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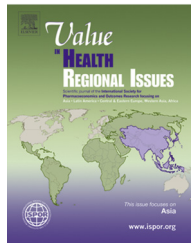

Lifestyle-Related Metabolic Disorders, Osteoporosis, and Fracture Risk in Asia: A Systematic Review

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ABSTRACT

Background: The prevalence of both lifestyle-related metabolic disorders and osteoporosis is increasing in Asia. **Objectives:** To conduct a systematic review of the published literature to identify studies examining disorders of glucose and lipid metabolism (type 2 diabetes, hyperglycemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, metabolic syndrome [MetS], and atherosclerosis) as risk factors for osteoporosis and fracture in Asian populations. Studies examining the relationship between metabolic disorders and bone mineral density (BMD) were also included. **Methods:** EMBASE (including MEDLINE) and the Cochrane Library were searched. Studies conducted only within Asia, which reported multivariate analysis with a sample size of 200 or more subjects, were included. **Results:** A total of 32 studies were included. All six studies examining diabetes and fracture found that subjects with diabetes had a significantly higher risk of fracture than did subjects without diabetes (risk estimate range 1.26–4.73). Two studies found that subjects with atherosclerosis had a significantly higher risk of fracture (risk estimate range 1.10–2.52). Studies consistently reported that MetS is likely associated with osteoporosis or decreased BMD in men but not women. No consistent association was found for diabetes and BMD, with studies reporting contrasting results. There was limited evidence investigating lipid metabolism and hyperglycemia and risk of fracture or bone loss in Asian populations. **Conclusions:** These findings suggest that diabetes is a risk factor for fracture in Asian populations. MetS may be associated with bone loss in Asian men and atherosclerosis associated with increased fractures; however, caution is needed interpreting these findings given limitations in study design.

Keywords: atherosclerosis, fracture, metabolic disorders, metabolic syndrome, osteoporosis, type 2 diabetes.

Introduction

Osteoporosis is a skeletal disorder characterized by decreased bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and susceptibility to fracture. Osteoporosis affects more than 200 million people worldwide [1]. The International Osteoporosis Foundation projects that by 2050 more than 50% of all osteoporotic fractures will occur in East and Southeast Asia [2]. Osteoporosis-related fractures have a major impact on patients' quality of life and health care costs [2].

Lifestyle-related metabolic disorders include disorders of glucose metabolism (e.g., diabetes and hyperglycemia) and lipid metabolism (e.g., hypercholesterolemia and dyslipidemia). Metabolic syndrome (MetS) consists of a combination of impaired glucose metabolism, dyslipidemia, elevated blood pressure, and obesity. These metabolic disorders are all important risk factors for the development of atherosclerosis [3], which is caused by the slow, progressive accumulation of lipid plaques in arterial walls.

The International Diabetes Federation estimates that more than 200 million people in East and South-East Asia have diabetes [4]. Furthermore, the prevalence of MetS in Asia is increasing to similar levels seen in Western countries [5,6]. Increased dietary consumption of fat and sugar, as well as decreased physical activity and above normal weight gain, has contributed to an increase in the prevalence of lifestyle-related metabolic disorders in Asia. In addition, healthy East and South-East Asians have been shown to have a higher percentage of body fat than do Caucasians at a given body mass index (BMI). Lower insulin sensitivity has also been reported in South Asian populations, suggesting greater genetic susceptibility to developing lifestyle-related metabolic disorders [6,7]. Research has also shown that Japanese subjects are at an increased risk of type 2 diabetes due to lower insulin secretion capacity [8,9].

The recent Japan Osteoporosis Society handbook has highlighted lifestyle-related metabolic disorders as potential risk factors for osteoporosis and fracture [10]. Research shows that

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glucose/fat metabolism and bone metabolism are linked. Insulin signaling regulates the differentiation of osteoblast cells and bone resorption by osteoclasts [11,12]. Furthermore, increased insulin resistance and body fat is associated with decreased osteocalcin levels [13]. Thus, it is hypothesized that imbalances in glucose/fat metabolism may affect bone quality, leading to the development of osteoporosis.

A systematic review of epidemiological studies found diabetes to be a risk factor for fracture in the United States and Europe [14]. At the time of the review (2006), there were no studies included in the review from Asia. In contrast, a meta-analysis examining the association of MetS and fracture suggested that MetS may have a small protective effect [15]. The authors noted caution in interpreting this finding, with a high degree of heterogeneity and wide confidence intervals (CIs) observed.

Meta-analyses examining the relationship between metabolic disorders and bone loss have produced differing results. Two meta-analyses showed that subjects with diabetes had higher bone mineral density (BMD) compared with subjects without diabetes [16,17]. Another meta-analysis found that subjects with and without MetS had similar BMD [15], whereas another review concluded that MetS is associated with increased risk for osteoporosis in men but not women [18]. A high degree of heterogeneity, both in the populations included and results found, was observed between studies included in the meta-analyses.

Given the rapidly increasing rate of lifestyle-related metabolic disorders, the aim of this systematic review was to summarize all published studies on the association between disorders of glucose and lipid metabolism (specifically type 2 diabetes, hyperglycemia, lipid metabolism, MetS, and atherosclerosis) and risk of fracture and osteoporosis in Asian populations. The relationship between metabolic disorders and BMD was also examined.

Methods

Literature Search Strategy

A systematic review of the published literature was conducted to identify studies examining metabolic disorders as risk factors for osteoporosis and fracture as well as studies examining the relationship between metabolic disorders and BMD. The databases searched were EMBASE.com (includes MEDLINE and EMBASE) (January 1, 1990, to October 8, 2013), and the Cochrane Library (to October 8, 2013). The overall search strategy included terms for osteoporosis, BMD, fracture, diabetes, metabolic syndrome, atherosclerosis, hyperglycemia, hypercholesterolemia, hyperlipidemia, and dyslipidemia. The search was not limited by country or language. In addition, a manual search of the references of relevant systematic reviews and included studies was conducted. The literature search strategies for EMBASE.com and Cochrane databases are included in Appendix Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.09.005.

Selection Criteria

Studies reporting the following risk factors were included:

- Type 2 diabetes
- Hyperglycemia
- Hypercholesterolemia, hyperlipidemia, and dyslipidemia
- MetS
- Atherosclerosis

Only those studies that reported the definition of risk factors used were included. Studies specifically in type 1 diabetes were excluded. Studies that did not distinguish between type 1 and type 2 diabetes were included.

Only studies conducted within Asia (including East, Southeast, and South Asia and the Middle East), which reported multivariate analysis in a sample size of 200 or more subjects, were included. A sample size cutoff of 200 was chosen to allow for dropout, confounding, and missing data for covariates. For fractures, studies reported risk estimates (odds ratio, hazard ratio, or relative risk) and corresponding CIs. For BMD, studies reported risk estimates for osteoporosis (i.e., BMD *T* score <-2.5) or osteopenia (i.e., BMD *T* score <-1 and >-2.5). In addition, studies reporting mean values of BMD and variance (standard errors, SDs, or 95% CIs) in patients with and without metabolic disorders were included. When studies reported multiple sites, BMD of lumbar spine (LSBMD), femoral neck (FNBMD), and total hip (THBMD) were included in the review.

Data Extraction and Quality Assessment

Data were extracted independently by two reviewers (F.D. and B. A.). The following data were retrieved from each article: first author, year of publication, year of patient recruitment, country where study was conducted, study design, length of follow-up (if applicable), participant inclusion/exclusion criteria, method of risk factor disease diagnosis, sample size, age, sex, controlled variables, adjusted fracture and osteoporosis risk estimates with corresponding 95% CIs, adjusted mean BMD, and corresponding standard errors, SDs, or 95% CIs.

Study quality was assessed using checklists for cohort and case-control studies developed by the Scottish Intercollegiate Guidelines Network [19]. Studies were assessed as ++ (high quality: most of the criteria met; little or no risk of bias. Results unlikely to be changed by further research), + (acceptable: most criteria met. Some flaws in the study with an associated risk of bias. Conclusions may change in the light of further studies) or 0 (low quality: either most criteria not met, or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies).

Results

A total of 6168 publications were identified from the literature search, including 5967 from EMBASE.com, 195 from Cochrane database, and 6 from a hand search of references from relevant studies. Following the review of titles and abstracts, 6115 were excluded and the remaining 53 articles were sourced for full-text review. After reviewing the full text, 21 articles were excluded (Fig. 1). Ultimately, the literature search identified 32 studies for inclusion [20–51].

The characteristics of included studies are summarized in Table 1. There were 28 studies conducted in East and Southeast Asia (9 studies in South Korea, 6 studies in Japan, 3 studies in mainland China, 3 studies in Hong Kong, 5 studies in Taiwan, 1 each in the Philippines and Singapore) and 4 in the Middle East (2 studies in Jordan, 1 each in Turkey and Israel). Most of the studies were cross-sectional study design (24 studies), with four retrospective cohort, two prospective cohort, and two case–control.

Diabetes was the most commonly reported metabolic disorder (16 studies including 6 specifically in type 2 diabetes), followed by MetS (10 studies), atherosclerosis (5 studies), lipid disorders (3 studies), and hyperglycemia (1 study). There were 10 studies examining the risk of fracture, 8 studies examining the risk of osteoporosis (defined as BMD *T* score <-2.5 in 5 studies), and 14 studies reporting differences in BMD between patients with and without metabolic disorders.