The searches were limited to the English language. Search results from both databases were imported into Reference Manager 12 (Thomson Reuters, Philadelphia, PA, USA). Duplicates were removed before two authors (NW and RH) scanned the list independently to identify relevant papers. Any discrepancies were resolved by consensus.

Full texts of all potentially relevant studies were obtained.

Study selection

Articles for review were selected, based on whether or not they seemed likely to have data on non-invasive alternatives to liver biopsy, ideally with liver biopsy used as a comparator. Reviews were selected in the first instance.

Quality assessment

The intention was to assess the quality of review articles using recognised appraisal frameworks, for example the Critical Appraisal Skills Programme (CASP)[130] or the Scottish Intercollegiate Guidelines Network (SIGN).[131] However, the majority of reviews did not describe the search strategy adopted, their inclusion and exclusion criteria or how included studies were appraised. Therefore, this section aims to simply summarise their findings and conclusions.

Diagnosis of non-alcoholic fatty liver disease

Guidelines recently published by the Italian Association for the Study of the Liver (AISF)[125] recommend that NAFLD can be diagnosed based on clinical history, clinical examination, laboratory tests [e.g. full blood count (FBC), LFTs, fasting glucose, etc.] and an abdominal ultrasound scan. The AISF guidelines recommend that liver biopsy be performed on individuals believed to be at high risk of NASH (e.g. age > 45 years, obesity, diabetes/insulin resistance, etc.), although the guidance does not state how many of these risk factors should be present before considering biopsy.[125] The guideline also recommends that biopsy should be considered if a patient still has evidence of steatosis on abdominal ultrasound scan or deranged LFTs 6–12 months after commencing lifestyle modifications following diagnosis.[125]

Myers[126] also advocates a multifaceted approach to the diagnosis of NAFLD, stating that individual parameters may be misleading.[126] People with NAFLD may have no or non-specific symptoms, and laboratory tests may also be of limited value when used on their own (e.g. ALT levels may vary in people with NAFLD).

Myers[126] states that abdominal ultrasound scans are the most frequently used imaging tool for diagnosing NAFLD in the USA. However, it is recognised that ultrasound is also subject to limitations. It may fail to detect mild steatosis,[126,127,132–134] suffers from poor performance when used on morbidly obese individuals[134] and is vulnerable to inter- and intra-observer variability.[134] Such variability may reflect factors such as differences in the criteria used to diagnose steatosis and differences in ultrasound transducers as well as differences in the populations studied.[132] Furthermore, ultrasound scans cannot distinguish between steatosis and NASH.[126,127,132–134]

Therefore, it might be argued that abdominal ultrasound may not add enough to the combination of clinical history, clinical examination and laboratory tests to influence clinical management,

because of the lack of proven treatment options, other than weight loss.[5] However, it could still be used to screen patients for trials.

Imaging with modalities other than ultrasound has also been explored. Computerised tomography (CT) scanning is also able to detect steatosis and has been said to be '… more reliable for detecting and grading fatty infiltration of the liver than ultrasonography.'[132] However, CT scanning requires the use of ionising radiation, reducing its usefulness.[123,125] In addition, CT scanning does not appear to have a role in distinguishing between steatosis and NASH.[5,122,129,135]

Magnetic resonance imaging has also been used as a means of diagnosing NAFLD, with Ma *et al.*[133] describing MRI as '… one of the most sensitive modalities for detection and characterisation of fatty infiltration of the liver'.

The AISF guideline states that MRS is '… probably the most accurate and fastest method of detecting liver fat'.[125] The technique allows detailed examination of particular areas of interest within the liver. However, MRS is expensive[125,126] and may not be routinely available in radiology departments.[123,125,126]

Chemical shift-based MRI techniques have also been reported as being able to diagnose steatosis.[5,122,123,135] Chemical shift imaging techniques have been modified during recent years, and have been described as '… the most common MRI modality to evaluate NAFLD…' in clinical practice.[122] In comparison with MRS, chemical shift imaging is said to have '… a shorter acquisition time, can measure fat content throughout the liver instead on in one or just a few voxels, no special misregistration errors, as well as easier and faster processing'.[122] Cassidy *et al.*[121] recommend the use of chemical shift imaging as opposed to MRS in clinical practice, stating that 'in most clinical situations, chemical shift imaging provides adequate detection in a fraction of time'. However, they state that the sensitivity of chemical shift imaging appears to increase with increasing steatosis,[121] although Charatcharoenwitthaya and Lindor[132] claim that '… gradient-echo techniques have been shown to accurately quantify the hepatic fat fraction at low or near normal level'.[132]

Biochemical tests have also been suggested for the diagnosis of NAFLD. The SteatoTest (BioPredictive, Paris, France) combines several demographic variables (e.g. age, gender) with laboratory analyses (e.g. cholesterol, TGs, glucose, ALT, etc.) to assess steatosis.[126,135] An initial study that recruited individuals with a range of chronic liver conditions (e.g. hepatitis C, alcoholic liver disease) in addition to NAFLD reported favourable results.[126] Further independent studies involving people with NAFLD are required to assess the utility of the test.[126,135]

In summary, there appears to be an emerging view that steatosis can be diagnosed without the need for liver biopsy on the basis of clinical history, clinical examination and laboratory tests, supported by imaging. Abdominal ultrasound scanning appears to be the most commonly used modality, although it is subject to several limitations. CT and MRI also appear to be useful tools, although their use may be limited by concerns regarding exposure to ionising radiation and cost, respectively.

Diagnosis of non-alcoholic steatohepatitis

Although it appears that NAFLD may be diagnosed without liver biopsy, the recently published guidelines produced by AISF describe biopsy as being '… an irreplaceable diagnostic tool to differentiate NASH from NAFLD',[125] a view shared by others.[127,132] Note that the terminology can

be confusing. The term NAFLD is sometimes used to cover the whole spectrum, but at other times to refer to the stages before NASH.

However, as previously described, the prevalence of NAFLD together with the invasive nature of, and the risks associated with, liver biopsy has led to interest in developing new means of differentiating between these conditions. Some of these are described below.

Laboratory markers of fibrosis

The guideline recently issued by AISF states that several biochemical indicators of fibrosis have been investigated as means of reducing the number of people requiring liver biopsy.[125] However, AISF describes these as having not yet been rigorously tested and validated, as well as being unavailable within many laboratories.[125] Therefore, AISF states that these 'do not avoid the need to perform liver biopsy in clinical practice.'[125]

Myers[126] categorised such markers as signifying oxidative stress, inflammation or hepatocyte apoptosis.[126] With respect to the evaluation of markers of oxidative stress, he describes the results as generally being '… disappointing and/or inconsistent …', concluding that '… additional studies are necessary before markers of oxidative stress can be used clinically to differentiate simple steatosis from NASH'.

With respect to biomarkers of inflammation, Myers[126] states that a marker which has been '… validated and is ready for clinical use is not available.' With respect to hepatocyte apoptosis, Myers discussed research concerning the use of caspase-generated fragments of cytokeratin-18 (CK-18). Although encouraging, Myers[126] states the findings require validation '… in large-scale, multicentre studies that include more diverse patient populations.'

Clinical scores for fibrosis

Several clinical scoring systems, or fibrosis marker panels, have been developed with the aim of differentiating NASH from NAFLD (e.g. NAFLD fibrosis score, European Liver Fibrosis panel, etc.).[125,126] Some of these are subject to patent.[126]

These scoring systems attempt to identify people at risk of fibrosis through measuring indicators such as BMI together with various biochemical parameters. The biochemical parameters can be described as:

- indirect markers of fibrosis in that they '… reflect alterations in hepatic function, but do not directly reflect extracellular matrix (ECM) metabolism (e.g. liver biochemistry, platelets)'[126]
- direct markers of fibrosis in that they '… reflect the dynamics of the ECM [extracellular matrix] turnover (e.g. matrix metalloproteinases and their inhibitors, collagens, hyaluronic acid)'.[126]

Both indirect and direct markers are subject to limitations. For example, changes in some indirect markers may be observed only in the advanced stages of chronic liver disease.[136] Changes in direct markers may be due to non-hepatic disease.[136]

In many cases, the biochemical parameters within fibrosis marker panels are a mixture of direct and indirect markers.[126] Many of these panels were developed for use among patients with chronic hepatitis C infection, but their use in other conditions, including NAFLD, is being explored.[126]

Poynard et al.[137] undertook a review of biomarkers of liver fibrosis associated with chronic hepatitis C, chronic hepatitis B, alcoholic liver disease, NAFLD and mixed causes. They identified 14 biomarkers, nine of which were not patented and five that were. Only patented biomarkers

were considered in detail within the review. Two of the authors have connections to a company marketing one of the patented biomarkers considered – FibroTest™ (Biopredictive, Paris, France). They found no significant differences between the five patented tests. With respect to performance in relation to the aetiology of fibrosis, the authors stated that most studies had been performed among patients with chronic hepatitis C, with only one test – FibroTest – having '… been investigated specifically in the four most frequent chronic liver disease(s)'. Only three of the studies of patented biomarkers included in the review – two involving FibroTest (267 patients) and one involving the European Liver Fibrosis panel (61 patients) – examined the use of biomarkers among individuals with NAFLD. The authors stated that 'neither biomarkers nor biopsy are sufficient alone to take definitive decision(s) in a given patient …' and suggested '… a moratorium on liver biopsy as a first line procedure while awaiting studies demonstrating biopsy cost-utility vs that of biomarkers'.

Poynard[137] and another author[138] contributing to the above review (both of whom have connections to the company marketing FibroTest) contributed to a further review focusing on FibroTest as a measure of liver fibrosis. The majority of studies identified assessed the use of the test among patients with chronic hepatitis C. Only two studies examining the use of the test among patients with NAFLD were identified, both of which were included in the earlier review.[137] Similar to the conclusions of the earlier review, the authors stated: 'FibroTest™ may be an alternative to liver biopsy in the four more common liver diseases – namely, HCV, HBV, NAFLD and ALD. However, neither biomarkers nor biopsy alone are sufficient to allow definitive decisions to be made for a given patient, and all clinical and biological data must be taken into account.'

The AISF guideline[125] did not refer to FibroTest, although it referred to several other fibrosis marker panels not included within the Poynard review[137] [e.g. BAD (BMI, age, T2DM), BAAT (BMI, age, ALT, TG), HAIR (hypertension, ALT, insulin resistance), BARG (BMI, age, AST/ALT ratio, HbA_{1c} or glucose), NAFLD Fibrosis Score, BARD (BMI, AST/ALT ratio, T2DM), Clinical Scoring System for Predicting NASH]. Studies describing the use of some of these were published outwith the time period covered by Poynard *et al.*[137] (February 2001 to July 2007). The AISF guideline states: 'These indices, particularly the NAFLD fibrosis score, should be considered in evaluating patients for liver biopsy.'[125]

The majority of studies evaluating the use of fibrosis marker panels have involved people with chronic hepatitis C. Some marker panels have been investigated among patients with NAFLD, although for some the findings of initial studies require to be confirmed by further research.[135,136] At the current time, the relative ability of these panels to differentiate NASH from NAFLD is unclear, and comparisons are difficult as a consequence of studies using a variety of scoring systems and end points in the assessment of fibrosis.[135]

At present, the consensus view appears to be that fibrosis panels should be used as an adjunct to liver biopsy rather than as a substitute. Myers[126] states:

> 'Most experts would agree that the most rational approach is to use these markers as a complement to liver biopsy on a case-by-case basis. It would be unrealistic to expect any index to completely replace liver biopsy which offers a wealth of additional information … It is important to remember that up to a third of patients suspected of having NAFLD have another cause of liver enzyme elevations identified by liver biopsy.'[126]

Imaging

Ultrasound scanning
Ultrasound scanning is said to be unable to distinguish between steatosis and steatohepatitis.[122,123,132] However, initial studies of contrast-enhanced ultrasound have been more

encouraging, although further evaluation involving larger numbers of patients with NAFLD is required.[127,132]

Transient elastography

Transient elastography (TE) is a technique that may supplement traditional USG. TE aims to measure liver stiffness, a variable that is believed to be associated with the degree of fibrosis. A mechanical pulse is generated at the skin surface, which is propagated through the liver. The velocity of the wave is measured by ultrasound. The velocity is directly related to the stiffness of the liver, which, in turn, affects the degree of fibrosis: the stiffer the liver is, the greater the degree of fibrosis.[139] The technique has been used in a range of liver conditions, but relatively few studies have described its use in NAFLD.[126,135,136]

The results of TE are influenced by factors including elevated ALT levels[124,125,136] and possibly by the degree of steatosis.[125,126,136] In addition, it is technically difficult in the presence of obesity.[126,127,132,135,136,140] Furthermore, cut-off points between stages of fibrosis have been said to be unclear, and may vary with aetiology.[126] As a consequence, Myers[126] states: 'In light of these unresolved issues, and despite the widespread use of TE in patients with NAFLD, much further investigation is necessary to guide the optimal incorporation of this promising technology into routine clinical practice',[126] a sentiment echoed by Charatcharoenwitthaya and Lindor.[132] Browning,[127] however, is less optimistic: 'Further study is required to determine if FibroScan [a commercially available TE machine] is a viable method for differentiating patients who have NAFLD with no fibrosis from those who have minimal or no fibrosis … However, based upon data available for staging other forms of liver disease, this seems unlikely.'[127]

Computed tomography scanning

The AISF guideline states that, in contrast to individuals with simple steatosis, those with NASH '… have a greater liver span and increased caudate-to-right-lobe-ratio.'[125] Charatcharoenwitthaya and Lindor, however, state that although some studies have reported differences between patients with NAFLD and NASH that are evident on CT scanning, in their opinion the technique is unable to reliably differentiate between steatosis and steatohepatitis,[132] a view also shared by others.[122,127,135]

Studies have examined the use of dynamic contrast-enhanced CT as a means of diagnosing fibrosis.[127,140] However, the majority of studies have been conducted among people with cirrhosis,[127,140] so it is uncertain if the technique will be able to diagnose earlier stage fibrosis.[140] Nevertheless, Browning believes that based upon current knowledge of liver perfusion in NAFLD '… the utility of this imaging modality in staging NAFLD is questionable.'[127]

Therefore, the current consensus appears to be that CT scanning does not have a role to play in distinguishing NAFLD from NASH.

Magnetic resonance imaging

Browning states that standard MRI cannot differentiate between NAFLD and NASH,[127] with Castera[140] describing its ability to diagnosis early-stage fibrosis as being 'limited'.[135] Although a small number of studies have described changes relating to liver fibrosis on MRI, its sensitivity or specificity has not been reported.[140]

Contrast-enhanced MRI has been suggested as a means of diagnosing fibrosis, and a limited number of studies having shown encouraging results in staging of advanced hepatic fibrosis.[140] Browning[127] states that 'Much more work is needed, however, to fully evaluate the utility and limitations of such contrast-based methodologies'. Furthermore, the possibility of allergic reactions associated with contrast agents[140] may also prove a barrier to the future use of the technique.

Diffusion-weighted MRI is another technique that has been investigated as a non-invasive means of diagnosing liver fibrosis.[140] It appears that the technique can distinguish between normal and cirrhotic liver, but its ability to differentiate earlier stages of fibrosis has been less positive.[140]

Magnetic resonance spectroscopy allows an assessment of the '… concentrations of different chemical components within tissues'.[140] However, the results of the technique are sensitive to movement, and require the patient being examined to lie as still as possible during the examination.[140]

Bonekamp[140] states that although proton MRS appears to be of limited use in distinguishing NAFLD from NASH, initial studies evaluating phosphorous MRS have shown some promise, although the technique requires more thorough evaluation. In addition, the need for special equipment, together with considerable operator experience, makes it unlikely that it will be a widely accessible technique in the short term, even if it is proved to be effective.[140]

The use of magnetic resonance elastography (MRE) has also been suggested as a means of differentiating NAFLD from NASH. In contrast to conventional TE, MRE is said to be unaffected by obesity, and may also be unaffected by steatosis.[126] However, although there appear to be some encouraging results using this technique, Myers[126] counsels that: 'Future studies will be necessary to validate these findings and confirm the cost-effectiveness of MRE before it gains widespread clinical use.'[126] Similarly, Bonekamp *et al.* state '… more studies including larger patient populations are needed to confirm the sensitivity and specificity of MRE and to standardise the technique to make results comparable.'[140]

Other considerations

Ability to compare markers

Interpreting the current data on the effectiveness of non-invasive markers of liver fibrosis is challenging as a consequence of:

- small number of patients recruited in some studies[135]
- assessment of fibrosis varies across studies[135]
- the performance of tests being dependent on the prevalence of severe fibrosis in the study population.[136]

Area under receiver operating characteristic curve (AUROC) estimates are a commonly used measure of the effectiveness of diagnostic and screening tests. However, Poynard *et al.*,[137] with reference to biochemical markers of liver fibrosis, have discussed the need for standardisation when comparing the AUROC estimates to take account of differences in the prevalence of stage of fibrosis between studies.[137]

Quality of reviews studied

Many of the reviews studied in the preparation of this section referred to an extensive body of research. However, as described above, methodological issues associated with primary studies limit the strength of the conclusions that they can draw.

Furthermore, with respect to identifying non-invasive means of distinguishing NAFLD from NASH, although a large number of techniques have been studied, in general the volume of evidence underpinning individual approaches among individuals with NAFLD appears limited. There is, therefore, a need for additional high-quality research in this area, focusing on those approaches assessed as holding greatest promise.

As described, many of the reviews studied in the preparation of this section referred to a large number of papers. However, the majority contained no description of how these papers were identified, inclusion and exclusion criteria or appraisal methods. In the majority of reviews, it was not clear if the conclusions were based upon an assessment of the quality of the primary studies referred to. Therefore, there is also a need for rigorous systematic reviews of methodologically robust primary research.

Conclusions

There appears to be an emerging view that simple steatosis can be diagnosed without the need for liver biopsy, on the basis of clinical history, clinical examination and laboratory tests, and ultrasound.

Although several non-invasive means of distinguishing simple steatosis from NASH have been studied, at the current time it appears that liver biopsy is required to differentiate between these conditions. However, this issue has been the focus of much research and further studies may help to identify if any of the approaches discussed, or novel techniques, could become acceptable alternatives. However, there is a need for high-quality research to enable approaches to be compared against liver biopsy and each other.

Implications for trials and diagnostic research needs

If we assume that (1) a definitive trial of drug intervention in NAFLD will require a large number of patients followed for several years and (2) liver biopsy will not be feasible or perhaps ethical, then we have to consider other approaches.

One consideration concerns who should be included in a trial. It would be desirable to intervene in time to prevent fibrosis, so the most important aspect of diagnosis might be to distinguish between those without fibrosis and those with. Progression to fibrosis might be a key end point.

Non-invasive methods of distinguishing those with simple steatosis from those with NASH are, as yet, unproven. However, it could be argued that inclusion of patients with simple steatosis in a trial of an old tried and tested drug, such as metformin, would do them no harm, and might well do good (e.g. reducing the chance of progression to diabetes), and that therefore a screening test that lacked specificity could be allowed. The Italian guideline panel of tests might be used, perhaps combined with MRS or MRE for follow-up, with reduction in steatosis as one outcome. Unfortunately, in trials to date, metformin does not appear to improve histology, and trials might be better done using newer and more expensive drugs such as liraglutide.

Several diagnostic measures appear promising, but require further evaluation. One is TE, except in the more obese. NFS has been reported to be reliable in the LEAD (Liraglutide Effect and Action in Diabetes) trials.[141] MRE appears promising but requires further evaluation and standardisation. Even if too expensive for routine use, it could be trialled against liver biopsy in a small trial and, if reliability is proven, it could then be used as the reference standard in trials of treatment to assess the accuracy of TE and NAFLD Fibrosis Score (NFS).

This chapter was only a rapid review of recent evidence on diagnostic options, and a full systematic review would be worthwhile as a prelude to primary diagnostics research.

Chapter 4

Review of economics studies

The search strategy used is in *Appendix 1*.

Few studies were found.

Baumeister *et al.*[142] set out to estimate the inpatient and outpatient costs for people with fatty liver disease (FLD), using data from the Study of Health in Pomerania database. They used ultrasound hyperechogenicity ('bright liver') and ALT levels to identify people with FLD. However, although they identified people with 'at-risk' drinking of alcohol, they did not provide data broken down by lesser levels of alcohol use, and so it is not possible to extract data on the costs of NAFLD. One problem with such studies is that people with FLD are at higher risk of other metabolic conditions such as diabetes and hypertension. Baumeister *et al.*[142] adjusted for comorbidities and found that people with FLD still had higher outpatient costs.

A study from the USA by Younossi and Singer,[143] available at present only as an abstract, used Markov modelling to estimate lifetimes costs of NAFLD and reported that NAFLD led to costs of several billion US dollars (undiscounted).

Dan *et al.*[144] surveyed health-related QoL in people with NAFLD who had been referred to a Liver Service. This implies that they were symptomatic, and may have been on the more severely affected end of the NAFLD spectrum. Dan *et al.*[144] compared the NAFLD group with patients with chronic hepatitis B or C (but who were not on treatment with interferon, which reduces QoL while patients are taking it). The NAFLD group had the poorest QoL. They differed from the hepatitis groups by being much more likely to be obese (76% vs 14% and 36%), diabetic (26% vs 4% and 8%) and hypertensive (39% vs 9% and 14%). However, Dan *et al.*[144] reported that the reduced QoL in the NAFLD group persisted after adjusting for obesity (which itself reduces QoL).

David *et al.*[145] from the NASH Clinical Research Network (CRN) Research Group administered the SF-36 to 713 people enrolled in two studies, one an observational cohort, the other the PIVENS (Pioglitazone Versus Vitamin E Versus Placebo for the Treatment of Non-diabetic Patients with Non-alcoholic Steatohepatitis) trial. Most (61%) had NASH, and 28% had fibrosis or cirrhosis. All had had liver biopsy. So as with the Dan study,[144] there is some selection towards the severe end of the NAFLD spectrum. The results in the NAFLD group were compared with the general US population and adjusted for age. Because the general population also have chronic diseases (including, at the relevant age, 22% with diabetes and 27% with hypertension), David *et al.*[145] compared the NAFLD group with the whole general population and after excluding those in the general population with chronic diseases. In the NAFLD/NASH group, 72% were obese.

The NASH groups had poorer SF-36 scores than the general population, by about five points (SF-36 is a 100-point scale) when compared with the whole general population, and by 11 points when compared with the general population with those with chronic diseases excluded. Within the NASH groups, there was a gradient, so that, overall, QoL declined along the spectrum: general population > NAFLD > NASH > fibrosis > cirrhosis.

Physical health status was reduced more than mental health, with vitality/fatigue most affected. As the authors note, in a cross-sectional study cause and effect cannot be determined, so either NAFLD reduces physical activity or those with reduced physical activity are more likely to develop NAFLD.

Another study[146] from the NASH CRN Network looked at the QoL in children aged 5–17 years with NAFLD, mean age 12.6 years, mean BMI 33, with nearly all obese (defined as BMI ≥ 95th percentile). The patients were recruited from the observational NAFLD database, and from a trial group [TONIC (Treatment of Nonalcoholic Fatty Liver Disease in Children), see *Chapter 5*]. All had biopsy-proven NAFLD. The measure used was the Pediatric Quality of Life Inventory (PedsQL), with healthy children used as control subjects. The NAFLD children had poorer QoL scores (mean 73) than the healthy children (mean 84). Thirty-nine per cent of the NAFLD group had reduced QoL. Interestingly, the parents of the NAFLD children scored them lower (65) than the children did themselves. The study did not adjust for the effect of obesity, so much of the QoL deficit might have been due to obesity. The authors called for a study of QoL in obese children without NAFLD.

Similar findings were reported by Kerkar *et al.*[147] from a pilot study in 17 children aged 8–18 years, also using PedsQL, but reported in abstract form only at present.

The value of early liver biopsy has been assessed by Gaidos *et al.*[128] by decision analysis modelling. They carried out modelling comparing two options, early biopsy and no biopsy. They assumed that patients with confirmed NASH would be treated with insulin sensitisers or bariatric surgery. Patients in the no-early-biopsy arm would not receive treatment until there was evidence of disease progression. They assumed that mortality from liver biopsy was 1 in 1000 biopsies, but that 3% would have sufficient complications to require a hospital stay. They concluded that an early biopsy policy would reduce mortality at 5 years from 0.53% to 0.32%, and progression to severe disease from 4.4% to 2.4%.

The conclusions from the sparse evidence available are that:

- More advanced degrees of NAFLD reduce QoL.
- NASH and its sequelae are costly to health services.
- Future studies need to disentangle the effects on QoL of NAFLD itself, from co-conditions such as obesity and diabetes.
- We need longer follow-up to assess frequency and speed of progression, in order to base modelling on more data and fewer assumptions.

Chapter 5

Discussion

Statement of principal findings

- NAFLD in its various stages is becoming more common and is an increasing health problem, because of the rising prevalence of obesity and insulin resistance.
- Three insulin-sensitising drugs were covered in this review. Rosiglitazone is no longer relevant because it has been withdrawn from use. Metformin is still used, but its effect on liver histology is modest. Pioglitazone was more effective in improving liver histology, but can have adverse effects, including oedema, weight gain, precipitation of heart failure and fractures.
- Weight loss by diet and exercise is effective in reducing liver fat, but compliance is often an issue. Bariatric surgery is highly effective.
- Simple steatosis can be diagnosed by non-invasive means, but, at present, liver biopsy remains the only proven method of distinguishing between steatosis and NASH. Newer non-invasive methods show promise, but further research is required. This seems to be the highest research priority at present because of the impracticality of doing large trials of new agents if liver biopsies are required at entry and end of trial.
- Of the newer agents, the angiotensin receptor blocker telmisartan (which also has PPAR gamma activity) and the glucagon-like peptide-1 (GLP-1) analogues show sufficient promise to be considered for trials.
- Trials should probably be in NASH rather than the relatively benign simple steatosis.
- As one of the (anonymous) NIHR HTA programme referees noted, an overall finding is a shortage of high-quality evidence, including health economics aspects.
- Lifestyle measures remain worthy of consideration. Weight loss by calorie restriction has been shown to be effective in reducing hepatic steatosis[77] but, as usual, the problem is compliance. When compliance is ensured by bariatric surgery, leading to the loss of large amounts of weight, there is improvement or resolution of NAFLD in up to 90% of patients.[98] There is general pessimism about the long-term success of non-surgical management of obesity,[148] but some successes have been achieved. Goodpaster et al.[149] found that severely obese people (mean BMI 44 kg/m^2) lost on average 12 kg over 12 months by a combination of calorie restriction and physical activity, with the activity (moderate intensity equivalent to brisk walking for 300 minutes a week) having an additive effect to calorie restriction. Lazo et al.[150] also had good results in a study of diet and physical activity in 96 people with T2DM. The patients had MRS at baseline and after 12 months. NAFLD was defined as steatosis of over 5.5%. The patients aimed to achieve 10% weight loss by 12 months. The mean reduction in BMI was 2.7% (34.7 kg/m^2 baseline, 32 kg/m^2 at 12 months). The proportion with liver fat content under 5.5% rose from 67% at baseline to 80% at end, with an impressive fall in those with 10–20% steatosis from 17.4% at baseline to 6.5% at 12 months.
- The usual caveats apply to both the Lazo and Goodpaster studies[149,150] – 12 months is a short time in lifestyle change and the effect may not be sustained after the intervention ends.

Some issues

Defining 'non-alcoholic'

Vuppalanchi and Chalasani[151] have pointed out the lack of a consistent definition of the level of alcohol consumption compatible with a definition of NAFLD.

Progression to diabetes

The trials have been too short to assess whether or not treatment with any drugs will prevent progression to diabetes.

Which drug?

If there is to be a large trial, would insulin sensitisers be the best drug to test? Rosiglitazone would not be included, because its cardiovascular risk profile makes pioglitazone the drug of choice in the TZDs, and rosiglitazone has been withdrawn from use in the UK. However, pioglitazone is not without risk – oedema, heart failure, fractures. The safety of the glitazones was reviewed in a recent report published in the *Health Technology Assessment* journal.[84]

Metformin, which has been used for more than 50 years, has been proven to be safe in those who can tolerate it – a small proportion have to stop because of gastrointestinal symptoms.

Evidence from the LEAD trials is that liraglutide is effective in improving NAFLD. Armstrong *et al.*,[141] so far, by abstract only, have reported that many patients in the LEAD trials had advanced NAFLD, but that liraglutide 1.8 mg reduced the NFS score. However, there were no data on the 1.2-mg dose in this abstract. The National Institute for Health and Clinical Excellence (NICE) in a recent appraisal concluded that the 1.8 mg was not recommended by NICE because the marginal benefits did not justify the large increase in marginal cost.[152] In passing, it should be noted that most of these patients were also on metformin, which casts doubt on its long-term effectiveness.

Two recent abstracts provide further information on the effects of GLP-1 analogues on NAFLD. Gardner *et al.*[153] in a small study gave an unspecified incretin mimetic to seven diabetic patients. Liver fat was reduced from mean 29% to 16%.

Horton *et al.*[154] pooled data from two DURATION (Diabetes therapy Utilization: Researching changes in A_{1c}, weight and other factors Through Intervention with Exenatide ONce weekly) trials on 223 patients on once-weekly exenatide and reported improvements in ALT and AST, although values are not given in the abstract.

A trial in non-alcoholic fatty liver disease/steatosis

If a trial is restricted to the steatosis stage of NAFLD, diagnosis could be on the basis of clinical history (particularly around alcohol intake, history of hypertension, obesity, T2DM, hyperlipidaemia, cardiovascular diseases), clinical examination (BMI, hypertension or stigmata of other liver disease), laboratory tests (the usual LFTs plus exclusion of viral hepatitis, autoimmune disease, haemochromatosis, Wilson's disease, and perhaps those with alpha-1 antitrypsin deficiency), plus some form of imaging to confirm the excess of fat in the liver, such as transabdominal ultrasound.

There would have to be long duration of follow-up because simple steatosis is fairly benign.

A trial in non-alcoholic steatohepatitis

The main problem with any trial in NASH is that at present we have insufficient knowledge that any other diagnostic test could replace liver biopsy. Various options such as panels of test could be assessed against liver biopsy (note that some panels are patented and affordability could be a problem). A NASH trial would also have to be long term (perhaps 10 years?). Assessment of diagnostic options would involve assessing surrogate markers to see how well they detected progression or regression of inflammatory infiltrates and fibrosis. It is worth noting that these are still surrogates whose importance is the risk of progression to liver failure or hepatocellular cancer.

The group in which intervention might be most likely to be cost-effective comprises those with NASH and fibrosis. End points would be similar to a NASH-alone group, but a trial would need smaller numbers. Unfortunately, to identify this group, we would currently need liver biopsy. Ultrasound elastography is becoming more available, but is less reliable in the more overweight patients, such as those with BMI > 30 or 35 kg/m². (There is a special probe for the more obese, but it is currently expensive.)

As reported in *Chapter 3*, other options such as MRI elastography appear promising, but cost and availability would cause problems.

Hence the main research need appears to be to identify reliable and affordable non-invasive alternatives to liver biopsy. It may be that methods such as MRI elastography, although not being affordable in routine care, could be trialled against liver biopsy, and if reliable as assessed against the histological gold standard, could then be used in larger trials to assess the reliability of less expensive non-invasive methods.

A Health Technology Assessment trial?

An HTA trial may therefore be a combined diagnostic and therapeutic one, possibly with the following features:

- It should be in a higher risk group, such as those with NASH.
- Biopsy would be done, in a least a subgroup, and compared with other diagnostic options.
- The drugs to be trialled might be pioglitazone versus a weekly GLP-1 agonist?
- There should also be more research into how to promote adherence to weight loss.

The main cause of death in people with NAFLD is cardiovascular disease rather than cirrhosis.

Current trials

Searches for current trials have identified the following from the Clinical Trials Register. Several rosiglitazone trials are still registered, but will probably be discontinued.

Pioglitazone

NCT00633282

A Phase II RCT of pioglitazone 15 mg every day (q.d.) for 16 weeks, compared with a lifestyle arm (aerobic exercise and calorie restriction) and berberine, in patients with T2DM of no more than 1 year's duration, and fatty liver confirmed by ultrasound. Start date March 2008, end date

September 2011. Primary outcome measure is glycaemic control. Secondary outcomes include liver fat content by nuclear magnetic resonance spectroscopy.

■   http://clinicaltrials.gov/ct2/show/NCT00633282

NCT00681733

Pentoxifylline Versus Pioglitazone In Non-Alcoholic Steatohepatitis (NASH). This trial may have been completed because the estimated completion date was December 2008.

■   http://clinicaltrials.gov/ct2/show/NCT00681733

NCT00994682 (University of Texas Health Science Center, San Antonio, TX, USA; Pentoxifylline Versus Pioglitazone In Non-Alcoholic Steatohepatitis trial)

This is reported to be a Phase IV RCT of pioglitazone 30 mg per day orally for 8 weeks, increased if well tolerated, titrated to 45 mg per day until end of study (18 and 36 months), compared with placebo, in patients with or without T2DM. Start date December 2008, end date July 2013. Primary outcome measure includes liver histology at 18 and 36 months. Secondary outcomes include measurement of liver fat content by MRS at 18 and 36 months.

■   http://clinicaltrials.gov/ct2/show/NCT00994682

NCT01002547

This seems to be a similar Phase IV RCT of pioglitazone 30 mg per day for 8 weeks, if well tolerated titrated to 45 mg per day until end of study (next 3 years) in combination with vitamin E 400 IU orally twice daily, compared against placebo in combination with vitamin E 400 IU orally twice daily in patients with T2DM. Start date June 2010, end date July 2015. Primary outcome measure is liver histology at 18 and 36 months. Secondary outcomes include measurement of liver fat content by MRS at 18 and 36 months.

■   http://clinicaltrials.gov/ct2/show/NCT01002547

NCT01068444

A Phase II RCT of pioglitazone 30 mg per day for 6 months and then 3 months' follow-up after treatment, compared against placebo in patients with the diagnosis of NASH with or without cirrhosis confirmed by liver biopsy. Start date April 2009, end date July 2012. Primary outcomes include comparison of steatosis and LFT at 9 months. Secondary outcomes include comparison of necroinflammation and fibrosis.

■   http://clinicaltrials.gov/ct2/show/NCT01068444

Metformin

NCT00063635 (Treatment of Nonalcoholic Fatty Liver Disease in Children; *TONIC*)

A Phase III RCT of metformin 500 mg twice daily compared with vitamin E 400 IU twice daily and matching dose of placebo, in patients with NAFLD confirmed by biopsy. Start date August 2005, end date April 2010 (last updated January 2010). Primary outcome measures include sustained reduction in ALT to either 50% of baseline value or < 40 U/l at 96 weeks. Secondary outcomes include reduction in AST, GGT, change in liver histology and change in insulin resistance indices.

■ http://clinicaltrials.gov/ct2/show/NCT00063635

NCT00081328 (TODAY; Treatment Options for type 2 Diabetes in Adolescents and Youth)

A Phase III RCT of metformin 1000 mg b.i.d. compared against metformin 100 mg b.i.d. + rosiglitazone 4 mg b.i.d. or metformin 1000 mg b.i.d. + behavioural TODAY lifestyle programme in patients aged 10–17 years with diabetes for < 2 years. Start date May 2004, end date February 2013. Primary outcome measures include loss of glycaemic control at 6 months. Secondary outcome measures include safety and other complications.

http://clinicaltrials.gov/show/NCT00081328

NCT00134303

A Phase IV RCT of metformin compared against placebo in patients receiving bariatric surgery for obesity. Start date June 2005, end date December 2010 (last updated June 2010). Primary outcome measures include number of patients with histological amelioration of NASH after 1 year. Secondary outcome measures include number of patients with normalisation of ALT and normalisation of steatosis on ultrasound after 1 year.

■ http://clinicaltrials.gov/ct2/show/NCT00134303

NCT00247117

An open-label, non-RCT of metformin in patients with NASH (types 2–4) and ALT level more than two times normal range. Start date January 2004, estimated to complete by August 2005 (last updated October 2006). Primary outcome includes histological and biochemical change in 1 year. Secondary outcome: none.

■ http://clinicaltrials.gov/ct2/show/NCT00247117

NCT00303537

A Phase II and III RCT of metformin compared against placebo in patients with histologically proven NAFLD of < 18 months. Start date November 2004, estimated to complete by June 2008 (last updated June 2007). Primary outcome measure is grade of steatosis during repeat biopsy at 6 months. Secondary outcome measures include grade of necroinflammation by repeat biopsy, liver density by computer scan and serum ALT level (all at 6 months).

■ http://clinicaltrials.gov/ct2/show/NCT00303537

NCT00736385

A Phase IV RCT of metformin 2000 mg (Glucophage) daily for 12 months compared against placebo 2000 mg daily in patients with biopsy-proven NAFLD within 12 months of study initiation. Start date April 2009, end date July 2011. Primary outcome measures include measurements of insulin sensitivity, hepatic insulin clearance, and altered parameters of lipid metabolism, changes in the histological features that define NAFLD, and quantitative measurements of visceral and peripheral fat during 24 months. Secondary outcome measures include insulin sensitivity and lipid metabolism during 24 months.

■ http://clinicaltrials.gov/ct2/show/NCT00736385

Conclusions

Given the number of pioglitazone and metformin studies listed above, the priority now is probably for trials involving newer agents such as the GLP-1 agonists, or possibly the less expensive and orally administered dipeptidyl peptidase-4 (DPP-4) inhibitors, the gliptins.

The most important question might be whether or not it is possible to prevent progression of NASH to fibrosis, but a study to determine that would be difficult because the timescale required would be uncertain (as we lack data on how many progress and over what timescale) and because of the need for liver biopsies to establish NASH and to monitor progression.

Acknowledgements

We would like to thank Lynn Robertson, NHS Grampian, for carrying out initial searches.

Contribution of authors

Chapter 1 was drafted by Nazim Ghouri, *Chapter 2* by Deepson Shyangdan and Christine Clar, *Chapter 3* by Rob Henderson, and *Chapters 4* and *5* by Norman Waugh. Tara Gurung carried out literature searches. Data extraction of trials was carried out by Deepson Shyangdan and Christine Clar. David Preiss, Naveed Sattar and Andrew Fraser provided expert advice and comments on the full draft report. The section on research needs was drafted mainly by Andrew Fraser and Norman Waugh. All authors reviewed the draft final report.

References

1. Nonalcoholic steatohepatitis clinical research network. *Hepatology* 2003;**37:**244.

2. Byrne CD, Olufadi R, Bruce KD, Cagampang FR, Ahmed MH. Metabolic disturbances in non-alcoholic fatty liver disease. *Clin Sci* 2009;**116:**539–64.

3. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980;**55:**434–8.

4. McCullough AJ. The epidemiology and risk factors of NASH. In Farrell GC, George J, de la M Hall P, McCullough AJ, editors. *Fatty liver disease*: *NASH and related disorders*. Oxford: Blackwell; 2005. pp. 23–37.

5. Preiss D, Sattar N. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. *Clin Sci* 2008;**115:**141–50.

6. Liou I, Kowdley KV. Natural history of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006;**40:**S11–16.

7. Ahmed MH, Byrne CD. Non-alcoholic steatohepatitis. In Byrne CD, D Wild S, editors. *Metabolic syndrome.* Chichester: John Wiley & Sons; 2005. pp. 279–305.

8. Propst A, Propst T, Zangerl G, Ofner D, Judmaier G, Vogel W. Prognosis and life expectancy in chronic liver disease. *Dig Dis Sci* 1995;**40:**1805–15.

9. Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, *et al.* Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;**123:**134–40.

10. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: Part I. Diagnosis and evaluation. *Am Fam Physician* 2006;**74:**756–62.

11. Bedogni G, Miglioli L, Masutti F, Castiglione A, Croce LS, Tiribelli C, *et al.* Incidence and natural course of fatty liver in the general population: the Dionysos study. *Hepatology* 2007;**46:**1387–91.

12. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest* 2005;**115:**1343–51.

13. Edmison J, McCullough AJ. Pathogenesis of non-alcoholic steatohepatitis: human data. *Clin Liver Dis* 2007;**11:**75–104.

14. London RM, George J. Pathogenesis of NASH: animal models. *Clin Liver Dis* 2007;**11:**55–74.

15. Kim JK, Fillmore JJ, Chen Y, Yu C, Moore IK, Pypaert M, *et al.* Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proc Natl Acad Sci USA* 2001;**98:**7522–7.

16. McCullough AJ. Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006;**40**(Suppl. 1):S17–S29.

17. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;**116:**1413–19.

18. Day CP, James OF. Steatohepatitis: a tale of two 'hits'? *Gastroenterology* 1998;**114:**842–5.

19. Day CP, James OF. Hepatic steatosis: innocent bystander or guilty party? *Hepatology* 1998;**27:**1463–6.

20. Dong W, Simeonova PP, Gallucci R, Matheson J, Fannin R, Montuschi P, *et al.* Cytokine expression in hepatocytes: role of oxidant stress. *J Interf Cytok Res* 1998;**18:**629–38.

21. Yang SQ, Lin HZ, Lane MD, Clemens M, Diehl AM. Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis. *Proc Natl Acad Sci USA* 1997;**94:**2557–62.

22. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, *et al.* Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001;**120:**1183–92.

23. Videla LA, Rodrigo R, Orellana M, Fernandez V, Tapia G, Quinones L, *et al.* Oxidative stress-related parameters in the liver of non-alcoholic fatty liver disease patients. *Clin Sci* 2004;**106:**261–8.

24. Parola M, Robino G. Oxidative stress-related molecules and liver fibrosis. *J Hepatol* 2001;**35:**297–306.

25. Goldstein BJ, Mahadev K, Wu X. Redox paradox: insulin action is facilitated by insulin-stimulated reactive oxygen species with multiple potential signaling targets. *Diabetes* 2005;**54:**311–21.

26. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, *et al.* High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology* 2001;**34:**738–44.

27. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. *Clin Gastroenterol Hepatol* 2004;**2:**262–5.

28. Muoio DM. Insulin resistance takes a trip through the ER. *Science* 2004;**306:**4285–426.

29. Garcia-Monzon C, Martin-Perez E, Iacono OL, Fernandez-Bermejo M, Majano PL, Apolinario A, *et al.* Characterization of pathogenic and prognostic factors of nonalcoholic steatohepatitis associated with obesity. *J Hepatol* 2000;**33:**716–24.

30. Koruk M, Taysi S, Savas MC, Yilmaz O, Akcay F, Karakok M. Oxidative stress and enzymatic antioxidant status in patients with nonalcoholic steatohepatitis. *Ann Clin Lab Sci* 2004;**34:**57–62.

31. Loguercio C, De Girolamo V, de Sio I, Tuccillo C, Ascione A, Baldi F, *et al.* Non-alcoholic fatty liver disease in an area of southern Italy: main clinical, histological, and pathophysiological aspects. *J Hepatol* 2001;**35:**568–74.

32. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, *et al.* Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 2001;**50:**1844–50.

33. Vendemiale G, Grattagliano I, Caraceni P, Caraccio G, Domenicali M, Dall'Agata M, *et al.* Mitochondrial oxidative injury and energy metabolism alteration in rat fatty liver: effect of the nutritional status. *Hepatology* 2001;**33:**808–15.

34. Abdelmalek MF, Angulo P, Jorgensen RA, Sylvestre PB, Lindor KD. Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. *Am J Gastroenterol* 2001;**96:**2711–17.

35. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, *et al.* Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nature Med* 2005;**11:**183–90.

36. Polyzos SA, Kountouras J, Zavos C, Tsiaousi E. The role of adiponectin in the pathogenesis and treatment of non-alcoholic fatty liver disease. *Diabetes Obes Metab* 2010;**12:**365–83.

37. Wallace K, Burt AD, Wright MC. Liver fibrosis. *Biochem J* 2008;**411:**1–18.

38. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006;**43:**S99–112.

39. Day CP. Natural history of NAFLD: remarkably benign in the absence of cirrhosis. *Gastroenterology* 2005;**129:**375–8.

40. Friedman SL. Hepatic fibrosis. In Schiff ER, Sorrell MF, Maddrey WC, editors. *Schiff's diseases of the liver.* Philadelphia, PA: Lippincott-Raven; 1999. pp. 371–85.

41. Hui JM, Kench JG, Chitturi S, Sud A, Farrell GC, Byth K, *et al.* Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. *Hepatology* 2003;**38:**420–7.

42. Gaiani S, Avogaro A, Bombonato GC, Bolognesi M, Amor F, Vigili de Kreutzenberg S, *et al.* Nonalcoholic fatty liver disease (NAFLD) in nonobese patients with diabetes: Prevalence and relationships with hemodynamic alterations detected with Doppler sonography. *J Ultrasound* 2009;**12:**1–5.

43. Preiss D, Sattar N. Metabolic syndrome, dysglycaemia and vascular disease: making sense of the evidence. *Heart* 2007;**93:**1493–6.

44. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, *et al.* Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007;**49:**403–14.

45. McCullough AJ. Update on nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2002;**34:**255–62.

46. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, *et al.* Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland coronary prevention study. *Diabetes* 2004;**53:**2855–60.

47. Sattar N, McConnachie A, Ford I, Gaw A, Cleland SJ, Forouhi NG, *et al.* Serial metabolic measurements and conversion to type 2 diabetes in the west of Scotland coronary prevention study: specific elevations in alanine aminotransferase and triglycerides suggest hepatic fat accumulation as a potential contributing factor. *Diabetes* 2007;**56:**984–91.

48. Sattar N, Wannamethee SG, Forouhi NG. Novel biochemical risk factors for type 2 diabetes: pathogenic insights or prediction possibilities? *Diabetologia* 2008;**51:**926–40.

49. Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* 2008;**51:**1781–9.

50. Clark JM, Diehl AM. Defining nonalcoholic fatty liver disease: implications for epidemiologic studies. *Gastroenterology* 2003;**124:**248–50.

51. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, *et al.* Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004;**40:**1387–95.

52. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990;**12:**1106–10.

53. Clark JM, Diehl AM. Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. *JAMA* 2003;**289:**3000–4.

54. Fassio E, Alvarez E, Dominguez N, Landeira G, Longo C. Natural history of nonalcoholic steatohepatitis: a longitudinal study of repeat liver biopsies. *Hepatology* 2004;**40:**820–6.

55. Whalley S, Puvanachandra P, Desai A, Kennedy H. Hepatology outpatient service provision in secondary care: a study of liver disease incidence and resource costs. *Clin Med* 2007;**7:**119–24.

56. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, *et al.* Prevalence of Nonalcoholic Fatty Liver Disease and Its Association With Cardiovascular Disease Among Type 2 Diabetic Patients. *Diabetes Care* 2007;**30:**1212–18.

57. Marchesini G, Marzocchi R, Agostini F, Bugianesi E. Nonalcoholic fatty liver disease and the metabolic syndrome. *Curr Opin Lipidol* 2005;**16:**421–7.

58. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;**346:**1221–31.

59. Day CP. Non-alcoholic fatty liver disease: current concepts and management strategies. *Clin Med* 2006;**6:**19–25.

60. Williamson RM, Price JF, Glancy S, Butcher I, Perry E, Nee LD, *et al.* Prevalence of and risk factors for hepatic steatosis and non-alcoholic fatty liver disease in type 2 Diabetes: The Edinburgh Type 2 Diabetes Study. *Diabetes* 2009;**58:**A271.

61. Gonzalez ELM, Johansson S, Wallander MA, Rodriguez LAG. Trends in the prevalence and incidence of diabetes in the UK: 1996–2005. *J Epidemiol Community Health* 2009;**63:**332–6.

62. Loria P, Lonardo A, Bellentani S, Day CP, Marchesini G, Carulli N. Non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease: An open question. *Nutr Metab Cardiovasc Dis* 2007;**17:**684–98.

63. Targher G, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in healthy men. *Diabetes Care* 2004;**27:**2498–500.

64. Ghouri N, Preiss D, Sattar N. Liver enzymes, nonalcoholic fatty liver disease, and incident cardiovascular disease: a narrative review and clinical perspective of prospective data. *Hepatology* 2010;**52:**1156–61.

65. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;**363:**1341–50.

66. Targher G, Bertolini L, Chonchol M, Rodella S, Zoppini G, Lippi G, *et al.* Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and retinopathy in type 1 diabetic patients. *Diabetologia* 2010;**53:**1341–8.

67. Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology* 2002;**123:**1705–25.

68. NIHR Health Technology Assessment programme. *Non-invasive methods for the assessment and monitoring of liver fibrosis and cirrhosis*. HTA no. 09/07. www.hta.ac.uk/search/results.asp?Action=Search&QU=09%2F07&go=Go 2011 (accessed 1 January 2011).

69. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, *et al.* Liver fibrosis in overweight patients. *Gastroenterology* 2000;**118:**1117–23.

70. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999;**30:**1356–62.

71. Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology* 1990;**99:**1408–13.

72. Park HS, Kim MW, Shin ES. Effect of weight control on hepatic abnormalities in obese patients with fatty liver. *J Korean Med Sci* 1995;**10:**414–21.

73. Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, *et al.* Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol* 1997;**27:**103–7.

74. Harrison SA, Fincke C, Helinski D, Torgerson S, Hayashi P. A pilot study of orlistat treatment in obese, non-alcoholic steatohepatitis patients. *Aliment Pharmacol Ther* 2004;**20:**623–8.

75. Hatzitolios A, Savopoulos C, Lazaraki G, Sidiropoulos I, Haritanti P, Lefkopoulos A, *et al.* Efficacy of omega-3 fatty acids, atorvastatin and orlistat in non-alcoholic fatty liver disease with dyslipidemia. *IJG* 2004;**23:**131–4.

76. Sabuncu T, Nazligul Y, Karaoglanoglu M, Ucar E, Kilic FB. The effects of sibutramine and orlistat on the ultrasonographic findings, insulin resistance and liver enzyme levels in obese patients with non-alcoholic steatohepatitis. *Rom J Gastroenterol* 2003;**12:**189–92.

77. Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. *Gut* 2007;**56:**1760–9.

78. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology* 2010;**52:**79–104.

79. Lawlor DA, Sattar N, Smith GD, Ebrahim S. The associations of physical activity and adiposity with alanine aminotransferase and gamma-glutamyltransferase. *Am J Epidemiol* 2005;**161:**1081–8.

80. Martens FM, Visseren FL, Lemay J, de Koning EJ, Rabelink TJ. Metabolic and additional vascular effects of thiazolidinediones. *Drugs* 2002;**62:**1463–80.

81. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, *et al.* Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. *N England J Med* 2007;**357:**28–38.

82. Zib I, Jacob AN, Lingvay I, Salinas K, McGavock JM, Raskin P, *et al.* Effect of pioglitazone therapy on myocardial and hepatic steatosis in insulin-treated patients with type 2 diabetes. *J Investig Med* 2007;**55:**230–6.

83. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;**356:**2457–71.

84. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, *et al.* Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(36).

85. Browning JD. Statins and hepatic steatosis: perspectives from the Dallas Heart Study. *Hepatology* 2006;**44:**466–71.

86. Ekstedt M, Franzen LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. *J Hepatol* 2007;**47:**135–41.

87. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, *et al.* A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol* 2005;**100:**1082–90.

88. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2003;**98:**2485–90.

89. Laurin J, Lindor KD, Crippin JS, Gossard A, Gores GJ, Ludwig J, *et al.* Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. *Hepatology* 1996;**23:**1464–7.

90. Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, *et al.* Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin e in nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2006;**4:**1537–43.

91. Yokohama S, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, *et al.* Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. *Hepatology* 2004;**40:**1222–5.

92. Georgescu EF, Georgescu M. Therapeutic options in non-alcoholic steatohepatitis (NASH). Are all agents alike? Results of a preliminary study. *J Gastrointestin Liver Dis* 2007;**16:**39–46.

93. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2008;**6:**1396–402.

94. Liu X, Lazenby AJ, Clements RH, Jhala N, Abrams GA. Resolution of nonalcoholic steatohepatits after gastric bypass surgery. *Obesity Surgery* 2007;**17:**486–92.

95. Furuya CK, Jr, de Oliveira CP, de Mello ES, Faintuch J, Raskovski A, Matsuda M, *et al.* Effects of bariatric surgery on nonalcoholic fatty liver disease: preliminary findings after 2 years. *J Gastroenterol Hepatol* 2007;**22:**510–14.

96. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology* 2004;**39:**1647–54.

97. Dixon JB, Bhathal PS, O'Brien PE. Weight loss and non-alcoholic fatty liver disease: falls in gamma-glutamyl transferase concentrations are associated with histologic improvement. *Obesity Surgery* 2006;**16:**1278–86.

98. Kushner RF, Noble CA. Long-term outcome of bariatric surgery: an interim analysis. *Mayo Clin Proc* 2006;**81:**S46–51.

99. Chekhov AP. The cherry orchard. Act 1, Scene 1. In: *Chekhov: five major plays*. Hingley R, trans. New York, NY: Bantam Books, 1982.

100. Torres DM, Jones FJ, Williams CD, Harrison S. The effect of 48 weeks of rosiglitazone alone versus combination rosigilitazone and metformin (avandamet) versus combination rosiglitazone and losartan in the treatment of nonalcohoholic steatohepatitis (NASH): a open-label prospective randomized clinical trial. *Hepatology* 2009;**50:**185.

101. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, *et al.* Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008;**135:**1176–84.

102. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;**355:**2297–307.

103. Sanyal AJ, Mofrad PS, Contos MJ, Sargeant C, Luketic VA, Sterling RK, *et al.* A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2004;**2:**1107–15.

104. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, *et al.* Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;**362:**1675–85.

105. Garinis GA, Fruci B, Mazza A, De SM, Abenavoli S, Gulletta E, *et al.* Metformin versus dietary treatment in nonalcoholic hepatic steatosis: a randomized study. *Int J Obes* 2010;**34:**1255–64.

106. Haukeland JW, Konopski Z, Eggesbo HB, von Volkmann HL, Raschpichler G, Bjoro K, *et al.* Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. *Scand J Gastroenterol* 2009;**44:**853–60.

107. Nadeau KJ, Ehlers LB, Zeitler PS, Love-Osborne K. Treatment of non-alcoholic fatty liver disease with metformin versus lifestyle intervention in insulin-resistant adolescents. *Pediatr Diabetes* 2009;**10:**5–13.

108. Nar A, Gedik O. The effect of metformin on leptin in obese patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. *Acta Diabetol* 2009;**46:**113–18.

109. Shields WW, Thompson KE, Grice GA, Harrison SA, Coyle WJ. The effect of metformin and standard therapy versus standard therapy alone in nondiabetic patients with insulin resistance and nonalcoholic steatohepatitis (NASH): a pilot trial. *Ther Adv Gastroenterol* 2009;**2:**157–63.

110. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, *et al.* Metformin in the treatment of patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2004;**19:**537–44.

111. Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, *et al.* Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled fatty liver improvement with rosiglitazone therapy (FLIRT) Trial. *Gastroenterology* 2008;**135:**100–10.

112. Idilman R, Mizrak D, Corapcioglu D, Bektas M, Doganay B, Sayki M, *et al.* Clinical trial: Insulin-sensitizing agents may reduce consequences of insulin resistance in individuals with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2008;**8:**200–8.

113. Omer Z, Cetinkalp S, Akyildiz M, Yilmaz F, Batur Y, Yilmaz C, *et al.* Efficacy of insulin-sensitizing agents in nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2010;**22:**18–23.

114. Angelico F, Burattin M, Alessandri C, Del BM, Lirussi F. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. *Cochrane Database Syst Rev* 2007;**1:**CD005166.

115. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999;**94:**2467–74.

116. Kleiner DE, Brunt EM, Van NM, Behling C, Contos MJ, Cummings OW, *et al.* Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;**41:**1313–21.

117. Haukeland-JW KZLE. A randomized, placebo controlled trial with metformin in patients with NAFLD. *Hepatology* 2008;**48:**334A.

118. Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, *et al.* How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Arch Dis Child* 2008;**93:**458–61.

119. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, Sanchez-Avila F, Montano-Reyes MA, Uribe M. Insulin sensitizers in treatment of nonalcoholic fatty liver disease: systematic review. *World J Gastroenterol* 2006;**12:**7826–31.

120. Socha P, Horvath A, Vajro P, Dziechciarz P, Dhawan A, Szajewska H. Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: a systematic review. *J Pediatr Gastroenterol Nutr* 2009;**48:**587–96.

121. Cassidy FH, Yokoo T, Aganovic L, Hanna RF, Bydder M, Middleton MS, *et al.* Fatty liver disease: MR imaging techniques for the detection and quantification of liver steatosis. *Radiographics* 2009;**29:**231–60.

122. Fabbrini E, Conte C, Magkos F. Methods for assessing intrahepatic fat content and steatosis. *Curr Opin Clin Nutr Metab Care* 2009;**12:**474–81.

123. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol* 2009;**51:**433–45.

124. Cheung O, Sanyal AJ. Recent advances in nonalcoholic fatty liver disease. *Curr Opin Gastroenterol* 2009;**25:**230–7.

125. Loria P, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, *et al.* Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. *Dig Liver Dis* 2010;**42:**272–82.

126. Myers RP. Noninvasive diagnosis of nonalcoholic fatty liver disease. *Ann Hepatol* 2009;**8:**S25–33.

127. Browning JD. New imaging techniques for non-alcoholic steatohepatitis. *Clin Liver Dis* 2009;**13:**607–19.

128. Gaidos JK, Hillner BE, Sanyal AJ. A decision analysis study of the value of a liver biopsy in nonalcoholic steatohepatitis. *Liver Int* 2008;**28:**650–8.

129. Ali R, Cusi K. New diagnostic and treatment approaches in non-alcoholic fatty liver disease (NAFLD). *Ann Med* 2009;**41:**265–78.

130. CASP. *10 questions to help you make sense of reviews.* www.sph.nhs.uk/sph-files/S. Reviews%20Appraisal%20Tool.pdf/?searchterm=review 2010 (accessed 15 June 2010).

131. SIGN. *Methodology Checklist **1:** Systematic Reviews and Meta-analyses.* www.sign.ac.uk/guidelines/fulltext/50/checklist1.html 2010 (accessed 15 June 2010).

132. Charatcharoenwitthaya P, Lindor KD. Role of radiologic modalities in the management of non-alcoholic steatohepatitis. *Clin Liver Dis* 2007;**11:**37–54, viii.

133. Ma X, Holalkere NS, Kambadakone RA, Mino-Kenudson M, Hahn PF, Sahani DV. Imaging-based quantification of hepatic fat: methods and clinical applications. *Radiographics* 2009;**29:**1253–77.

134. Wieckowska A, Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. *Semin Liver Dis* 2008;**28:**386–95.

135. Castera L. Non-invasive diagnosis of steatosis and fibrosis. *Diabetes Metab* 2008;**34:**674–9.

136. Pinzani M, Vizzutti F, Arena U, Marra F. Technology Insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. *Nat Clin Pract Gastroenterol Hepatol* 2008;**5:**95–106.

137. Poynard T, Morra R, Ingiliz P, Imbert-Bismut F, Thabut D, Messous D, *et al.* Biomarkers of liver fibrosis. *Adv Clin Chem* 2008;**46:**131–60.

138. Halfon P, Munteanu M, Poynard T. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. *Gastroenterol Clin Biol* 2008;**32:**22–39.

139. The Princess Grace Hospital. *Patient Information on the FibroScan*. www.fibroscan.co.uk/fibroscan_leaflet.pdf 2010 (accessed 21 December 2010).

140. Bonekamp S, Kamel I, Solga S, Clark J. Can imaging modalities diagnose and stage hepatic fibrosis and cirrhosis accurately? *J Hepatol* 2009;**50:**17–35.

141. Armstrong MJ, Falahati A, Braun OO, Schmidt WE, Gough S, Newsome PN. High prevalence of advanced NAFLD in type 2 diabetic patients with normal liver enzymes and effect of liraglutide on NAFLD: meta-analysis of the LEAD program. *Diabetes* 2010;**59:**A411.

142. Baumeister SE, Volzke H, Marschall P, John U, Schmidt CO, Flessa S, *et al.* Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. *Gastroenterology* 2008;**134:**85–94.

143. Younossi ZM, Singer ME. Lifetime medical and economic impact of patients with non-alcoholic fatty liver disease (NAFLD) in the United States (US). *Hepatology* 2006;**44:**1233.

144. Dan AA, Kallman JB, Wheeler A, Younoszai Z, Collantes R, Bondini S, *et al.* Health-related quality of life in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2007;**26:**815–20.

145. David K, Kowdley KV, Unalp A, Kanwal F, Brunt EM, Schwimmer JB. Quality of life in adults with nonalcoholic fatty liver disease: baseline data from the nonalcoholic steatohepatitis clinical research network. *Hepatology* 2009;**49:**1904–12.

146. Kistler KD, Molleston J, Unalp A, Abrams SH, Behling C, Schwimmer JB. Symptoms and quality of life in obese children and adolescents with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2010;**31:**396–406.

147. Kerkar N, Kochin IN, Miloh TA, Arnon R, Suchy FJ, Annunziato R. A pilot study to assess quality of life in children with nonalcoholic fatty liver disease. *Hepatology* 2008;**48:**1644.

148. Ryan DH, Kushner R. The state of obesity and obesity research. *JAMA* 2010;**304:**1835–6.

149. Goodpaster BH, Delany JP, Otto AD, Kuller L, Vockley J, South-Paul JE, *et al.* Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. *JAMA* 2010;**304:**1795–802.

150. Lazo M, Solga SF, Horska A, Bonekamp S, Diehl AM, Brancati FL, *et al.* Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care* 2010;**33:**2156–63.

151. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: selected practical issues in their evaluation and management. *Hepatology* 2009;**49:**306–17.

152. Cummins E, Royle P, Shyangdan D, Waugh N. *Evidence review: liraglutide for the treatment of type 2 diabetes: a single technology appraisal.* www.hta.ac.uk/erg/reports/2157.pdf 2010 (accessed 20 December 2010).

153. Gardner CJ, Irwin A, Goenka N, Furlong N, Adams V, Kemp G, *et al.* The effect of incretin mimetics on liver fat in type 2 diabetes. *Diabet Med* 2011;**28:**60.

154. Horton E, Walsh B, Han J, Lutz K, Taylor K, Magg D. Improvements in glycaemic control, body weight and markers of cardiovascular risk and hepatic injury are demonstrated after 52 weeks' treatment with exenatide once weekly. *Diabet Med* 2011;**28:**71.

155. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, *et al.* A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 2004;**39:**188–96.

156. Yajima Y, Ohta K, Narui T, Abe R, Suzuki H, Ohtsuki M. Ultrasonographical diagnosis of fatty liver: significance of the liver-kidney contrast. *Tohoku J Exp Med* 1983;**139:**43–50.

Appendix 1

Search strategy

Literature search strategy

For the introduction

- We checked NICE, HTA, SIGN and NHS evidence.
- Searched MEDLINE for general reviews.
- Aetiology, pathology, natural history – searched MEDLINE, limits clinical queries.
- Checked guidelines from the following professional bodies:
  - American Gastroenterological Association
  - American Association for the Study of the Liver; The British Association for the Study of the Liver
  - The British Society of Gastroenterology
  - The European Association for the Study of the Liver.

Epidemiology (prevalence and incidence)

- MEDLINE 1990 – current and EMBASE 1990 – current.
- Non-alcoholic fatty liver disease terms plus (incidence or prevalence).tw.
- Web of Science for abstracts.
- Google search for grey literature.

Ovid MEDLINE(R) 1996 to week 3 August 2009

1. exp *fatty liver/
2. (non-alcoholic or non alcoholic or nonalcoholic).tw.
3. (fatty and liver).tw.
4. 3 and 2
5. steato*.tw.
6. 2 and 5
7. (NAFL or NAFLD or NASH).tw.
8. 6 or 4 or 1 or 7
9. limit 8 to (English language and yr="1999 -Current" and "diagnosis (specificity)").

Clinical effectiveness search strategy

Ovid MEDLINE(R) 1950 to week 2 June 2010

1. fatty liver/
2. liver.tw.
3. (non-alcoholic or non alcoholic or nonalcoholic).tw.
4. (fatty or steato*).tw.
5. (NAFLD or NAFLD or NASH).tw.
6. 4 and 3 and 2
7. 6 or 1 or 5
8. exp Metformin/
9. exp Thiazolidinediones/

10. (insulin sensit* or metformin or pioglitazone or rosiglitazone or thiazolidinedione* or glitazone*).tw.
11. 8 or 9 or 10
12. 7 and 11.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, 22 June 2010

1. liver.tw.
2. (non-alcoholic or non alcoholic or nonalcoholic).tw.
3. (fatty or steato*).tw.
4. (NAFLD or NAFLD or NASH).tw.
5. 1 and 2 and 3
6. 4 or 5
7. (insulin sensit* or metformin or pioglitazone or rosiglitazone or thiazolidinedione* or glitazone*).tw.
8. 6 and 7.

EMBASE 1980 to 2010 week 24

1. *fatty liver/
2. liver.tw.
3. (non-alcoholic or non alcoholic or nonalcoholic).tw.
4. (fatty or steato*).tw.
5. (NAFLD or NAFLD or NASH).tw.
6. 2 and 3 and 4
7. 1 or 5 or 6
8. exp metformin/
9. exp thiazolidinediones/
10. (insulin sensit* or metformin or pioglitazone or rosiglitazone or thiazolidinedione* or glitazone*).tw.
11. 8 or 9 or 10
12. 7 and 11.

Science Citation Index – Expanded plus Conference Proceedings Citation Index – Science, 1970 to June 2010

The following conferences were also covered:

- American Gastroenterological Association (*Gastroenterology*)
- American Association for the Study of Liver Diseases (*Hepatology*)
- European Association for the Study of the Liver (*J Hepatol*)
- American College of Gastroenterology (*Am J Gastroenterol*).

1. TS=liver
2. TS=(non-alcoholic or non alcoholic or 'nonalcoholic')
3. TS=(fatty or steato*)
4. #3 and #2 and #1
5. TS=(NAFL or NAFLD or NASH)
6. #5 OR #4
7. TS= (insulin sensit* or metformin or piolitazone or rosiglitazone or thiazolidinedione*)
8. #7 AND #6
9. #7 AND #6 Refined by: Document Type=(MEETING ABSTRACT).

Cochrane

Up to June 2010

1. (liver):ti,ab,kw and (non-alcoholic or non alcoholic or nonalcoholic):ti,ab,kw and (fatty or steato*):ti,ab,kw
2. (NAFL or NASH or NAFLD):ti,ab,kw
3. (#1 OR #2)
4. MeSH descriptor **Metformin** explode all trees
5. MeSH descriptor **Thiazolidinediones** explode all trees
6. (insulin sensit* or metformin or pioglitazone or rosiglitazone or glitazone* or thiazolidinediones*):ti,ab,kw
7. (#4 OR #5 OR #6)
8. (#3 AND #7).

Search alerts

Search alerts were set up in MEDLINE and EMBASE to run daily.

Diagnostics search strategy

Ovid MEDLINE(R) 1950 to June 2010

1. liver.tw.
2. (non-alcoholic or non alcoholic or nonalcoholic).tw.
3. (fatty or steato*).tw.
4. (NAFL or NAFLD or NASH).tw.
5. exp *Diagnosis/
6. diagnos*.tw.
7. Fatty Liver/di [Diagnosis]
8. 1 and 3 and 2
9. 8 or 4
10. 6 or 5
11. 10 and 9
12. 11 or 7
13. limit 12 to English language.

June 2010

EMBASE 1980 to June 2010

1. liver.tw.
2. (non-alcoholic or non alcoholic or nonalcoholic).tw.
3. (fatty or steato*).tw.
4. (NAFL or NAFLD or NASH).tw.
5. exp *Diagnosis/
6. diagnos*.tw.
7. Fatty Liver/di [Diagnosis]
8. 1 and 3 and 2
9. 8 or 4
10. 6 or 5
11. 10 and 9
12. 11 or 7
13. limit 12 to English language.

Cost effectiveness search strategy

Ovid MEDLINE(R) 1950–2010

1. Fatty Liver/
2. liver.tw.
3. (non-alcoholic or non alcoholic or nonalcoholic).tw.
4. (fatty or steato*).tw.
5. (NAFLD or NAFLD or NASH).tw.
6. 2 and 3 and 4
7. 1 or 5 or 6
8. "Costs and Cost Analysis"/
9. "Cost of Illness"/
10. exp Economics/
11. exp Health Status/
12. exp "Quality of Life"/
13. Quality-Adjusted Life Years/
14. (health state* or health status).tw.
15. (qaly$or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36).tw.
16. (markov or time trade off or standard gamble or hrql or hrqol or diabilit$).tw.
17. (quality adj2 life).tw.
18. (decision adj2 model).tw.
19. (pharmacoeconomics$or pharmaco-economic$or economics$or cost-effective* or cost benefit).tw.
20. (utilit* adj3 (cost* or analys* or score* or health or value* or assessment*)).tw.
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 and 21.

Web of Science 2010 (meeting abstracts)

TS=liver
TS=(non-alcoholic or nonalcoholic or 'non alcoholic')
TS=(fatty or steato*)
#3 AND #2 AND #1
TS=(NAFL or NAFLD or NASH)
#5 OR #4
TS=quality of life
TS=(pharmacoeconomic* or pharmaco-economic* or economic* or cost-effective* or cost–benefit or decision model or health state* or health status)
TS= (qaly$or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or decision model or utilit*)
#9 OR #8 OR #7
#10 AND #6
#10 AND #6 Refined by: Document Type=(MEETING ABSTRACT).

Appendix 2

Characteristics of included studies

TABLE 13 Characteristics of included trials

Study/design	Participants	Interventions	Outcome measures
Pioglitazone			
Aithal 2008[101] *Country*: UK *Focus*: effect of pioglitazone in non-diabetic participants with NASH *Design*: randomised, double-blind, placebo-controlled trial *Multicentre*: two hospitals (Nottingham, Derby) *Duration*: 1 year *Follow-up*: no post-intervention follow-up	*Total number*: 74 *n* Pio: 37; 31 completed *n* Pbo: 37; 30 completed *Inclusion criteria*: age 18–70 years, NASH *Diagnosis*: liver biopsy (standard protocol) and ultrasound; NASH: histology, presence of fat plus evidence of hepatocyte injury and inflammation or fibrosis *Definition of non-alcoholic*: Men <210 g/week, women <140 g/week *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: alcohol excess, other liver diseases, diabetes mellitus, only hepatic steatosis, weight-reduction medication, pregnant or lactating women, current or previous heart failure, renal impairment; taking drugs associated with fatty liver, e.g. methotrexate, amiodarone, tamoxifen, valproate, etc.); diabetes mellitus diagnosed before or at the time of recruitment *Age*: Pio: 52 years (28–71 years); Pbo: 55 years (27–73 years) *Sex*: Pio: 30% female; Pbo: 49% female *BMI*: Pio: 29.8 kg/m², SD 3.0; Pbo: 30.8 kg/m², SD 4.1 *Ethnicity*: NR *Fibrosis*: (Brunt scores) *Pio*: none: 26%, 1; 7%, 2; 45%, 3; 16%, 4; 6% *Pbo*: none: 17%, 1; 7%, 2; 40%, 3; 23%, 4; 13% *Stage/severity of NAFLD*: NASH (see *Results* section for detailed Brunt scores) *Previous treatment*: NR *Comorbidities*: NR	*Pio*: 30 mg/day pioglitazone *Pbo*: placebo tablets *Both groups*: diet/exercise advice *Adherence*: 1/61 missed 3.3% of tablets, 60/61 were >99% adherent; 18/30 in placebo group and 14/31 in pioglitazone group fully compliant with lifestyle advice, the rest partly compliant *Run-in period*: 3 months, seen by a dietician, instructed to reduce calorie intake by 500 kcal/day and to perform modest exercise 30–40 minutes per day at least 5 days/week *Co-interventions/co-medications*: four patients on lipid-lowering drugs (stable dose for 3 months); advice on diet/exercise reinforced at each follow-up visit	*Primary*: liver histology *Progression/regression of liver disease*: liver histology; liver biopsy specimens graded according to the NASH histological scoring system (Promrat *et al.* 2004,[155] Brunt *et al.* 1999[115]) *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA$_{1c}$*: yes *FPG*: yes *Weight change*: weight, BMI, waist–hip ratio *Blood pressure*: diastolic, systolic BP *Lipid parameters*: TC, HDL, LDL, TGs *Liver biochemistry*: bilirubin, albumin, ALT, GGT, ferritin *Insulin resistance*: yes, HOMA *Health-related QoL*: no *Mortality*: no *Other*: C-peptide, fasting insulin, adiponectin, leptin, resistin *Timing of assessment*: at 2-month intervals throughout the study

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Belfort 2006[102] *Country*: USA *Focus*: effect of pioglitazone plus a calorie-restricted diet in participants with NASH *Design*: randomised, double-blind, placebo-controlled trial *Multicentre*: three centres in San Antonio, TX (University Health Centre; Audie L Murphy Division, South Texas Veterans Health Care System; Brooke Army Medical Center) *Duration*: 6 months *Follow-up*: 4 weeks	*Total number*: 55 with impaired glucose tolerance or diabetes enrolled; control group of 10 healthy participants with normal glucose tolerance and without fatty liver *n* Pio: 26; 23 completed *n* Pbo: 21; 17 completed *Inclusion criteria*: NASH *Diagnosis*: liver biopsy (standard clinical indications), medical history, physical examination, routine blood tests *Definition of non-alcoholic*: >12–15 g of alcohol per day, or >12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits *IGT/diabetes (including diagnostic criteria)*: impaired glucose tolerance or T2DM (75-g oral glucose tolerance test) *Exclusion criteria*: levels of plasma ALT and AST ≥ 2.5 upper limit of normal; FPG ≥ 13.3 mmol/l; type 1 diabetes, heart disease, hepatic disease (other than NASH), renal disease; receiving metformin, TZDs or insulin *Age*: *Pio*: 51 years, SD 7.0; *Pbo*: 51 years, SD 10.0 *Sex*: *Pio*: 46% female; *Pbo*: 67% female *BMI*: *Pio*: 33.5 kg/m², SD 4.9; *Pbo*: 32.9 kg/m², SD 4.4 *Ethnicity*: NR *Fibrosis*: (Kleiner scores) *Pio*: none: 8%, 1; 46%, 2; 19%, 3; 27%, 4; 0% *Pbo*: none: 28.5%, 1; 43%, 2; 19%, 3; 9.5%, 4; 0% *Stage/severity of NAFLD*: NASH (see *Results* section for detailed Kleiner scores) *Diabetes duration*: NR *Previous treatment*: NR *Comorbidities*: NR	*Pio*: 30 mg/day pioglitazone for the first 2 months and then increased to 45 mg/day until the end of the study *Pbo*: placebo pills *Both groups*: diet (reduce calorie intake by 500 kcal per day) *Adherence*: assessed by means of a pill count on follow-up visits *Run-in period*: 4 weeks, interviewed by research dietician, instructed not to change the calorie content of their diet or their level of physical activity *Co-interventions/co-medications*: advice on diet reinforced at each follow-up visit	*Primary*: liver histology *Progression/regression of liver disease*: liver histology; liver biopsy specimens graded according to the NASH histological scoring system (Kleiner *et al.*)[116] *IGT→diabetes*: no *NGT→IGT/diabetes*: no *HbA₁c*: yes *FPG*: yes *Weight change*: weight, BMI, fat (%) *Blood pressure*: no *Lipid parameters*: TC, HDL, LDL, TGs *Liver biochemistry*: ALT, AST *Health-related QoL*: no *Insulin resistance/sensitivity*: yes *Mortality*: no *Other*: hepatic fat content (MRS), whole body fat, lipid insulin, free fatty acids, cytokine, adiponectin concentrations, tumour necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), insulin secretion, endogenous glucose production, and the rate of glucose disappearance after a 75-g oral glucose load (oral glucose tolerance test) *Timing of assessment*: metabolic variables assessed at baseline at the end of the study, liver biopsy at baseline and after 6 months; every 2 weeks participants seen at the general clinic and vital signs, physical examination, the results of home glucose monitoring, compliance with the study drug (confirmed by pill count) and adverse events were assessed

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Sanyal 2004[103] *Country*: USA *Focus*: effect of insulin sensitiser (pioglitazone) along with an antioxidant (vitamin E) in participants with NASH *Design*: prospective RCT, single centre *Duration*: 6 months *Run-in before randomisation*: 3 months *Treatment*: 6 months *Follow-up*: no post-intervention follow-up	*Total number*: 20 *n* Pio + Vit E: 10; 8 completed *n* Vit E: 10; all completed *Inclusion criteria*: NASH *Diagnosis*: liver biopsy; included if macrovesicular steatosis, and (1) ≥ 1 of the following: cytological ballooning, Mallory's hyaline, pericellular fibrosis, and (2) varying degrees of inflammation and portal fibrosis *Definition of non-alcoholic*: non-alcoholic induced nature of the disease established by clinical interview of the participants *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: age <18 years; diabetes mellitus; cirrhosis; weight gain or loss of >5 lb in past month; severe comorbid conditions limiting life expectancy to <1 year; pregnancy; symptomatic gallstone disease; those being considered for or who had bariatric surgery; iatrogenic NASH; concomitant presence of other causes of liver disease (e.g. hepatitis C); participants on stable doses of drugs for hyperlipidaemia for >6 months could continue, those requiring dose modification or starting drugs within this time frame were excluded *Age*: Pio + Vit E: 47.0 years, SD 12.0; *Vit E*: 46.0 years, SD 13.0 *Sex*: Pio + Vit E: 40% female; Vit E: 60% female *BMI*: Pio + Vit E: 32.5 kg/m², SD 4.3; Vit E: 30.7 kg/m², SD 4.7 *Ethnicity*: all Caucasians *Fibrosis*: *Pio + Vit E*: (from graph) pericellular fibrosis grade 1.3, SD 0.3; portal fibrosis grade 1, SD 0.3 *Vit E*: (from graph) pericellular fibrosis grade 1.2, SD 0.3; portal fibrosis grade 0.7, SD 0.3 *Stage/severity of NAFLD*: NASH (details see results section) *Previous treatment*: drugs for hyperlipidaemia	*Pio + Vit E*: pioglitazone 30 mg/day + Vitamin E 400 IU orally every day *Vit E*: Vitamin E 400 IU orally every day *Both groups*: standardised recommendations about diet and exercise *Adherence*: not reported *Run-in period*: followed up for 3 months prior study to ensure that everyone had a stable weight and had been given similar diet and exercise prescriptions. *Co-interventions/co-medications*: participants receiving stable doses of drugs for hyperlipidaemia for more than 6 months continued to take these	*Primary*: improvement in liver histology *Progression/regression of liver disease*: liver histology; liver biopsy specimens graded according to the NASH histological scoring system (modified Brunt scores) *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA₁c*: no *FPG*: no *Weight change*: BMI, waist–hip ratio, fat (%) *Blood pressure*: no, (hypertension) *Lipid parameters*: TC, HDL, TG *Liver biochemistry*: ALT, AST, bilirubin *Health-related QoL*: no *Insulin resistance/sensitivity*: metabolic clearance of glucose measured by glucose infusion rate during low-dose insulin infusion, fasting insulin level and fasting free fatty acid level *Mortality*: no *Other*: metabolic end points included: overall insulin sensitivity; sensitivity of lipolysis to insulin; lipid and carbohydrate oxidation rates; mitochondrial fatty acid oxidation; hepatic glucose output and its sensitivity to insulin *Timing of assessment*: after randomisation, seen initially at week 2 and then at week 4, subsequently seen at months 3 and 6. Laboratory studies were obtained at monthly intervals and reviewed by the principal investigator. End of the study, participants underwent a euglycaemic hyperinsulinaemic clamp and then after 1–2 weeks a liver biopsy examination was performed

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Sanyal 2010[104] *Country*: USA *Focus*: effects of TZDs and vitamin E in NASH *Design*: multicentre, randomised, placebo-controlled, double-masked clinical trial *Centre*: multicentre *Duration*: 96 weeks *Follow-up*: additional 24 weeks	*Total number*: 247 randomised *n* Pio: 80; 70 completed *n* Vit E: 84; 80 completed *n* Pbo: 83; 72 completed *Inclusion criteria*: ≥ 18 years; liver biopsy obtained within 6 months before randomisation *Diagnosis*: liver biopsy; definite or possible NAS of ≥ 5, or definite steatohepatitis (confirmed by two pathologists) with NAS of 4, a score of at least 1 for hepatocellular ballooning was required in all cases *Definition of non-alcoholic*: alcohol consumption of more than 20 g per day in women and more than 30 g in men of at least three consecutive months during the previous 5 years, as assessed with the use of the Lifetime Drinking History questionnaire of Skinner et al. and the self-administered Alcohol Use and Disorders Identification Test (AUDIT) *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: adults with diabetes; alcohol consumption as given above; cirrhosis, hepatitis C or other liver diseases, heart failure (NYHA class II or IV), receiving drugs known to cause steatohepatitis *Age*: Pio: 47.0 years, *Vit E*: 46.6 years, *Pbo*: 45.5 years *Sex*: Pio: 58.8% female, *Vit E*: 61.9% female, *Pbo*: 57.8% female *BMI*: Pio: 34.0 kg/m², *Vit E*: 34 kg/m², *Pbo*: 35 kg/m² *Ethnicity*: Hispanic *Pio*: 18.8%, *Vit E*: 19.0%, *Pbo*: 7.2%; Non-White *Pio*: 18.8%, *Vit E*: 15.2%, *Pbo*: 11.0% *Fibrosis*: Pio: 86.2%, *Vit E*: 83.1%, *Pbo*: 80.7% *Stage/severity of NAFLD*: see *Results* section *Previous treatment*: NR *Comorbidities*: NR	*Pio*: pioglitazone 30 mg once daily *Vit E*: 800 IU, natural form, once daily *Pbo*: placebo identical to Pio once daily or placebo identical to Vitamin E *Both groups*: all participants were given a standardised set of pragmatic recommendations about lifestyle changes and diet; discouraged from adding other drugs that are used for nonalcoholic steatohepatitis to their regimen *Adherence*: NR *Run-in period*: participants were not allowed to use any prescription or over-the-counter medication or herbal remedy taken with an intent to improve or treat NASH or liver disease or obesity or diabetes for the 3 months before liver biopsy as well as the 3 months before randomisation *Co-interventions/co-medications*: NR	*Primary*: Improvement in histological findings, which required an improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for NAFLD to a score of 3 or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score *Progression/regression of liver disease*: liver biopsy (analysis based on Kleiner scores) *IGT → diabetes*: no *NGT → IGT/diabetes*: yes *HbA₁c*: no *FPG*: yes *Weight change*: weight, BMI, waist circumference, waist–hip ratio, triceps skinfold, mid-upper arm circumference, trunk (% fat), total (% fat) *Blood pressure*: no *Lipid parameters*: TG, TC, HDL, LDL *Liver biochemistry*: ALT, AST, GGT, bilirubin, alkaline phosphatase *Health-related QoL*: yes *Insulin resistance/sensitivity*: HOMA–IR *Mortality*: yes *Timing of assessment*: Participants were seen at 8 weeks (2-month intervals) after randomisation through 96 weeks; a follow-up liver biopsy was conducted at the week 96 visit

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Metformin			
Bugianesi 2005[87]	*Total number*: 110 participants with NAFLD	*Met*: metformin daily maximum dose of 2000 mg/day, the dose was progressively increased from 250 mg b.i.d. to the maximum dose at 500-mg weekly intervals	*Primary*: ALT normalisation
Country: Ankara, Turkey	*n* Met: 55; 55 completed		*Progression/regression of liver disease*: liver histology
Focus: effect of metformin, prescriptive diet or vitamin E in participants with NAFLD	*n* Vit E: 28; 28 completed		*IGT → diabetes*: no
	n diet: 27; 27 completed		*NGT → IGT/diabetes*: change in proportion of participants with metabolic syndrome
	Inclusion criteria: NAFLD	*Vit E*: vitamin E 400 IU b.i.d.	*HbA$_{1c}$*: yes
	Diagnosis: liver biopsy (Brunt criteria with minor modifications)		*FPG*: yes
Design: open-label RCT	*Definition of non-alcoholic*: alcohol consumption < 20 g/day	*Diet*: weight reducing prescriptive diet to determine a caloric deficit of 500 kcal per day (determining a weight loss of approximately 500 g/week)	*Weight change*: BMI, waist–hip ratio
Multicentre: two units – Bologna (BU) and Turin (TU), Italy	*IGT/diabetes (including diagnostic criteria)*: oral glucose tolerance test		*Blood pressure*: diastolic and systolic BP
	Met: IGT: Bologna 4%, Turin 15%; diabetes: Bologna 10%, Turin 12%		*Lipid parameters*: TC, HDL, TGs
Duration: 12 months	Vit E: IGT: 7%; diabetes: 4%		*Liver biochemistry*: ALT level, AST level, GGT, alkaline phosphatase
Follow-up: no post-intervention follow-up	*Diet*: IGT: 7%; diabetes: 4%	*All groups*: 2 hours nutritional counselling by an experienced dietician on the basis of a dietary investigation; all participants encouraged to walk or to jog at least 30 minutes daily	*Health-related QoL*: no
	Exclusion criteria: evidence of advanced clinical or biochemical liver disease or cirrhosis, alcohol consumption > 20 g/day, positive screening for viral hepatitis B and C, autoimmune phenomena indicating autoimmune hepatitis or celiac disease, presence of gene markers of familial haemochromatosis, previously diagnosed diabetes, severe or morbid obesity (≥ 35 kg/m²)		*Mortality*: no
			Other: insulin resistance (HOMA), assessment of iron status (serum iron, transferrin saturation, ferritin), lactic acid
	Age: *Met*: Bologna 42 years, SD 10.0, Turin 45 years, SD 10.0; *Vit E*: 40 years, SD 10.0; *Diet*: 41 years, SD 10.0	*Adherence*: compliance tested by pill counts in participants on metformin and vitamin E; in participants on prescriptive diet only weight loss was considered as a compliance marker; compliance always exceeded 90% of prescribed dose	*Timing of assessment*: biochemical and clinical control visits every 3 months; second liver biopsy only on 17 metformin-treated participants and in none of the two control groups
	Sex: *Met*: Bologna 24% female, Turin 31% female; *Vit E*: 0% female; *Diet*: 15% female (*p* = 0.006)		
	BMI: *Met*: 28.7 kg/m², SD 3.6; *Vit E*: 29.1 kg/m², SD 2.7; *Diet*: 28.2 kg/m², SD 3.6		
	Ethnicity: NR	*Run-in period*: none	
	Fibrosis: *Met*: 93%; *Vit E*: 91%; *Diet*: 77%	*Co-interventions/co-medications*: NR	
	Stage/severity of NAFLD: NASH index (details see *Results* section)		
	Previous treatment: NR		

continued

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Garinis 2010[105] *Country*: Italy *Focus*: comparison of the efficacy of low-dose metformin plus dietary treatment vs dietary treatment alone *Design*: prospective, randomised study *Centre*: Endocrine Unit of University Magna Graecia of Cantanzaro for treatment of obesity and overweight *Duration*: 6 months *Follow-up*: no post-intervention follow-up	*Total number*: 50 participants *n* Met: 20; 15 completed *n* C: 25; 25 completed *Inclusion criteria*: BMI > 25 kg/m², liver steatosis *Diagnosis*: USG *Definition of non-alcoholic*: alcohol intake < 20 g/day *Exclusion criteria*: participants with evidence of heart disease, renal failure and diabetes, even if newly discovered, smoking habits, alcohol intake of more 20 g per day, signs of hepatic virus infection (participants were tested for hepatitis B antigen or hepatitis C antibodies), the presence of clinical or biochemical evidence of autoimmune, metabolic or genetic liver diseases and use of drugs known to induce liver steatosis *Age*: *Met*: 40.8 years, SD 13; *C*: 45.8 years, SD 13.6 *Sex*: *Met*: 90% female; *C*: 80% female *BMI*: *Met*: 36.5 kg/m², SD 4. 9; *diet alone*: 34.7 kg/m², SD 2.5 *Ethnicity*: NR *Fibrosis*: NR *Stage/severity of NAFLD*: see *Results* section *Previous treatment*: NR *Comorbidities*: NR	*Met:* Metformin was started at a dose of 250 mg b.i.d. and was increased after a week to the final dose of 500 mg b.i.d. *C*: dietary treatment alone *Both groups*: hypocaloric (1300 kcal) diet *Adherence*: NR *Run-in period*: no *Co-interventions/co-medications*: none	*Primary*: liver steatosis amelioration or disappearance, as evaluated by USG *Progression/regression of liver disease*: USG (liver steatosis graded as mild, moderate and severe: mild, mild increase in liver echogenicity; moderate, increased liver echogenicity that obscured hepatic and portal vein walls; severe, posterior attenuation of the deep liver parenchyma) *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA$_{1c}$*: no *FPG*: yes *Weight change*: BMI, waist–hip ratio, waist circumference (cm) *Blood pressure*: no *Lipid parameters*: TC, HDL, TGs, *Liver biochemistry*: ALT level, AST level, alkaline phosphatase *Health-related QoL*: no *Mortality*: no *Other*: Insulin resistance (HOMA), HOMA–IR, assessment of iron status (serum iron, transferrin, ferritin concentration) *Timing of assessment*: once in every 8 weeks

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Haukeland 2009[106] *Country*: Norway *Focus*: effect of metformin on liver histology in participants with NAFLD *Design*: randomised, double-blind, placebo-controlled trial *Multicentre*: Four University hospitals *Duration*: 6 months *Follow-up*: no post-intervention follow-up	*Total number*: 48 *n* Met: 24; 20 completed *n* Pbo: 24; 24 completed *Inclusion criteria*: adults with NAFLD *Diagnosis*: histologically verified NAFLD within 18 months prior to inclusion; participants with simple steatosis where included if they had elevated transaminases (>ULN) and impaired glucose tolerance or T2DM *Definition of non-alcoholic*: alcohol consumption <24 g/day (alcohol history assessed by the physicians who admitted the participants based on all alcohol-containing drinks ingested during a typical 4-week period) *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: weight change >5 kg since biopsy, previous or ongoing treatment with insulin, metformin or TZDs, kidney failure, pharmacologically treated heart failure, significant coronary heart disease (NYHA classes III and IV), moderate to severe chronic obstructive lung disease, liver cirrhosis or liver diseases other than NAFLD and alcohol consumption >24 g/day *Age*: *Met*: 44.3 years, SD 9.0; *Pbo*: 49.9 years, SD 12.8 *Sex*: *Met*: 20% female; *Pbo*: 33% female *BMI*: *Met*: 31.4 kg/m², SD 3.9; *Pbo*: 30.3 kg/m², SD 3.3 *Ethnicity*: Caucasian *Met*: 85%; *Pbo*: 88% *Fibrosis*: *Met*: 40%; *Pbo*: 58% *Stage/severity of NAFLD*: see *Results* section for detailed Kleiner scores *Previous treatment*: NR *Comorbidities*: *Met*: 45% abnormal glucose tolerance, 20% T2DM, 25% hypertension; *Pbo*: 50% abnormal glucose tolerance, 33% T2DM, 54% hypertension	*Met*: metformin maximal daily dose 2500 mg or 3000 mg (if body weight was >90 kg); starting dose 500 mg/day, medication was increased every week until maximum dose was reached after 4 or 5 weeks (if side effects occurred, dose was transiently or permanently reduced to a dose tolerated by the patient) (average dose at 4 or 5 weeks was 2.6, SD 0.4 g/day) *Pbo*: equivalent dosing of placebo tablets *Both groups*: all participants received general advice about a healthy lifestyle i.e. physical activity at least 30 min daily and diet low in fats, particularly saturated fat, and refined carbohydrates *Adherence*: pill counting *Run-in period*: none *Co-interventions/co-medications*: NR	*Primary*: changes in liver steatosis between the index biopsy and the second biopsy *Progression/regression of liver disease*: liver biopsy, histopathological changes assessed according to the criteria defined by Kleiner *et al.*;[116] liver steatosis by CT; NAS *IGT→diabetes*: NR *NGT→IGT/diabetes*: NR *HbA₁c*: yes *FPG*: yes *Weight change*: BMI, body weight *Blood pressure*: yes *Lipid parameters*: TC, HDL, TGs, TGs *Liver biochemistry*: AST level, ALT level, GGT *Health-related QoL*: NR *Mortality*: NR *Other*: Insulin resistance (HOMA–IR), insulin, leptin, adiponectin, tumour necrosis factor *Timing of assessment*: participants were seen monthly at the research units for blood sampling and assessment of the compliance (pill counting), body weight and adverse events; second liver biopsy taken at the end of treatment

continued

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Nadeau 2009[107] *Country*: USA *Focus*: effect of metformin and lifestyle recommendations in adolescents with fatty liver and elevated liver associated enzymes *Design*: double-blind design *Centre*: urban health-care system including school-based health centres in Denver, CO, USA *Duration*: 6 months *Follow-up*: no post-intervention follow-up	*Total number*: 55 enrolled *n* Met: 37; 28 completed *n* Pbo: 13; 10 completed *Inclusion criteria*: adolescents aged 12–18 years; two of the three of the following: acanthosis nigricans, BMI > 30 kg/m^2 or > 95% for age, or family history of T2DM *Diagnosis*: liver ultrasound *Definition of non-alcoholic*: adolescents with current or prior alcohol consumption excluded *IGT/diabetes (including diagnostic criteria)*: insulin resistance (fasting insulin level > 25 microunits/ml or homeostasis model assessment > 3.5) *Exclusion criteria*: pre-existing diabetes; pregnancy; serum creatinine > 1.5 mg/dl; significant heart disease; liver disease other than NAFLD *Age*: 15.1 years (range 12–18 years) *Sex*: *Met*: 68% female; *Pbo*: 62% female *BMI*: *Met*: 39.6 kg/m^2, SE 0.98; *Pbo*: 40.2 kg/m^2, SE 1.8 *Ethnicity*: *Met*: 32% African American, 62% Hispanic, 3% Caucasian, 3% Asian/Pacific Islanders; *Pbo*: 38% African American, 46% Hispanic, 8% Caucasian *Fibrosis*: NR *Stage/severity of NAFLD*: see *Results* sections for details *Previous treatment*: NR *Comorbidities*: NR *Subgroups*: fatty vs normal liver parameters	*Met*: metformin capsules, started initially with 500 mg once daily, increased to 500 mg twice daily at 1 month and then to 850 mg twice daily at 2 months *Pbo*: placebo capsules, equivalent dosing scheme to metformin *Both groups*: underwent a dietary assessment and watched a standardised video about healthy eating habits. Wellness education emphasised balanced meals with modest calorie reduction; decreased fat and simple sugar consumption; increased fibre, fruit and vegetable intake; and regular aerobic exercise. Participants chose three specific dietary or exercise goals and were given a calendar to record progress on their goals and medication compliance *Adherence*: pill count and review of the participants' pill calendar to assess compliance (pill counts similar between groups) *Run-in period*: none *Co-interventions/co-medications*: NR	*Primary*: fatty liver *Progression/regression of liver disease*: liver ultrasound; severity of fatty liver was quantitated using a scoring system (0 = no fatty liver, 1 = mild fatty liver, 2 = moderate fatty liver and 3 = severe fatty liver); participants with an ultrasound reading of 1, 2 or 3 were considered to have NAFLD *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA$_{1c}$*: no *FPG*: yes *Weight change*: BMI *Blood pressure*: no *Lipid parameters*: Cholesterol, HDL, LDL, TG *Liver biochemistry*: GGT, AST, ALT *Health-related QoL*: no *Insulin resistance/sensitivity*: insulin, 2 hours glucose, 2 hours insulin *Mortality*: no *Other*: insulin, total protein, creatinine *Timing of assessment*: outcomes reported for screening and 6-month visit

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Nar 2009[108] *Country*: Turkey *Focus*: effect of metformin on plasma leptin levels in obese patients with T2DM and NAFLD *Design*: parallel RCT, single centre *Duration*: 6 months *Follow-up*: no post-intervention follow-up	*Total number*: 34 *n* Met: 19/19 completed (presumably) *n* C: 15/15 completed (presumably) *Inclusion criteria*: newly diagnosed T2DM, no anti-diabetic medications, obese (BMI > 30 kg/m²) *Diagnosis*: ultrasonic evidence of NAFLD (both liver-kidney contrast and vascular blurring) *Definition of non-alcoholic*: 30 patients with no alcohol consumption, 4 patients with < 100 g of ethanol/month *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: suspected acute or chronic viral hepatitis, autoimmune hepatitis, history of malignancy, impaired renal function, haemodynamic instability, diseases or pituitary, adrenal glands or pancreas, prolonged use of corticosteroids or sex hormones, use of anti-hyperlipidaemic agents, use of anti-obesity medication *Age*: *Met*: 49.4 years SE 8.6; *C*: 44.5 years SE5.9 *Sex*: *Met*: 79% female; *C*: 67% female *BMI*: *Met*: 31.0 kg/m², SE 4.0; *C*: 33.7 kg/m², SE 6.0 *Ethnicity*: NR *Fibrosis*: NR *Stage/severity of NAFLD (grade of hepatic steatosis)*: *Met*: normal: 21%, low: 63%, moderate: 16%; *C*: normal: 27%, low: 53%, moderate: 20% *Diabetes duration*: newly diagnosed *Previous treatment*: NR *Comorbidities*: *Met*: macroangiopathy: 26.7%, autonomic neuropathy: 5.6%, peripheral neuropathy: 26.7%, retinopathy: 35.7%; *C*: macroangiopathy: 15.4%, autonomic neuropathy: 7.1%, peripheral neuropathy: 15.4%, retinopathy: 25.0%	*Met*: 1700 mg/day metformin (starting at 850 mg/day in week 1 and increased to 1700 mg/day thereafter) plus diet/exercise *C*: diet/exercise only *Both groups*: exercise: walking a minimum of 30 minutes at least 3 days/week; consultation with dietician *Adherence*: adherence to metformin (pill count) and diet/exercise; 74% with good dietary/exercise adherence *Run-in period*: none *Co-interventions/co-medications*: NR	*Primary*: plasma leptin *Progression/regression of liver disease*: USG: low grade (< 30%), moderate grade (30 to 50%), high grade (> 50%) (Yajima *et al.* 1983)[156] *IGT → diabetes*: NR *NGT → IGT/diabetes*: NR HbA_{1c}: yes *FPG*: yes *Weight change*: yes, BMI, waist–hip ratio *Blood pressure*: no *Lipid parameters*: yes, total and HDL, LDL cholesterol, TGs *Liver biochemistry*: ALT, AST *Insulin resistance*: yes, HOMA *Health-related QoL*: no *Mortality*: no *Other*: leptin, insulin *Timing of assessment*: every 2 months

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Shields 2009[109] *Country*: USA *Focus*: effect of diet, exercise and metformin in participants with insulin resistance and NASH *Design*: prospective, randomised, placebo-controlled trial *Centre*: gastroenterology clinics at the Naval Medical Centre, San Diego, CA *Duration*: 1 year *Follow-up*: no post-intervention follow-up	*Total number*: 19 *n* Met: 9; 9 completed *n* Pbo: 10; 7 completed *Inclusion criteria*: NASH and one of the following: BMI > 27 kg/m², a fasting blood sugar between 6.11 and 6.94 mmol/l; a diagnosis of polycystic ovarian syndrome; metabolic syndrome; age > 17 years, an unremarkable serological evaluation for chronic liver *Diagnosis*: histological diagnosis of NASH defined by the presence of cytological ballooning and inflammation in addition to steatosis, liver biopsy within 18 months of enrolment *Definition of non-alcoholic*: > 20 g/day or 80 g/week *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: known diabetes mellitus (type 1 or 2), a fasting blood sugar > 6.94 mmol/l, prior history of alcoholic liver disease, any other known chronic liver disease, renal insufficiency (serum creatinine > 1.2), a known allergic reaction to metformin, prior use of an insulin-sensitising agent such as metformin or a TZD, gastric bypass within 2 years, untreated thyroid disease, coagulopathy, chronic thrombocytopenia, significant alcohol use during previous 2 years *Age*: *Met*: 50.2 year, SD 9.1; *Pbo*: 44.4 years, SD 12 *Sex*: *Met*: 11% female; *Pbo*: 50% female *BMI*: *Met*: 32.2 kg/m², SD 4.9; *Pbo*: 32.8 kg/m², SD 4.9 *Ethnicity*: *Met*: Hispanic 11%, Caucasian 67%, Asian 11%, African American 11%; *Pbo*: Hispanic 10%, Caucasian 50%, Asian 40%, African American 0% *Fibrosis*: (Brunt scores) *Met*: 1.61; *Pbo*: 1.7 *Stage/severity of NAFLD*: Kleiner score, see *Results* section *Previous treatment*: NR *Comorbidities*: NR	*Met*: metformin 500 mg daily, titrated to 1000 mg daily if serum amino transferases did not show improvement *Pbo*: placebo *Both groups*: referred to a dietician for a dietary counselling (DASH-Dietary Approaches to Stop Hypertension), recommendations for weight loss and 30 minutes aerobic exercise four times a week *Adherence*: NR *Run-in period*: none *Co-interventions/co-medications*: NR	*Primary*: liver histology *Progression/regression of liver disease*: liver histology; liver biopsy specimens graded according to the NASH histological scoring system (Brunt scores); in addition all biopsies were given a NAS as proposed by Kleiner *et al.*[116] *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA₁c*: no *FPG*: no *Weight change*: yes *Blood pressure*: no *Lipid parameters*: yes *Liver biochemistry*: yes *Health-related QoL*: no *Insulin resistance/sensitivity*: yes *Mortality*: no *Other*: overall improvement in BMI, HOMA–IR and serum aminotransferase *Timing of assessment*: participants seen 2 weeks after enrolment and at 6-week intervals thereafter; repeat liver biopsy was performed after completion of the therapy

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Uygun 2004[110] *Country*: Turkey (Ankara) *Focus*: effect of metformin in participants with NASH, insulin resistance and elevated liver enzyme concentrations *Design*: RCT *Centre*: outpatient clinics *Duration*: 6 months *Follow-up*: 6 months – MET group	*Total number*: 36 participants enrolled *n* Met: 17; 15 (88%) completed in 6 months and 11 (65%) in 12 months *n* Pbo: 17; 17 completed *Inclusion criteria*: *Diagnosis*: liver biopsy and histopathological examination; ultrasound of the abdomen; a detailed clinical and laboratory evaluation, including liver enzyme concentrations, hepatitis markers and autoantibodies *Definition of non-alcoholic*: < 100 g ethanol per month; diagnosed by history and also participants spouse or one of the family members asked about the alcohol intake *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: contraindication for metformin, possible liver disease other than NASH, history of malignant disease, impaired renal function (serum creatinine > 1.5 mg/dl), heart failure, history of lactic acidosis, severe infection, hypoxic status, serious acute and chronic illnesses, homodynamic instability, age > 70 years, diabetes mellitus or the current use of any drugs that may affect the results; elevated gamma-glutamyl transpeptidase activity (> 75 U/l, indicating possible concealed alcohol intake) *Age*: *Met*: 39.8 years, SD 10.6 (range 22–64); *Pbo*: 41.5 years, SD 9.1 (range: 23–61) *Sex*: *Met*: 35% female; *Pbo*: 41% female *BMI*: *Met*: 30.1 kg/m², SD 3.4; *Pbo*: 28.4 kg/m², SD 3.9 *Ethnicity*: NR *Fibrosis*: (Brunt fibrosis scores) *Met*: 0.94, SD 1.02*; Pbo*: 1.05, SD 1.1 *Stage/severity of NAFLD*: see *Results* section for Brunt scores *Previous treatment*: NR *Comorbidities*: *Met*: obesity (6), hyperlipidaemia (2), obesity and hyperlipidaemia (8) and undefined (1); *Pbo*: obesity (5), hyperlipidaemia (3), obesity and hyperlipidaemia (7) and undefined (2)	*Met*: metformin 850 mg twice daily plus dietary treatment *Pbo*: dietary treatment alone *Both groups*: consultation with dietician for restriction of patients' intake of lipids and non-complex carbohydrates; all obese and overweight participants were advised to lose weight with a restriction of daily calorie intake to 1600–1800 calories per day *Adherence*: assessed by questionnaire; in both groups nearly one-half of patients reported good compliance with their dietary recommendations whereas the compliance was moderate or poor in the others *Run-in period*: none *Co-interventions/co-medications*: NR	*Primary*: unclear Progression/regression of liver disease: liver histology; liver biopsy specimens graded according to the NASH histological scoring system (Brunt scores) *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA$_{1c}$*: no *FPG*: yes *Weight change*: BMI *Blood pressure*: no *Lipid parameters*: cholesterol, TGs *Liver biochemistry*: ALT, AST, *Health-related QoL*: no *Insulin resistance/sensitivity*: HOMA (%) *Mortality*: no *Other*: insulin, C-peptide, *Timing of assessment*: participants in the metformin group contacted by telephone in the first and second weeks of treatment and questioned about any side effects attributed to the drug; also warned of possible hypoglycaemia and gastrointestinal side effects due to metformin; in both groups all serum parameters (and, in the metformin group, the serum lactate level) were repeated at the end of the first, third and sixth months of treatment; ultrasound of the abdomen and liver biopsy at baseline and at the end of the study if informed consent had been obtained. In both groups, the participants were advised to maintain their dietary recommendations after the study period and were recalled for clinical evaluation and liver enzyme concentrations every 3 months Four participants in Met group and seven in the dietary-alone group refused the control liver biopsy, even though written consent was given prior the study. Therefore, control biopsy was done in 13 in the Met and 10 in the diet-alone group

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Rosiglitazone			
Ratziu 2008 (FLIRT trial)[111] *Country*: France *Focus*: efficacy and safety of rosiglitazone in participants with NASH *Design*: randomised, double-blind, placebo-controlled trial *Centre*: single institution (presumably hospital) *Duration*: 12 months *Follow-up*: 4 months	*Total number*: 64 *n* Rosi: 32; 32 completed *n* Pbo: 32; 31 completed *Inclusion criteria*: 18–75 years, histological diagnosis of NASH *Diagnosis*: liver biopsy performed within 12 months before inclusion; steatosis >20% and the presence of either hepatocyte ballooning or intralobular hepatocyte necrosis, all signs with centrolobular accentuation; elevated ALT level was defined as a baseline level >28 IU/l in women and 35 IU/l in men and at least two other abnormal values in the 6 months before baseline *Definition of non-alcoholic*: daily alcohol consumption of <30g in men and 20 g in women whether current or in the past *IGT/diabetes (including diagnostic criteria)*: NR *Exclusion criteria*: presence of bland steatosis on liver biopsy or steatosis with non-specific inflammation; any cause of liver disease other than NASH, including suspicion of drug-induced liver injury; treatment with insulin for diabetes or with UDCA; cardiac insufficiency (NYHA Class >1); current or past treatment with drugs that can induce steatohepatitis; neoplastic disease; Child class B or C cirrhosis; pregnancy; organ transplantation; haemoglobin level <10 g/dl; polymorphonuclear count <750/mm;[3] platelet count <50,000/mm^3 *Age*: *Rosi*:53.1, SD 11.5, *Pbo*: 54.1, SD 10.4 *Sex*: *Rosi*: 41% female, *Pbo*: 42% female BMI: *Rosi*: 31.5, SD 6 kg/m^2, *Pbo*: 30.5, SD 4.4 kg/m^2 *Ethnicity*: NR *Fibrosis*: (Brunt scores) *Rosi*: 91%, *Pbo*: 97% *Stage/severity of NAFLD*: see *Results* section *Previous treatment*: History of treatment with diabetes – metformin: 16 (*Rosi*: 7, *Pbo*: 9); sulfamide: 10 (*Rosi*: 7, *Pbo*: 3); none: 3 (*Rosi*: 1, *Pbo*: 2) *Comorbidities*: NR	*Rosi*: rosiglitazone 4 mg daily for the first month, 8 mg daily until end of treatment and then discontinued *Pbo*: placebo *Both groups*: instructed to lose weight if they were obese or overweight, to follow a healthy diet and to exercise at least twice a week; no specialised nutritional counselling was implemented *Adherence*: NR *Run-in period*: no *Co-interventions/co-medications*: NR	*Primary*: reduction in steatosis >30% between baseline and end of treatment or disappearance of steatosis at end of treatment *Progression/regression of liver disease*: liver histology; liver biopsy specimens graded according to the NASH histological scoring system (Brunt scores); steatosis semi-quantitatively assessed by the per cent of hepatocyte involved within a lobule (0–100% steatosis score) and by using a four-grade classification modified from Kleiner *et al.*; non-alcoholic fatty liver disease activity score (NAS) calculated according to Kleiner *et al.*[116] *IGT→diabetes*: no *NGT→IGT/diabetes*: no *HbA$_{1c}$*: yes *FPG*: yes *Weight change*: BMI, waist circumference, *Blood pressure*: no (but arterial hypertension) *Lipid parameters*: TGs, HDL *Liver biochemistry*: ALT, AST, GGT level, bilirubin level *Health-related QoL*: no *Insulin resistance/sensitivity*: HOMA index and quantitative insulin-sensitivity check index (QUICKI) *Mortality*: no *Other*: serum leptin, adiponectin, insulin level, metabolic syndrome (%) *Timing of assessment*: during treatment, participants were followed up at months 1 and 2 and then every 2 months until end of treatment when liver biopsy was performed. At the end of the follow-up, all participants were asked to participate in a 2-year, open-label, extension trial of rosiglitazone irrespective of what they received during the 1-year, double-blinded phase of the trial

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Rosiglitazone/metformin			
Idilman 2008[112] *Country*: Turkey *Focus*: insulin sensitisers (metformin, rosiglitazone) in the treatment of NASH *Design*: parallel RCT, single centre *Duration*: 48 weeks *Follow-up*: 6 months post-intervention	*Total number*: 74 *n* Met: 24; 24 completed *n* Rosi: 25; 24 completed *n* C: 25; 25 completed *Inclusion criteria*: newly diagnosed NASH, age >18 years *Diagnosis*: diagnosis based on biochemical, radiological and histological criteria, including abnormal serum ALT levels, abnormal ECHO pattern on sonography consistent with fatty infiltration; liver biopsy documenting steatosis and ballooning degeneration, with or without necroinflammatory activity, portal inflammation, fibrosis or cirrhosis *Definition of non-alcoholic*: women < 15 g/day, men < 20 g/day *IGT/diabetes (including diagnostic criteria)*: unclear *Exclusion criteria*: confounding disease including acute hepatitis (A, B, C) and/or chronic viral hepatitis; heart or renal disease, other forms of liver disease (e.g. autoimmune, drug induced, metabolic) *Age*: insulin sensitisers: 47.9 years, SD 8.3; C: 45.8 years, SD 10.4 *Sex*: insulin sensitisers: 56% female; C: 64% female *BMI*: insulin sensitisers: 31.2 kg/m^2, SD 3.6; C: 32.2 kg/m^2, SD 5.1 *Ethnicity*: NR *Fibrosis*: unclear *Stage/severity of NAFLD (NAS)*: insulin sensitisers: 5 (3 to 8); C: 4 (3 to 8) *Previous treatment*: NR *Comorbidities*: insulin sensitisers: 21% hyperlipidaemia; C: 20% hyperlipidaemia	*Met*: diet and exercise plus metformin 850 mg b.i.d. (1700 mg) *Rosi*: diet and exercise plus rosiglitazone 8 mg/day *C*: diet and exercise alone *All groups*: diet and exercise programme: exercise included walking (initially 300 steps/day for 3 days, then adding 500 steps at 3-day intervals until 10,000 steps attained) and jogging (20 minutes b.i.d.), improvement in associated conditions such as moderate/severe hyperlipidaemia, discontinuation of potentially hepatotoxic drugs; diet: 25 kcal/kg × ideal body weight, three meals containing 60% carbohydrate, 25% fat and 15% protein provided for each individual; adherence to diet and exercise encouraged during 6-month follow-up *Adherence*: adherence to diet and exercise monitored; adherence was judged to be insufficient in both groups *Run-in period*: none *Co-interventions/co-medications*: 15 patients with hyperlipidaemia (five in diet/exercise-only group and 10 in insulin sensitiser group) were on lipid-reduced diet and anti-hyperlipidaemic agents and continued this treatment throughout the study	*Primary*: unclear *Progression/regression of liver disease*: liver histology; liver biopsy performed before intervention and after 48 weeks; histological features interpreted according to the criteria given by Brunt *et al.*,[115] NAS according to Kleiner *et al.*[116] *IGT → diabetes*: no *NGT → IGT/diabetes*: no *HbA$_{1c}$*: no *FPG*: yes *Weight change*: BMI, body fat content, waist and hip circumference *Blood pressure*: no *Lipid parameters*: cholesterol, TGs *Liver biochemistry*: ALT, AST, GGT, ALP, bilirubin *Insulin resistance*: yes, HOMA *Health-related QoL*: NR *Mortality*: NR *Other*: insulin, serum iron, ferritin, copper, ceruloplasmin; anti-nuclear, anti-smooth muscle and anti-mitochondrial antibodies *Timing of assessment*: baseline, after 4 weeks, then at 3-month intervals

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Omer 2010[113] *Country*: Turkey *Focus*: effects of insulin-sensitising agents in participants with NAFLD with T2DM or impaired glucose metabolism *Design*: open-label, randomised, single-centre study *Multicentre*: hepatology and endocrinology outpatients clinic *Duration*: 12 months *Follow-up*: no post-intervention follow-up	*Total number*: 64 *n* Met: 22; 19 completed *n* Rosi: 20; 20 completed *n* Met + Rosi: 22; 22 completed *Inclusion criteria*: NAFLD; being on a dietary and exercise programme for at least 12 weeks before enrolment *Diagnosis*: elevated ALT for at least 6 months before enrolment; NAS at least five in liver biopsy performed within 6 months before enrolment *Definition of non-alcoholic*: alcohol consumption < 20 g/day *IGT/diabetes (including diagnostic criteria)*: patients with impaired glucose metabolism (T2DM or impaired glucose tolerance) *Exclusion criteria*: use of oral anti-diabetics, insulin or a chemotherapeutic agent; presence of other chronic liver diseases, such as metabolic liver diseases, autoimmune liver diseases, and chronic viral hepatitis B or C, HIV infection; pregnancy or lactation; being a candidate for organ transplantation; presence of a malignancy; renal function impairment (serum creatinine > 1.5 mg/dl in men and > 1.4 mg/dl in women), and clinically significant systematic illness *Age (years)*: *Met*: 48.0 years, SD 9.8; *Rosi*: 49.3 years, SD 6; *Met + Rosi*: 49.6 years, SD 9.1 *Sex*: *Met*: 32% female; *Rosi*: 55% female, *Met + Rosi*: 50% female *BMI*: *Met*: 30.8 kg/m², SD 6.6; *Rosi*: 28.4 kg/m², SD 4.1; *Met + Rosi*: 32.5 kg/m², SD 7.0 *Ethnicity*: NR *Fibrosis*: proportion not reported *Stage/severity of NAFLD*: NAS – see *Results* section *Previous treatment*: NR *Comorbidities*: NR	*Met*: metformin 1700 mg/day *Rosi*: rosiglitazone 4 mg/day *Met + Rosi*: metformin 1700 mg/day and rosiglitazone 4 mg/day *Both groups*: dietary counselling by endocrinologists and dieticians, and encouraged to do exercise for 12 weeks before study medication and also to continue this programme during the entire study *Adherence*: NR *Run-in period*: 12 weeks with exercise programme *Co-interventions/co-medications*: NR	*Primary*: histological changes in liver *Progression/regression of liver disease*: Liver biopsy, assessed according to criteria by Kleiner *et al.*;[116] NAS; total NAFLD score *IGT → diabetes*: NR *NGT → IGT/diabetes*: NR *HbA₁c*: yes *FPG*: no *Weight change*: BMI, waist circumference *Blood pressure*: NR *Lipid parameters*: TC, HDL, LDL, TGs *Liver biochemistry*: AST level, ALT level, GGT, alkaline phosphates *Health-related QoL*: NR *Insulin sensitivity/resistance*: HOMA–IR *Mortality*: NR *Other*: transferrin saturation, ferritin, insulin, blood urea nitrogen, creatinine *Timing of assessment*: follow-up every months for the first 3 months and then every 3 months

TABLE 13 Characteristics of included trials *(continued)*

Study/design	Participants	Interventions	Outcome measures
Torres 2009[100] *Country*: NR (presumably USA – San Antonio, TX) *Focus*: effect of rosiglitazone or rosiglitazone and metformin in combination after 1 year of therapy in participants with NASH *Design*: randomised open-label trial *Multicentre*: NR *Duration*: 1 year *Follow-up*: no post-intervention follow-up	*Total number*: 108 randomised, preliminary results for 49 participants reported *n* Rosi: 15 completed *n* Rosi + Met: 16 completed *Rosi + Los*: 18 completed *(not considered here)* *Inclusion criteria*: screened for other aetiologies of chronic liver disease including daily alcohol intake of 20 g *Definition of non-alcoholic*: < 20 g per day *IGT/diabetes (including diagnostic criteria)*: *Exclusion criteria*: *Age (years)*: mean age 48.9? SD 9.2 years *BMI*: mean BMI 33.3? SD 5.1 kg/m^2 *Ethnicity*: NR *Fibrosis*: NR *Stage/severity of NAFLD*: NR *Previous treatment*: NR *Comorbidities*: NR	*Rosi*: 4 mg rosiglitazone twice daily *Rosi + Met*: 4 mg rosiglitazone and 500 mg metformin twice daily *Rosi + Los*: 4 mg rosiglitazone and 50 mg losartan once daily for 48 weeks (not considered here) *Both groups*: NR *Adherence*: NR *Run-in period*: NR *Co-interventions/co-medications*: NR	*Primary*: histopathological changes in liver *Progression/regression of liver disease*: liver biopsy *IGT → diabetes*: NR *NGT → IGT/diabetes*: NR *HbA$_{1c}$*: no *FPG*: no *Weight change*: weight *Blood pressure*: no *Lipid parameters*: no *Liver biochemistry*: AST level, ALT level, *Health-related QoL*: no *Insulin sensitivity/resistance*: mean HOMA–IR *Mortality*: NR *Timing of assessment*: NR

ECHO, echocardiogram; IGT, impaired glucose tolerance; lb, pound; Los, losartan; Met, metformin; NGT, normal glucose tolerance; NR, not reported; NYHA, New York Heart Association; oz, ounce; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; ULN, upper limit of normal; Vit E, vitamin E.

Appendix 3

Quality of included studies

TABLE 14 Quality of included trials

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation	Total score
Pioglitazone									
Aithal 2008[101]	Computer randomisation in blocks of four	Not given	Double blind	Not given	I: 84% C: 81%	Yes (requiring 33 in each group)	Most parameters; lower alkaline phosphatase and fasting insulin in pioglitazone group at baseline	Unclear, investigator-initiated study, but Takeda UK provided pioglitazone and placebo tablets; one author received funding by Takeda to attend meetings	4
Belfort 2006[102]	Computer generation by research pharmacy	Not given	Double blind	Not given	Pio: 23/26 (88%) Pbo: 17/21 (81%)	No	Yes	Grants from the National Centre for Research Resources, Takeda Pharmaceuticals, and the Veterans Affairs Medical Research Fund. One of the authors is a member of the speakers bureau of Eli Lilly, one a consultant to Eli Lilly and the third a member of the advisory board and speakers bureau of Takeda Pharmaceuticals. No other conflict of interest	5
Sanyal 2004[103]	By an independent statistician in random blocks of two, four and six	No	Pathologist blinded	No	Pio: 8/10 (80%) Vit E: 10/10 (100%)	No	Yes	Supported in part by a grant from the National Institutes of Health to the General Clinical Research Centre at Virginia Commonwealth University and by an award to AJS	4
Sanyal 2010[104]	Administered centrally by the DCC, web-based application; assigned participants in permuted blocks of treatments stratified by clinical centre	Randomisation centrally, request made by a web based application and participants randomised in permuted blocks	Double blind	Yes	Pio: 70/80 (88%) Vit E: 80/84 (95%) Pbo: 72/83 (87%)	Yes	Yes	Supported by National Institute of Diabetes and Digestive and Kidney Disease. Additional funding by Takeda Pharmaceuticals North America Inc.	8

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation	Total score
Metformin									
Bugianesi 2005[87]	Randomisation procedure was centralised in Bologna, and based on a random sequence	Sealed envelopes were used to conceal randomisation	Both patients and investigator were not blind to the treatment	ITT, LOCF analysis	I: 100% C: 100%	No	Most parameters; significant difference in sex between groups (100% men in Vit E group) and in cholesterol levels (significantly lower in diet group)	Not given	4
Garinis 2010[105]	Not given	Not given	Open label	Not given	I: 15/20(75%) C: 25/25 (100%) Five participants dropped out because of non-compliance to the treatment	Not given	Two treatment groups showed similar clinical and biochemical variables	Not clear	2
Haukeland 2009[106]	Computer-assisted process of minimalisation (to minimalise baseline difference in serum ALT and liver histology)	Allocation code was blinded to participants and investigators; two pathologists blinded	Double blind	Per-protocol analyses (44 participants that completed the trial)	I: 83% C: 100% Four participants treated with metformin did not complete the study due to gastrointestinal side effects (n=1), development of exanthema (n=1), withdrawal of consent (n=1) and erroneous use of study medication (n=1)	Yes, based on liver steatosis, at least 36 participants in each group to have 80% power to detect a significant difference between Met and placebo and 10% mean reduction; only 44 participants completed the trial, the power to detect a significant difference between treatment groups was reduced to 60%	Metformin-treated participant were younger, less often treated for hypertension and slightly more obese (significance not reported)	Eastern Norway Regional Health Authority (grant) and Merck Santé (delivery of study medication); no conflicts of interest	7

TABLE 14 Quality of included trials (continued)

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation	Total score
Nadeau 2009[107]	Research pharmacist. Stratified by ethnic group as well as insulin level >40 or <40 to assure similar distributions of drug and placebo groups	No	Double blind; study radiologist blinded	No	I: 28/37 (76%) C: 10/13 (77%)	No	Yes	Grant by General Clinical Research Centers Program, National Centers for Research Resources, Insulin Control of Fat Regulation and Exercise in Teens and the Kettering Family Foundation	4
Nar 2009[108]	Not given	Not given	Operator performing ultrasound blind to treatment	Not given but presumably all patients completed the study	Not given, presumably 100%	Not given	Yes	Not given	3
Shields 2009[109]	Randomised by the pharmacy using a computer-generated program into group A or B	No	Two study pathologists were blinded	Yes	I: 7/10 (70%) C: 9/9 (100%)	No	Yes; two groups similar regarding their laboratory and anthropometric data; treatment group was older and predominantly male; (but difference not significant)	No conflict of interest; funding source not reported	5
Torres 2009[100]	Not given; randomised	Not given	Open label; pathologist blinded	Not given	Total number of participants allocated in each group is reported in the abstract as 108 till date	Not given	Not given	Not given	1
Uygun 2004[110]	Random sampling numbers	No	Unblinded	No	I: 15/17 (88%) completed in 6 months and 11/17 (65%) in 12 months; liver biopsies at study end by 13 only C: 17/17 (100%); liver biopsies at study end by 10 only	No	Yes	Not given	3

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation	Total score
Rosiglitazone									
Ratziu 2008[111]	Randomisation (pre-sealed envelopes) conducted by blocks of four and stratified on metformin use	Pre-sealed envelopes	Double blind Pathologist blinded	No	I: 32/32 (100%) C: 31/31 (100%)	The inclusion of 29 participants per arm was deemed necessary for rejecting the null hypothesis with 80% power and a type I error rate of 0.05. The total number of included participants was set at 32 per arm to account for 20% lost to follow-up	Yes	GlaxoSmithKline partly funded the trial, investigator-initiated trial. One of the authors is a consultant to Astellas, Gilead, Pfizer, Sanofi-Aventis, and Trophos. Another author is a consultant for, and owns 15% of, BioPredictive, a company that markets FibroTest and SteatoTest. None of the authors has a personal conflict of interest with the manufacturer of any of the marketed TZDs	7
Metformin/rosiglitazone									
Idilman 2008[112]	Random assignment 1 : 2, method not reported	Not given	Pathologist assessing liver biopsies blinded to patient and treatment	No (but only one patient did not complete the study)	Met: 100% Rosi: 96% C: 100%	Not given	Yes	Stated that there was no conflict of interest with respect to funding	3
Omer 2010[113]	Not given	Not given	Open label	Not given	Met: 86% Rosi: 100% Met + Rosi: 100%	Not given	All three groups were similar at baseline except baseline serum insulin level (significantly higher in the metformin group and metformin-plus-rosiglitazone group compared with the rosiglitazone group)	Committee of Ege University Medical School, Department of Gastroenterology and Endocrinology	2

C, control; I, intervention; LOCF, last observation carried forward; Met, metformin; Pbo, placebo; Pio, pioglitazone; Rosi, rosiglitazone; Vit E, vitamin E.

Appendix 4

Protocol

Technology Assessment Report commissioned by the NIHR HTA programme on behalf of the National Institute for Health and Clinical Excellence

Project 09/16

Final protocol 23 February 2010

Title Insulin sensitizers in treatment of non-alcoholic fatty liver disease
Aberdeen TAR team

Contact
Professor Norman Waugh
Section of Population Health
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
n.r.waugh@abdn.ac.uk

Plain English summary

Non-alcoholic fatty liver disease (NAFLD) is a common disease due to a build up of fat in the cells of the liver. It can range from causing no symptoms at all, to severe damage (cirrhosis) of the liver, and death. Liver disease is common in those who drink to excess, but liver disease can also occur in people who drink little or no alcohol (defined as less than one unit, 10g, a day), especially if they are fat.

NAFLD is becoming more common because of the rise in obesity, and it is estimated that about 20% of people in the USA have it. It is also the most common cause of liver disease in children.

In the early stages of NAFLD, the liver is simply full of fat (steatosis), but this can progress to inflammation (steatohepatitis), and then to scarring and cirrhosis. It used to be seen typically in middle age, but with increasing levels of obesity in children, cases have been reported in children under 10.

Most people who get NAFLD are overweight or obese, and there is a close association with insulin resistance. More than half of the people with NAFLD will also have type 2 diabetes, and many will have high cholesterol levels. There is an increased risk of heart disease.

Treatment should start with diet and weight loss, aided by physical activity, and if sufficient weight is lost, the condition will improve. However adherence to lifestyle changes is often poor.

Because NAFLD is usually seen in people who have insulin resistance, a group of drugs which improve the body's sensitivity to insulin have been tried. These drugs are called the insulin sensitisers – metformin, pioglitazone and rosiglitazone.

This review will examine the evidence for the effectiveness of these drugs in NAFLD.

Decision problem

- Key question: what is the clinical and cost-effectiveness of metformin, rosiglitazone and pioglitazone in NAFLD?
- Should the HTA Programme seek to commission further primary research in the value of insulin-sensitisers in NAFLD?

It will be assumed that first-line treatment will be with lifestyle changes (diet, physical activity and weight loss), and that the insulin-sensitisers will be used as a second-line addition to those. A Cochrane review on dietary interventions by Rex Wang and colleagues is in progress, and we will not examine the literature on that.

Given recent evidence on the relative vascular risks of pioglitazone and rosiglitazone (summarised in the HTA monograph on newer drugs for type 2 diabetes), our prior position will be that pioglitazone is preferred. We will exclude any studies which used troglitazone, an earlier glitazone which is no longer used because it caused liver damage.

The population of interest will be those with diagnosed NAFLD, and the HTA Programme commissioning brief specifies that the patient group of most interest is people with evidence of fibrosis.

Sub-groups will include:

- Those with type 2 diabetes.
- Children and adolescents.
- Those with other features of the metabolic syndrome such as hypertension and hyperlipidaemia.
- Those with and without fibrosis.
- Ethnic groups at higher risk.

Diagnosis

There is a problem with the diagnosis of NAFLD. The current consensus is that it can only be diagnosed on the basis of a liver biopsy. This could be a major hindrance to any trials which need to recruit large numbers of patients, perhaps especially if young people are involved. Liver biopsy can have complications, such as bleeding, at any age.

Hence it would not be feasible to mount a large trial of insulin-sensitisers if the diagnosis has to be based on liver biopsy. We are aware that research into alternative methods of diagnosis, such as panels of liver tests, ultrasound and MRI, is underway. For detecting NAFLD, ultrasound and MRI have been suggested. For detecting liver fibrosis, various non-invasive alternatives to liver biopsy have been suggested, including combinations of blood tests ("serum marker panels"), and either transient or real-time elastography.

The HTA Programme is commissioning a full review of evidence on non-invasive methods for the assessment and monitoring of more advanced stages, liver fibrosis and cirrhosis (HTA number 09/07), and so this review will not duplicate that. This review is more concerned with a trial which would seek to prevent people reaching those stages.

The aim for diagnosis is therefore to distinguish those patients with simple steatosis from those who have steatohepatitis.

We will therefore carry out a brief review of alternatives to biopsy at earlier stages, such as NASH.

What we will try to do is identify non-invasive tests which could be used to recruit patients to a trial, even if that meant accepting that the tests were sensitive but not specific. The safety and adverse effects of the drugs under review are well-known and that the drugs are well tolerated and safe. Hence a case could be made that using a test which had good sensitivity but not very good specificity, would be suitable for identifying patients for a trial, on the grounds that including some people who had fatty livers but had not progressed to NASH, would do them no harm, but possibly some good.

However it might reduce the power of the study by reducing the frequency of adverse outcomes in the placebo arms.

Our aim will not be to make a firm recommendation as to what diagnostic tests should be used in a trial, but rather to suggest non-invasive options which the HTA Programme could include in the vignette and then the CB. It would then be up to bidders to justify their choices.

Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in NHS CRD Report No.4.

Criteria for considering studies for this review

Types of studies: systematic reviews and randomised clinical trials. There will be no size restriction on number of patients in trials, since those with inadequate numbers and hence power, might be useful when combined in a meta-analysis. Observational studies may be used for data on safety and for assessing diagnostic methods.

We note the Cochrane review on insulin sensitisers by Francesco Angelico and colleagues in Rome. It excluded people with type 2 diabetes, and only included three trials, two of metformin and one with pioglitazone. Our scoping searches suggest that there may be another nine trials which need to be considered.

Types of participants: Participants of any age, sex, or ethnic origin with NAFLD proven by liver biopsy or other methods.

Types of interventions: Metformin, pioglitazone, or rosiglitazone at any dose or duration, given separately or in combination versus no intervention, placebo, or other pharmacological interventions of proven effectiveness.

Types of outcome measures: Measures of disease progression such as fibrosis and cirrhosis, other hepatic-related morbidity such as variceal bleeding liver failure, hepatic-related and all-cause mortality, cardiovascular events, quality of life, new diabetes, adverse events. We include some of these for completeness but do not expect studies to be large enough or long enough to report on all of these outcomes.

We will check the diagnostic methods used in previous trials, and if data permit, we will compare the findings of liver biopsy with those of non-invasive tests. We will carry out searches on

diagnostic methods other than liver biopsy. Ideally, these would compare new tests with liver biopsy as the gold standard.

Search methods for identification of studies
We will search the following sources

- MEDLINE
- EMBASE
- The Cochrane Library (all sections)
- Science Citation Index Expanded (SCI expanded) and Conference Proceedings Citation Index- Science (CPCI-S)
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

We will search for articles published since 2005, since a Cochrane review included studies found by searches to February 2006. No language restrictions will be applied to the search strategy, but we may not be able to translate studies in languages other than English, German and French.

Data collection and analysis
Study Selection
Study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Data extraction
Data will be extracted by one reviewer, using a standardised data extraction form, and checked by a second. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No.4.

Existing systematic reviews will be quality assessed, summarised and results compared. Reasons for differences between the reviews will be investigated and possible reasons for conflicting results will be investigated in a narrative review.

RCTs published since the existing systematic reviews will be added and included if appropriate in a new meta-analysis. If not, evidence synthesis of all RCTs which meet our inclusion criteria will be done using a narrative review.

Searches will be carried out for on-going research.

We will contact the authors of the Cochrane review and if they are updating it in our timescale, will offer collaboration. If they are not doing it in our timescale, we will invite them to act as peer reviewers of the unpublished draft final report.

Report methods for synthesising evidence of cost-effectiveness
We will review the literature on cost-effectiveness but will not undertake any de novo modelling.

Products

The main product from this review will be a short report for publication in the HTA monograph series, but as requested in the commissioning brief, we will also produce a vignette on the desirability of new primary research for the Pharmaceutical Panel of the HTA Programme.
We will also aim to submit a version suitable for publication in an appropriate journal. We will contact the authors of the Cochrane review with a view to helping them update their review.

Competing interests of authors

None.

Details of TAR team

Dr Deepson Shyangdan
Section of Population Health
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD

Dr Christine Clar
Researcher in Systematic Reviews
Hasenheide 67
D-10697 Berlin
Germany
clar@cc-archie.de

Dr Tara Gurung
Section of Population Health
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD

Dr Nazim Ghouri
BHF Glasgow Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow G12 8TA

Professor Naveed Sattar
Professor of metabolic medicine
BHF Glasgow Cadiovascular Research Centre
126 University Place
University of Glasgow
Glasgow G12 8TA

Dr Ewen Cummins
Health Economist
McMaster Development Consultants
46 Polwarth Street
Glasgow G12 9TJ
ecummins@mcmdc.com

Norman Waugh
Professor of Public Health
University of Aberdeen
Tel. 01224 555998
n.r.waugh@abdn.ac.uk

An expert in liver disease is being approached to join the team.

Timetable/milestones

Assessment Report to be delivered by end July 2010.

Health Technology Assessment programme

Director,
Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Deputy Director,
Professor Hywel Williams,
Professor of Dermato-Epidemiology, Centre of Evidence-Based Dermatology, University of Nottingham

Prioritisation Group

Members

Chair,
Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham
Chair – Pharmaceuticals Panel

Dr Bob Coates, Consultant Advisor – Disease Prevention Panel

Dr Andrew Cook, Consultant Advisor – Intervention Procedures Panel

Dr Peter Davidson, Director of NETSCC, Health Technology Assessment

Dr Nick Hicks, Consultant Adviser – Diagnostic Technologies and Screening Panel, Consultant Advisor–Psychological and Community Therapies Panel

Ms Susan Hird, Consultant Advisor, External Devices and Physical Therapies Panel

Professor Sallie Lamb, Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick
Chair – HTA Clinical Evaluation and Trials Board

Professor Jonathan Michaels, Professor of Vascular Surgery, Sheffield Vascular Institute, University of Sheffield
Chair – Interventional Procedures Panel

Professor Ruairidh Milne, Director – External Relations

Dr John Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust
Chair – External Devices and Physical Therapies Panel

Dr Vaughan Thomas, Consultant Advisor – Pharmaceuticals Panel, Clinical Lead – Clinical Evaluation Trials Prioritisation Group

Professor Margaret Thorogood, Professor of Epidemiology, Health Sciences Research Institute, University of Warwick
Chair – Disease Prevention Panel

Professor Lindsay Turnbull, Professor of Radiology, Centre for the MR Investigations, University of Hull
Chair – Diagnostic Technologies and Screening Panel

Professor Scott Weich, Professor of Psychiatry, Health Sciences Research Institute, University of Warwick
Chair – Psychological and Community Therapies Panel

Professor Hywel Williams, Director of Nottingham Clinical Trials Unit, Centre of Evidence-Based Dermatology, University of Nottingham
Chair – HTA Commissioning Board
Deputy HTA Programme Director

HTA Commissioning Board

Chair,
Professor Hywel Williams,
Professor of Dermato-Epidemiology, Centre of Evidence-Based Dermatology, University of Nottingham

Deputy Chair,
Professor Jon Deeks,
Department of Public Health and Epidemiology, University of Birmingham

Professor Tom Walley, CBE,
Professor of Clinical Pharmacology, Director, NIHR HTA programme, University of Liverpool

Members

Professor Ann Ashburn, Professor of Rehabilitation and Head of Research, Southampton General Hospital

Professor Peter Brocklehurst, Professor of Women's Health, Institute for Women's Health, University College London

Professor Jenny Donovan, Professor of Social Medicine, University of Bristol

Professor Jonathan Green, Professor and Acting Head of Department, Child and Adolescent Psychiatry, University of Manchester Medical School

Professor John W Gregory, Professor in Paediatric Endocrinology, Department of Child Health, Wales School of Medicine, Cardiff University

Professor Steve Halligan, Professor of Gastrointestinal Radiology, University College Hospital, London

Professor Freddie Hamdy, Professor of Urology, Head of Nuffield Department of Surgery, University of Oxford

Professor Allan House, Professor of Liaison Psychiatry, University of Leeds

Dr Martin J Landray, Reader in Epidemiology, Honorary Consultant Physician, Clinical Trial Service Unit, University of Oxford

Professor Stephen Morris, Professor of Health Economics, University College London, Research Department of Epidemiology and Public Health, University College London

Professor Irwin Nazareth, Professor of Primary Care and Head of Department, Department of Primary Care and Population Sciences, University College London

Professor E Andrea Nelson, Professor of Wound Healing and Director of Research, School of Healthcare, University of Leeds

Professor John David Norrie, Chair in Clinical Trials and Biostatistics, Robertson Centre for Biostatistics, University of Glasgow

Dr Rafael Perera, Lecturer in Medical Statisitics, Department of Primary Health Care, University of Oxford

HTA Commissioning Board *(continued)*

Professor Barney Reeves,
Professorial Research Fellow
in Health Services Research,
Department of Clinical Science,
University of Bristol

Professor Martin Underwood,
Professor of Primary Care
Research, Warwick Medical
School, University of Warwick

Professor Marion Walker,
Professor in Stroke Rehabilitation,
Associate Director UK Stroke
Research Network, University of
Nottingham

Dr Duncan Young,
Senior Clinical Lecturer and
Consultant, Nuffield Department
of Anaesthetics, University of
Oxford

Observers

Dr Tom Foulks,
Medical Research Council

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

HTA Clinical Evaluation and Trials Board

Chair,
Professor Sallie Lamb,
Director,
Warwick Clinical Trials Unit,
Warwick Medical School,
University of Warwick and Professor of
Rehabilitation,
Nuffield Department of Orthopaedic,
Rheumatology and Musculoskeletal Sciences,
University of Oxford

Deputy Chair,
Professor Jenny Hewison,
Professor of the Psychology of Health Care,
Leeds Institute of Health Sciences,
University of Leeds

Programme Director,
Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of
Clinical Pharmacology, University of Liverpool

Members

Professor Keith Abrams,
Professor of Medical Statistics,
Department of Health Sciences,
University of Leicester

Professor Martin Bland,
Professor of Health Statistics,
Department of Health Sciences,
University of York

Professor Jane Blazeby,
Professor of Surgery and
Consultant Upper GI Surgeon,
Department of Social Medicine,
University of Bristol

Professor Julia M Brown,
Director, Clinical Trials Research
Unit, University of Leeds

Professor Alistair Burns,
Professor of Old Age Psychiatry,
Psychiatry Research Group, School
of Community-Based Medicine,
The University of Manchester &
National Clinical Director for
Dementia, Department of Health

Dr Jennifer Burr,
Director, Centre for Healthcare
Randomised trials (CHART),
University of Aberdeen

Professor Linda Davies,
Professor of Health Economics,
Health Sciences Research Group,
University of Manchester

Professor Simon Gilbody,
Prof of Psych Medicine and Health
Services Research, Department of
Health Sciences, University of York

Professor Steven Goodacre,
Professor and Consultant in
Emergency Medicine, School of
Health and Related Research,
University of Sheffield

Professor Dyfrig Hughes,
Professor of Pharmacoeconomics,
Centre for Economics and Policy
in Health, Institute of Medical
and Social Care Research, Bangor
University

Professor Paul Jones,
Professor of Respiratory Medicine,
Department of Cardiac and
Vascular Science, St George's
Hospital Medical School,
University of London

Professor Khalid Khan,
Professor of Women's Health and
Clinical Epidemiology, Barts and
the London School of Medicine,
Queen Mary, University of London

Professor Richard J McManus,
Professor of Primary Care
Cardiovascular Research, Primary
Care Clinical Sciences Building,
University of Birmingham

Professor Helen Rodgers,
Professor of Stroke Care, Institute
for Ageing and Health, Newcastle
University

Professor Ken Stein,
Professor of Public Health,
Peninsula Technology Assessment
Group, Peninsula College
of Medicine and Dentistry,
Universities of Exeter and
Plymouth

Professor Jonathan Sterne,
Professor of Medical Statistics
and Epidemiology, Department
of Social Medicine, University of
Bristol

Mr Andy Vail,
Senior Lecturer, Health Sciences
Research Group, University of
Manchester

Professor Clare Wilkinson,
Professor of General Practice and
Director of Research North Wales
Clinical School, Department of
Primary Care and Public Health,
Cardiff University

Dr Ian B Wilkinson,
Senior Lecturer and Honorary
Consultant, Clinical Pharmacology
Unit, Department of Medicine,
University of Cambridge

Observers

Ms Kate Law,
Director of Clinical Trials,
Cancer Research UK

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies and Screening Panel

Members

Chair,
Professor Lindsay Wilson Turnbull,
Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, University of Manchester

Mr Angus S Arunkalaivanan, Honorary Senior Lecturer, University of Birmingham and Consultant Urogynaecologist and Obstetrician, City Hospital, Birmingham

Dr Diana Baralle, Consultant and Senior Lecturer in Clinical Genetics, University of Southampton

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Dr Diane Eccles, Professor of Cancer Genetics, Wessex Clinical Genetics Service, Princess Anne Hospital

Dr Trevor Friedman, Consultant Liason Psychiatrist, Brandon Unit, Leicester General Hospital

Dr Ron Gray, Consultant, National Perinatal Epidemiology Unit, Institute of Health Sciences, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, Academic Unit of Radiology, University of Sheffield

Mr Martin Hooper, Public contributor

Professor Anthony Robert Kendrick, Associate Dean for Clinical Research and Professor of Primary Medical Care, University of Southampton

Dr Nicola Lennard, Senior Medical Officer, MHRA

Dr Anne Mackie, Director of Programmes, UK National Screening Committee, London

Mr David Mathew, Public contributor

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Department of Pathology & Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mrs Una Rennard, Public contributor

Dr Stuart Smellie, Consultant in Clinical Pathology, Bishop Auckland General Hospital

Ms Jane Smith, Consultant Ultrasound Practitioner, Leeds Teaching Hospital NHS Trust, Leeds

Dr Allison Streetly, Programme Director, NHS Sickle Cell and Thalassaemia Screening Programme, King's College School of Medicine

Dr Matthew Thompson, Senior Clinical Scientist and GP, Department of Primary Health Care, University of Oxford

Dr Alan J Williams, Consultant Physician, General and Respiratory Medicine, The Royal Bournemouth Hospital

Observers

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health

Dr Joanna Jenkinson, Board Secretary, Neurosciences and Mental Health Board (NMHB), Medical Research Council

Professor Julietta Patnick, Director, NHS Cancer Screening Programme, Sheffield

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health

Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health

Disease Prevention Panel

Members

Chair,
Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

Dr Robert Cook, Clinical Programmes Director, Bazian Ltd, London

Dr Colin Greaves, Senior Research Fellow, Peninsula Medical School (Primary Care)

Mr Michael Head, Public contributor

Professor Cathy Jackson, Professor of Primary Care Medicine, Bute Medical School, University of St Andrews

Dr Russell Jago, Senior Lecturer in Exercise, Nutrition and Health, Centre for Sport, Exercise and Health, University of Bristol

Dr Julie Mytton, Consultant in Child Public Health, NHS Bristol

Professor Irwin Nazareth, Professor of Primary Care and Director, Department of Primary Care and Population Sciences, University College London

Dr Richard Richards, Assistant Director of Public Health, Derbyshire County Primary Care Trust

Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Dr Kenneth Robertson, Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow

Dr Catherine Swann, Associate Director, Centre for Public Health Excellence, NICE

Mrs Jean Thurston, Public contributor

Professor David Weller, Head, School of Clinical Science and Community Health, University of Edinburgh

Observers

Ms Christine McGuire, Research & Development, Department of Health

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health

Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

External Devices and Physical Therapies Panel

Members

Chair,
Dr John Pounsford,
Consultant Physician North Bristol
NHS Trust

Deputy Chair,
Professor E Andrea Nelson,
Reader in Wound Healing and
Director of Research, University
of Leeds

Professor Bipin Bhakta,
Charterhouse Professor in
Rehabilitation Medicine,
University of Leeds

Mrs Penny Calder,
Public contributor

Dr Dawn Carnes,
Senior Research Fellow, Barts and
the London School of Medicine
and Dentistry

Dr Emma Clark,
Clinician Scientist Fellow & Cons.
Rheumatologist, University of
Bristol

Mrs Anthea De Barton-Watson,
Public contributor

Professor Nadine Foster,
Professor of Musculoskeletal
Health in Primary Care Arthritis
Research, Keele University

Dr Shaheen Hamdy,
Clinical Senior Lecturer and
Consultant Physician, University
of Manchester

Professor Christine Norton,
Professor of Clinical Nursing
Innovation, Bucks New University
and Imperial College Healthcare
NHS Trust

Dr Lorraine Pinnington,
Associate Professor in
Rehabilitation, University of
Nottingham

Dr Kate Radford,
Senior Lecturer (Research),
University of Central Lancashire

Mr Jim Reece,
Public contributor

Professor Maria Stokes,
Professor of Neuromusculoskeletal
Rehabilitation, University of
Southampton

Dr Pippa Tyrrell,
Senior Lecturer/Consultant,
Salford Royal Foundation
Hospitals' Trust and University of
Manchester

Dr Nefyn Williams,
Clinical Senior Lecturer, Cardiff
University

Observers

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Professor Tom Walley, CBE,
Director, NIHR HTA
programme, Professor of Clinical
Pharmacology, University of
Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy
Research Programme, Department
of Health

Interventional Procedures Panel

Members

Chair,
Professor Jonathan Michaels,
Professor of Vascular Surgery,
University of Sheffield

Deputy Chair,
Mr Michael Thomas,
Consultant Colorectal Surgeon,
Bristol Royal Infirmary

Mrs Isabel Boyer,
Public contributor

Mr Sankaran Chandra Sekharan,
Consultant Surgeon, Breast
Surgery, Colchester Hospital
University NHS Foundation Trust

Professor Nicholas Clarke,
Consultant Orthopaedic Surgeon,
Southampton University Hospitals
NHS Trust

Ms Leonie Cooke,
Public contributor

Mr Seumas Eckford,
Consultant in Obstetrics &
Gynaecology, North Devon
District Hospital

Professor Sam Eljamel,
Consultant Neurosurgeon,
Ninewells Hospital and Medical
School, Dundee

Dr Adele Fielding,
Senior Lecturer and Honorary
Consultant in Haematology,
University College London
Medical School

Dr Matthew Hatton,
Consultant in Clinical Oncology,
Sheffield Teaching Hospital
Foundation Trust

Dr John Holden,
General Practitioner, Garswood
Surgery, Wigan

Dr Fiona Lecky,
Senior Lecturer/Honorary
Consultant in Emergency
Medicine, University of
Manchester/Salford Royal
Hospitals NHS Foundation Trust

Dr Nadim Malik,
Consultant Cardiologist/Honorary
Lecturer, University of Manchester

Mr Hisham Mehanna,
Consultant & Honorary Associate
Professor, University Hospitals
Coventry & Warwickshire NHS
Trust

Dr Jane Montgomery,
Consultant in Anaesthetics and
Critical Care, South Devon
Healthcare NHS Foundation Trust

Professor Jon Moss,
Consultant Interventional
Radiologist, North Glasgow
Hospitals University NHS Trust

Dr Simon Padley,
Consultant Radiologist, Chelsea &
Westminster Hospital

Dr Ashish Paul,
Medical Director, Bedfordshire
PCT

Dr Sarah Purdy,
Consultant Senior Lecturer,
University of Bristol

Dr Matthew Wilson,
Consultant Anaesthetist,
Sheffield Teaching Hospitals NHS
Foundation Trust

Professor Yit Chiun Yang,
Consultant Ophthalmologist,
Royal Wolverhampton Hospitals
NHS Trust

Observers

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Professor Tom Walley, CBE,
Director, NIHR HTA
programme, Professor of Clinical
Pharmacology, University of
Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy
Research Programme, Department
of Health

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)

Pharmaceuticals Panel

Members

Chair,
Professor Imti Choonara,
Professor in Child Health,
University of Nottingham

Deputy Chair,
Dr Yoon K Loke,
Senior Lecturer in Clinical
Pharmacology, University of East
Anglia

Dr Martin Ashton-Key,
Medical Advisor, National
Commissioning Group, NHS
London

Dr Peter Elton,
Director of Public Health, Bury
Primary Care Trust

Dr Ben Goldacre,
Research Fellow, Epidemiology
London School of Hygiene and
Tropical Medicine

Dr James Gray,
Consultant Microbiologist,
Department of Microbiology,
Birmingham Children's Hospital
NHS Foundation Trust

Dr Jurjees Hasan,
Consultant in Medical Oncology,
The Christie, Manchester

Dr Carl Heneghan,
Deputy Director Centre for
Evidence-Based Medicine and
Clinical Lecturer, Department of
Primary Health Care, University
of Oxford

Dr Dyfrig Hughes,
Reader in Pharmacoeconomics
and Deputy Director, Centre for
Economics and Policy in Health,
IMSCaR, Bangor University

Dr Maria Kouimtzi,
Pharmacy and Informatics
Director, Global Clinical Solutions,
Wiley-Blackwell

Professor Femi Oyebode,
Consultant Psychiatrist and Head
of Department, University of
Birmingham

Dr Andrew Prentice,
Senior Lecturer and Consultant
Obstetrician and Gynaecologist,
The Rosie Hospital, University of
Cambridge

Ms Amanda Roberts,
Public contributor

Dr Gillian Shepherd,
Director, Health and Clinical
Excellence, Merck Serono Ltd

Mrs Katrina Simister,
Assistant Director New Medicines,
National Prescribing Centre,
Liverpool

Professor Donald Singer,
Professor of Clinical
Pharmacology and Therapeutics,
Clinical Sciences Research
Institute, CSB, University of
Warwick Medical School

Mr David Symes,
Public contributor

Dr Arnold Zermansky,
General Practitioner, Senior
Research Fellow, Pharmacy
Practice and Medicines
Management Group, Leeds
University

Observers

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

Mr Simon Reeve,
Head of Clinical and Cost-
Effectiveness, Medicines,
Pharmacy and Industry Group,
Department of Health

Dr Heike Weber,
Programme Manager, Medical
Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA
programme, Professor of Clinical
Pharmacology, University of
Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy
Research Programme, Department
of Health

Psychological and Community Therapies Panel

Members

Chair,
Professor Scott Weich,
Professor of Psychiatry, University
of Warwick, Coventry

Deputy Chair,
Dr Howard Ring,
Consultant & University Lecturer
in Psychiatry, University of
Cambridge

Professor Jane Barlow,
Professor of Public Health in
the Early Years, Health Sciences
Research Institute, Warwick
Medical School

Dr Sabyasachi Bhaumik,
Consultant Psychiatrist,
Leicestershire Partnership NHS
Trust

Mrs Val Carlill,
Public contributor

Dr Steve Cunningham,
Consultant Respiratory
Paediatrician, Lothian Health
Board

Dr Anne Hesketh,
Senior Clinical Lecturer in Speech
and Language Therapy, University
of Manchester

Dr Peter Langdon,
Senior Clinical Lecturer, School
of Medicine, Health Policy and
Practice, University of East Anglia

Dr Yann Lefeuvre,
GP Partner, Burrage Road Surgery,
London

Dr Jeremy J Murphy,
Consultant Physician and
Cardiologist, County Durham and
Darlington Foundation Trust

Dr Richard Neal,
Clinical Senior Lecturer in General
Practice, Cardiff University

Mr John Needham,
Public contributor

Ms Mary Nettle,
Mental Health User Consultant

Professor John Potter,
Professor of Ageing and Stroke
Medicine, University of East
Anglia

Dr Greta Rait,
Senior Clinical Lecturer and
General Practitioner, University
College London

Dr Paul Ramchandani,
Senior Research Fellow/Cons.
Child Psychiatrist, University of
Oxford

Dr Karen Roberts,
Nurse/Consultant, Dunston Hill
Hospital, Tyne and Wear

Dr Karim Saad,
Consultant in Old Age Psychiatry,
Coventry and Warwickshire
Partnership Trust

Dr Lesley Stockton,
Lecturer, School of Health
Sciences, University of Liverpool

Dr Simon Wright,
GP Partner, Walkden Medical
Centre, Manchester

Observers

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Professor Tom Walley, CBE,
Director, NIHR HTA
programme, Professor of Clinical
Pharmacology, University of
Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy
Research Programme, Department
of Health

Expert Advisory Network

Members

Professor Douglas Altman,
Professor of Statistics in Medicine,
Centre for Statistics in Medicine,
University of Oxford

Professor John Bond,
Professor of Social Gerontology
& Health Services Research,
University of Newcastle upon Tyne

Professor Andrew Bradbury,
Professor of Vascular Surgery,
Solihull Hospital, Birmingham

Mr Shaun Brogan,
Chief Executive, Ridgeway
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Regulation and
Improvement Authority, Belfast

Ms Tracy Bury,
Project Manager, World
Confederation of Physical Therapy,
London

Professor Iain T Cameron,
Professor of Obstetrics and
Gynaecology and Head of the
School of Medicine, University of
Southampton

Professor Bruce Campbell,
Consultant Vascular & General
Surgeon, Royal Devon & Exeter
Hospital, Wonford

Dr Christine Clark,
Medical Writer and Consultant
Pharmacist, Rossendale

Professor Collette Clifford,
Professor of Nursing and Head
of Research, The Medical School,
University of Birmingham

Professor Barry Cookson,
Director, Laboratory of Hospital
Infection, Public Health
Laboratory Service, London

Dr Carl Counsell,
Clinical Senior Lecturer in
Neurology, University of Aberdeen

Professor Howard Cuckle,
Professor of Reproductive
Epidemiology, Department
of Paediatrics, Obstetrics &
Gynaecology, University of Leeds

Professor Carol Dezateux,
Professor of Paediatric
Epidemiology, Institute of Child
Health, London

Mr John Dunning,
Consultant Cardiothoracic
Surgeon, Papworth Hospital NHS
Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon,
Gloucestershire Royal Hospital,
Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness,
Centre for Health Services
Research, University of Newcastle
upon Tyne

Professor Pam Enderby,
Dean of Faculty of Medicine,
Institute of General Practice
and Primary Care, University of
Sheffield

Professor Gene Feder,
Professor of Primary Care
Research & Development, Centre
for Health Sciences, Barts and The
London School of Medicine and
Dentistry

Mr Leonard R Fenwick,
Chief Executive, Freeman
Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher,
Antenatal Teacher and Tutor and
President, National Childbirth
Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, University
of Birmingham

Mr Tam Fry,
Honorary Chairman, Child
Growth Foundation, London

Professor Fiona Gilbert,
Consultant Radiologist and NCRN
Member, University of Aberdeen

Professor Paul Gregg,
Professor of Orthopaedic Surgical
Science, South Tees Hospital NHS
Trust

Bec Hanley,
Co-director, TwoCan Associates,
West Sussex

Dr Maryann L Hardy,
Senior Lecturer, University of
Bradford

Mrs Sharon Hart,
Healthcare Management
Consultant, Reading

Professor Robert E Hawkins,
CRC Professor and Director of
Medical Oncology, Christie CRC
Research Centre, Christie Hospital
NHS Trust, Manchester

Professor Richard Hobbs,
Head of Department of Primary
Care & General Practice,
University of Birmingham

Professor Alan Horwich,
Dean and Section Chairman,
The Institute of Cancer Research,
London

Professor Allen Hutchinson,
Director of Public Health and
Deputy Dean of ScHARR,
University of Sheffield

Professor Peter Jones,
Professor of Psychiatry, University
of Cambridge, Cambridge

Professor Stan Kaye,
Cancer Research UK Professor of
Medical Oncology, Royal Marsden
Hospital and Institute of Cancer
Research, Surrey

Dr Duncan Keeley,
General Practitioner (Dr Burch &
Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme
Director and Reader in
Psychology, Health Services
Research Unit, London School of
Hygiene and Tropical Medicine,
London

Professor James Lindesay,
Professor of Psychiatry for the
Elderly, University of Leicester

Professor Julian Little,
Professor of Human Genome
Epidemiology, University of
Ottawa

Professor Alistaire McGuire,
Professor of Health Economics,
London School of Economics

Professor Neill McIntosh,
Edward Clark Professor of Child
Life and Health, University of
Edinburgh

Professor Rajan Madhok,
Consultant in Public Health, South
Manchester Primary Care Trust

Professor Sir Alexander Markham,
Director, Molecular Medicine
Unit, St James's University
Hospital, Leeds

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Public Health Director,
Southampton City Primary Care
Trust

Dr Sue Moss,
Associate Director, Cancer
Screening Evaluation Unit,
Institute of Cancer Research,
Sutton

Professor Miranda Mugford,
Professor of Health Economics
and Group Co-ordinator,
University of East Anglia

Professor Jim Neilson,
Head of School of Reproductive
& Developmental Medicine
and Professor of Obstetrics
and Gynaecology, University of
Liverpool

Mrs Julietta Patnick,
Director, NHS Cancer Screening
Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe, Stoke
Poges

Professor William Rosenberg,
Professor of Hepatology and
Consultant Physician, University
of Southampton

Professor Peter Sandercock,
Professor of Medical Neurology,
Department of Clinical
Neurosciences, University of
Edinburgh

Dr Philip Shackley,
Senior Lecturer in Health
Economics, Sheffield Vascular
Institute, University of Sheffield

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St
James's University Hospital, Leeds

Dr Margaret Somerville,
Director of Public Health
Learning, Peninsula Medical
School, University of Plymouth

Professor Sarah Stewart-Brown,
Professor of Public Health,
Division of Health in the
Community, University of
Warwick, Coventry

Dr Nick Summerton,
GP Appraiser and Codirector,
Research Network, Yorkshire
Clinical Consultant, Primary Care
and Public Health, University of
Oxford

Professor Ala Szczepura,
Professor of Health Service
Research, Centre for Health
Services Studies, University of
Warwick, Coventry

Dr Ross Taylor,
Senior Lecturer, University of
Aberdeen

Dr Richard Tiner,
Medical Director, Medical
Department, Association of the
British Pharmaceutical Industry

Mrs Joan Webster,
Consumer Member, Southern
Derbyshire Community Health
Council

Professor Martin Whittle,
Clinical Co-director, National
Co-ordinating Centre for Women's
and Children's Health, Lymington

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)