Selenium supplementation to improve bone health in postmenopausal women: the SeMS three-arm RCT

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Scientific summary

The SeMS three-arm RCT

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Scientific summary

Background

About 30% of women aged > 65 years have osteopenia (bone mineral density *T*-score of −1.0 to −2.5). These women are at increased risk of fracture and are likely to develop osteoporosis, but their bone mineral density is not low enough for osteoporosis treatment such as bisphosphonates. Previously, these women may have been offered hormone replacement therapy as a bone protective measure, but adverse events have reduced the use of hormone replacement therapy, so there is a large unmet clinical need.

Selenium is a chemical element present in several human enzymes regulating the pathways for synthesis of thyroid hormones, and in anti-inflammatory and anti-oxidant proteins. Large-scale population data show that selenium status is associated with all-cause mortality and that the optimum range of serum selenium for human health is around 120–150 µg/l. Selenium status is suboptimal in the UK; average serum selenium is about 85 µg/l. Anti-oxidant selenoproteins reduce interleukin 6 and reactive oxygen species, both of which are potent stimuli for osteoclast bone resorption. We have previously published a European study showing that plasma selenium is associated with bone mineral density and bone turnover in a population-based sample of older women. There are also data to suggest associations with muscle function and strength. Subsequent studies by other groups have reported associations between selenium status, bone mineral density and fracture risk.

We hypothesised that selenium supplementation would reduce bone resorption in postmenopausal women through reduced reactive oxygen species. If effective, selenium supplements could be a safe, inexpensive and easily available bone health intervention, and would be attractive to patients because it is perceived as a 'natural' treatment. The potential adverse effects of selenium supplementation are thyroid dysfunction (because selenium is present in thyroid hormone synthesis enzymes) and increased risk of diabetes (from population studies of selenium status but not confirmed by any of the previous randomised supplementation trials).

Objective

The objective was to determine if selenium supplementation in postmenopausal women improved bone health or muscle function.

Methods

We conducted a 6-month double-blind, randomised, placebo-controlled trial of selenium supplementation in 120 postmenopausal women in the UK. The interventions were sodium selenite as Selenase 200 µg/day, Selenase 50 µg/day (biosyn, Germany) and placebo. We chose a dose of 200 µg/day because this dose has shown to be effective for treatment of Graves' eye disease and in some cancer prevention studies. In addition, we estimated that this dose would increase serum selenium to about 120 µg/l. The primary end point was urine N–terminal cross-linking telopeptide of type I collagen/Cr (NTX/Cr), which is a biochemical marker of bone resorption. We used a biochemical marker as the primary end point because biochemical markers are proven to predict bone mineral density change and fracture risk reduction with osteoporosis treatment. Furthermore, biochemical markers change much more quickly than bone mineral density. We chose NTX/Cr as the primary end point because it was the marker that was most strongly correlated with serum selenium in our previous study. Secondary end points were other biochemical markers of bone turnover (procollagen type I N propeptide, C-terminal cross-linking

telopeptide of type I collagen and osteocalcin), bone mineral density by dual-energy X-ray absorptiometry and physical function scores (short physical performance battery and grip strength). Mechanistic end points were markers of inflammation and anti-oxidant activity (glutathione peroxidase, highly sensitive C-reactive protein and interleukin 6). Safety end points were symptoms of selenium toxicity, thyroid function, blood glucose and glycated haemoglobin. The study had 90% power to detect a 20% between-group difference (approximately 10 nmol BCE/mmolCr) in NTX/Cr. The mean NTX/Cr between the groups was compared with an analysis of covariance, adjusting for baseline NTX/Cr. The primary analysis was by intention to treat.

The study recruited to target, and the study was conducted and analysed according to the protocol and statistical analysis plan. The only deviation from the original plan was that we did not make the planned measurement of hydroperoxidases because the commercial assay we planned to use was withdrawn before the study was complete.

Results

In the 200 µg/day group, mean serum selenium increased from 78.8 µg/l to 105.7 µg/l. Urine NTX/Cr did not differ between treatment groups at 26 weeks. None of the secondary or mechanistic end points differed between treatment groups at 26 weeks. The number and type of adverse events were similar between groups.

Conclusions

We conclude that selenium supplementation at these doses does not affect bone turnover (assessed by NTX/Cr) and is not beneficial for musculoskeletal health in postmenopausal women.

Trial registration

This trial is registered as IRAS 200308, EUDRACT 2016-002964-15 and Clinicaltrials.gov NCT02832648.

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