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Selenium and bone health: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Bone health affects the ability of human body to stay active, and its degradation can cause considerable morbidity and mortality. The factors related to bone health play an important role in preventing osteoporosis and its adverse consequences. However, the risk factors for osteoporosis have not been fully elucidated. Deficiency in the trace element selenium may be one of the risk factors for the development of osteoporosis. Previous studies have investigated the effects of selenium on osteoporosis; however, the results are inconclusive. Therefore, the present study aimed to systematically examine the existing literature on the associations between dietary or serum selenium and bone mineral density (BMD), osteoporosis or osteoporotic fractures, and to quantify such associations through meta-analysis.

Methods and analysis PubMed, Embase and Cochrane Library will be searched using a specified search strategy to identify relevant studies up to October 2019. Both interventional and observational studies in humans will be included. The outcomes will include BMD and the prevalence or incidence of osteoporosis and osteoporotic fractures. For dietary or serum selenium and BMD, osteoporosis or osteoporotic fractures pooled analyses, estimates will be expressed as the mean difference, and the pooled OR, relative risk, HR or beta coefficient, and corresponding 95% CIs. Heterogeneity of the studies and publication bias will be investigated accordingly. To assess the quality and the risk of bias of the included studies, the Newcastle-Ottawa Quality Scale or the Cochrane risk of bias assessment tool will be used where appropriate.

Ethics and dissemination Since no private and confidential patient data will be included in the reporting, approval from an ethics committee is not required. The results will be published in a peer-reviewed journal. The study raises no ethical issues.

PROSPERO registration number CRD42019147188.

Strengths and limitations of this study

- As the first meta-analysis to evaluate the associations between dietary selenium intake or serum selenium concentrations and bone mineral density, osteoporosis or osteoporotic fractures, the findings of this study will deepen the existing knowledge base on the pathogenesis of osteoporosis and promote the development of effective preventive or treatment strategies.
- Two investigators will perform the study selection, data extraction and quality assessments independently, and disagreements will be resolved by discussions.
- Both quality and risk of bias of the included studies will be properly assessed using the Newcastle-Ottawa Quality Scale or the Cochrane risk of bias assessment tool where appropriate.
- Both prospective and retrospective studies will be included in this meta-analysis, which may also incur bias and impact the final results, and the differences in study design and sample characteristics may lead to a high level of heterogeneity.
- We wish to investigate the associations between selenium and the different types of primary and secondary osteoporosis; however, such subgroup analysis is difficult or even impossible given the small number of studies that will probably be included.

INTRODUCTION

Bone health affects the ability of the human body to stay active throughout life, and its degradation can cause considerable morbidity and mortality.[1 2] The various factors related to bone health at different ages play an important role in preventing osteoporosis and its adverse consequences.[3] Bone health is mainly reflected in diseases caused by bone mass loss, such as osteoporosis and fragility fracture.[4 5] Osteoporosis, which is characterised by low bone mass and microarchitectural deterioration of bone tissue, is a systemic skeletal disease that can result in increased bone fragility and increased fracture risk as a consequence.[3 6] With an ageing population, the socioeconomic and medical impact of osteoporosis will increase rapidly. It is estimated that by 2020 there will be over 200 million people worldwide affected by osteoporosis, and the expenses related to osteoporosis will rise to about $25.3 billion by 2025.[7] Osteoporosis is practically diagnosed by the presence of a fragility fracture or low bone mineral density (BMD), which is a commonly used

proxy measure that accounts for approximately 70% of bone strength.[3] However, osteoporosis can occur without a known underlying cause, and its risk factors have not been fully elucidated.

Nutrition has a significant influence on bone health, and adequate nutrition is among the crucial cornerstones in the prevention of osteoporosis.[8] The trace element selenium, as a critical constituent of about 25 selenoenzymes, plays an essential role in a variety of physiological processes, and it has been confirmed that the beneficial effects of selenium are related to human health.[9 10] Some studies collectively suggested that the preservation of selenoproteins in bone was essential for normal skeletal development.[11] Animal studies have shown that selenium deprivation can retard growth and change bone metabolism.[12] Such effects are associated with reduced BMD, impaired bone microarchitecture and increased bone resorption. Previous clinical studies have investigated the effects of selenium on bone health; however, the results are inconclusive. Some suggested that serum and dietary selenium were positively correlated with BMD,[13 14] while others showed that neither serum nor dietary selenium was associated with osteoporosis.[15 16] Meanwhile, some case–control studies revealed that dietary intake of selenium was associated with reduced risk of osteoporotic hip fracture.[17 18]

Meta-analysis is an effective tool for revealing trends that may not be apparent and also helps in establishing clinical policies and guidelines. Thus, we aimed to systematically examine the existing literature in this field to test the hypothesis that dietary or serum selenium concentrations are associated with BMD, osteoporosis or osteoporotic fractures.

METHODS

Study design

The aim of this meta-analysis is to investigate the associations between dietary intake or serum levels of selenium and BMD, osteoporosis or osteoporotic fractures. This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement,[19] and has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) network.

Eligibility criteria

Types of studies

The meta-analysis will include both interventional and observational studies in humans, inclusive of case–control studies, randomised controlled trials, cross-sectional studies and cohort studies which focus on the associations between dietary intake or serum levels of selenium and BMD, osteoporosis or osteoporotic fractures.

Types of participants

The participants in the included studies must have provided information on dietary intake or serum levels of selenium, and BMD measures or diagnosis of osteoporosis or osteoporotic fractures. No age, sex, ethnicity, economic status, geographical limitations or education restrictions will be applied.

Types of exposure/intervention

Two main forms of exposure will be included, that is, dietary intake of selenium and serum levels of selenium.

Types of outcome measures

The primary outcomes will include T-score, BMD values and the prevalence or incidence of osteoporosis. The diagnostic criteria of osteoporosis shall be based on the WHO criteria.[20] A T-score between 0 and −1 is considered normal and a T-score ≤−2.5 is considered osteoporosis. BMD corresponds to osteopaenia if the T-score ranges between −1 and −2.5. Osteoporosis is classified as 'primary' and 'secondary', and secondary osteoporosis is due to certain clinical disorders independent of age and oestrogen deficiency.[21] We will catalogue and categorise the different types of primary and secondary osteoporosis according to the included studies. The secondary outcome will be the prevalence or incidence of osteoporotic fractures. There will be no restriction on site and measuring method, but we will give priority to extracting T-score for analysis rather than to extracting BMD values. When T-score is not available, we will try to analyse BMD measured with Lunar and Hologic machines separately.

Information sources

Systematic literature searches will be undertaken across PubMed, Embase and Cochrane Library using a specified search strategy to identify relevant studies up to October 2019 on each platform or database. In addition, the references of the retrieved literature will be manually searched. Study registries will also be searched for grey literature (eg, ClinicalTrials.gov and Google Scholar). Relevant studies and systematic reviews will be scanned for additional eligible studies.

Search strategy

Keyword terms or medical subject heading terms will be used to search for eligible studies in the databases mentioned. The electronic search strategy is presented in table 1. All the search terms will be adapted according to the different syntax rules of the databases.

Study selection

The search results from the three electronic databases will be sent to EndNote. After removing duplicates, two investigators will be responsible for screening the titles and abstracts of all the retrieved literature to identify eligible studies. In case the eligibility of a study cannot be determined, the full text will be reviewed for inclusion according to prespecified inclusion and exclusion criteria. There will be no restriction on publication date and language. The study selection process will be summarised based on the PRISMA flow diagram.

Table 1 Electronic search strategy in PubMed

Number	Search terms
1	selenium[mesh] or "selenious acid"[mesh] or selen*[tiab] or selepen[tiab] or organoselen*[tiab] or natriumselen*[tiab] or methylseleninic[tiab] or methylselenium[tiab] or selenomethionin*[tiab] or selenit*[tiab)
2	bone demineralization[mesh] or bone density[mesh] or osteopenia[mesh] or osteoporosis[mesh] or bone densitometry[mesh] or osteoporo*[tiab] or bone densit*[tiab] or bone loss[tiab] or osteomalacia[tiab] or osteodystrophy[tiab] or bone demineral?ation[tiab] or osteopenia[tiab] or bone mass[tiab] or bone mineral content*[tiab] or bone defect*[tiab] or bone strength[tiab] or BMC[tiab] or "fracture"[mesh] or fracture* [tiab)
3	1 AND 2

Disagreements between the two investigators will be resolved by discussing with a third investigator.

Data extraction

Two investigators will be engaged in independently extracting the following data in a standardised collection form: publication information (author, year of publishing); study information (country of origin, study setting, data sources, study period); demographic information (sample size, age, sex distribution); exposure information (dietary or serum selenium concentrations); and outcome information (T-score, BMD values, prevalence or incidence of osteoporosis or osteoporotic fractures). Then, both the adjusted and unadjusted effect sizes (mean difference (MD), OR, relative risk (RR), HR or beta coefficient (β)) will be either extracted directly or calculated based on the information in the original studies whenever possible. If relevant data are not reported in an included study, the missing information will be obtained by contacting the authors directly as far as possible. The two investigators responsible for reviewing the literature will resolve any disagreements through discussions, and a third independent investigator may be involved into the discussion if required.

Assessment of risk of bias

The Cochrane risk of bias assessment tool will be used to assess the quality of randomised controlled trials,[22] while the Newcastle-Ottawa Quality Scale will be used to assess the quality of observational studies.[23] Two investigators will be engaged in conducting risk of bias assessment independently, and disagreements will be resolved through discussions.

Data analysis

First, the characteristics of the included studies will be summarised using baseline tables and narrative texts. The proposed study will calculate the MD, the pooled OR, RR, HR or β, and the corresponding 95% CIs. Unadjusted risk estimates and adjusted estimates will be pooled in the meta-analysis. Then, Cochrane's Q test and the I^2 statistics will be used to assess the heterogeneity of the included studies, where $p>0.05$ of the Q statistics and I^2 value <50% indicate statistical homogeneity.[24 25] If the included studies are found to be statistically homogeneous, the fixed effects models will be used to pool the data during meta-analysis; otherwise, the random effects models will be used instead. Statistical analyses will be conducted in Review Manager V.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) and Stata V.11.0 statistical software. Statistical significance is considered at $p<0.05$. Finally, to minimise heterogeneity between included studies, subgroup analyses based on different age, sex, ethnicity, economic status, geographical limitations, education restrictions or causes of osteoporosis will be conducted where feasible.

Assessment of publication bias

If the number of included studies is greater than 10, a funnel plot will be constructed and the Egger test will be conducted to observe publication bias. The existence of publication bias is confirmed when the funnel plot shows an asymmetric pattern. Then, bias, if any, will be explained through discussions after assessment.

Patient and public involvement

As our systematic review will be implemented based on published studies, no patients and members of the public will be directly involved. All the data to be used in this study already exist in published literature and/or the aforementioned sources.

Ethics and dissemination

As this meta-analysis will be performed based on published studies and no private and confidential patient data will be included in the reporting, approval from an ethics committee is not required. The results will be disseminated through publication in a peer-reviewed journal. The study raises no ethical issues.

DISCUSSION

The health of the skeletal system is important for elderly people.[1] An indepth understanding of the relationship between selenium and bone health is useful for designing early life interventions. Selenoproteins expressed in human fetal osteoblasts would appear to protect the bone against oxidative stress, which may contribute to the development of osteoporosis by inhibiting osteoblastic differentiation of bone marrow stromal cells.[26 27] The trace element selenium, as a critical constituent of selenoproteins, is much more likely to have an essential role in the associations between selenium and BMD. To our best knowledge, there are at least 10 studies that have investigated the associations between dietary or serum selenium concentrations and BMD, osteoporosis or osteoporotic fractures. Of them, two studies suggested that serum and

dietary selenium were likely to positively correlate with BMD,[13 14] and three studies showed that dietary selenium was negatively associated with osteoporotic fractures.[17 18 28] On the contrary, one study found no association between dietary selenium and BMD,[29] and four studies reported that neither serum nor dietary selenium was related to osteoporosis.[15 16 30 31] Contradictory results of these studies might be related to differences in study design and sample characteristics. So it remains controversial whether the content of selenium can directly influence BMD and affect the pathogenesis of osteoporosis. The sample size of previous studies might have been too small to achieve sufficient statistical power, which could explain, at least in part, why statistical difference in some instances was not reached, despite the obvious trends. Therefore, the aim of this systematic review and meta-analysis is to summarise the available evidence to investigate the associations between selenium and bone health. The results of this study will deepen the existing knowledge base on the pathogenesis of osteoporosis and promote the development of preventive or treatment strategies in this field.

Contributors Conceptualisation: YW and DX. Data curation: JW, ZW, HH, ZY. Methodology: JW, ZW, HH, ZY. Writing of original draft: NW and DX. Review and editing: YW and TY.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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