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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.

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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, South-east, 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.

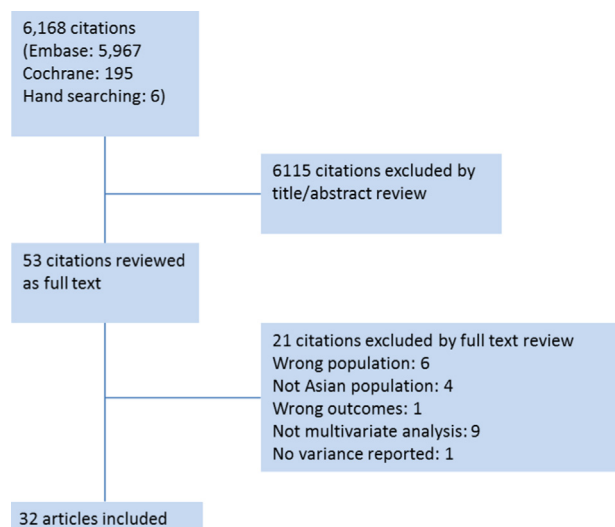


Fig. 1 – Flow diagram of study selection.

Most studies were assessed as adequate quality (+), which was the highest quality score that could be assigned to studies with a cross-sectional or retrospective design. One prospective cohort study was rated as high quality (++) (Table 1). All studies met at least 70% of applicable criteria. Importantly, all studies reported well-defined outcomes and appropriately adjusted for confounders via multivariate analyses.

The studies varied in patient inclusion/exclusion criteria (see Appendix Table 4 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.vhri.2015.09.005>). There were 13 studies that included both men and women, 2 studies in men only and 17 studies in women only. Of the studies in women, 14 studies specified postmenopausal. In general, larger, population-based studies had less restrictive exclusion criteria compared with smaller studies. Common exclusion criteria were patients taking osteoporosis medication (17 studies), hormone medication (13 studies), or with other disorders known to affect bone metabolism (9 studies).

Studies reporting risk estimates (relative risk [RR], odds ratio [OR], hazard ratio) for fracture or osteoporosis are summarized in Figs. 2 and 3. Further details of these studies are presented in Appendix Table 5 in Supplemental Material found at <http://dx.doi.org/10.1016/j.vhri.2015.09.005>. In addition, there were three studies reporting mean difference in BMD between patients with and without metabolic disorders [24,37,38] (see Appendix Table 5). Appendix Table 2 summarizes cross-sectional studies reporting mean BMD for patients with and without metabolic disorders. For most of the studies, the metabolic risk factor was the predictor, with fracture, osteoporosis, or BMD as the outcome. In addition, two studies [22,23] presented osteoporosis as the predictor and atherosclerosis as the outcome.

Studies varied in the potential confounders, which were adjusted for in the analyses (see Appendix Table 5). The most commonly controlled variables were age (29 studies), BMI or weight (22 studies), and smoking (18 studies).

Atherosclerosis

Two studies reported the risk of fractures associated with atherosclerosis [20,21] (Fig. 2). Both studies found that subjects with atherosclerosis had a significantly higher risk of fracture than did subjects without atherosclerosis (risk estimate range 1.10–2.52).

Two studies examined the relationship between atherosclerosis and bone loss [22,23]. Choi et al. [22] reported that women but not men with a BMD T score of less than -1.5 (i.e., including subjects with osteoporosis or osteopenia) had a significantly higher risk of atherosclerosis (OR 5.84; 95% CI 1.09–31.20) (Fig. 3). Tamaki et al. [23] reported that women with osteoporosis (BMD T score <-2.5) had higher intima-media thickness of carotid bifurcation (a measure of atherosclerosis development) (Appendix Table 2).

Two studies reported BMD in subjects with and without atherosclerosis [22,24]. Wong et al. [24] reported that subjects with atherosclerosis had significantly lower THBMD than did subjects without atherosclerosis (see Appendix Table 5). This was not significant for LSBMD. Choi et al. [22] did not report a significant association between BMD and atherosclerosis (Appendix Table 2).

Diabetes

All 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) [25–30] (Fig. 2). This included the high-quality, prospective cohort study by Koh et al. [28], which found that men and women with diabetes were at a significantly higher risk of hip fracture (RR 1.98; 95% CI 1.71–2.29).

Six studies examined diabetes as a risk factor for osteoporosis (as defined by BMD) [31–36] (Fig. 3). Of these, two studies in women [31,32] and one study in men and women [33] reported that patients with diabetes had a higher risk of osteoporosis. In contrast, two studies in women reported a lower risk [34,35]. Shan et al. [35] reported a significantly lower risk when osteoporosis was assessed at the spine (OR 0.68; 95% CI 0.56–0.83) but not at femoral neck or total hip. One study reported no significant association between osteoporosis and type 2 diabetes; however, wide CIs were reported [36].

Four studies reported BMD in subjects with and without diabetes [37–40] (see Appendix Tables 2 and 5 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.vhri.2015.09.005>). Two studies found that men and women with diabetes had significantly higher BMD than did subjects without diabetes [37,38]. One study reported significantly lower BMD [39], and one study reported no significant difference [40]. Notably, neither study controlled for age, BMI, or weight in the analysis.

Metabolic Syndrome

In one study reporting fractures, MetS was not associated with fracture risk [41] (Fig. 2). Kim et al. [42] found that men but not women with MetS had a significantly increased risk of osteopenia or osteoporosis (OR 1.49; 95% CI 1.04–2.14) (Fig. 3).

Eight studies reported BMD in subjects with and without MetS [43–50] (Appendix Table 2). Two studies reported that men with MetS have significantly lower FNBMD or THBMD than did men without MetS [43,44], whereas one study observed no significant difference in men [45].

Three studies reported significantly lower LSBMD or FNBMD in women with MetS compared with subjects without MetS [43,46,47]. Four studies reported no significant difference at LSBMD, FNBMD, or foot BMD [44,45,48,49]. One longitudinal study reported that women with MetS have significantly less reduction in LSBMD and FNBMD than do women without MetS [50].

Lipids

Two studies reported the risk of fractures associated with lipid levels [30,51] (Fig. 2). No association was found between fracture and hypercholesterolemia [51] or dyslipidemia [30]. Women with

Table 1 – Study characteristics.

Publication ID	Country	Study type	Time period (year)	Metabolic disorder	Diagnosis definition	Outcome	Length of follow-up	Quality assessment of study
Lai et al. [20]	Taiwan	Retrospective cohort	2000–2007 (baseline)	Atherosclerosis	ICD-9 440–448	Fracture	6 y	+
Wada et al. [21]	Japan	Cross-sectional	2008–2009	Atherosclerosis	Breast arterial calcification	Fracture	NA	+
Choi et al. [22]	Korea	Cross-sectional	2005–2008	Atherosclerosis	Aortic valve sclerosis	Osteoporosis	NA	+
Tamaki et al. [23]	Japan	Prospective cohort	1996–2006	Atherosclerosis	Intima-media thickness of carotid bifurcation	BMD	10 y	+
Wong et al. [24]	Hong Kong	Cross-sectional	2001–2004	Atherosclerosis	Peripheral vascular disease as ankle brachial index <0.90	BMD	NA	+
Chen et al. [25]	Taiwan	Retrospective cohort	1997–2002	Diabetes	ICD-9 250 or A code 181	Fracture	NA	+
Segal et al. [26]	Israel	Case-control	NR	Diabetes	Medical examination	Fracture	NA	+
Yamamoto et al. [27]	Japan	Cross-sectional	NR	Diabetes type 2	Referred to clinic for treatment of diabetes	Fracture	NA	+
Koh et al. [28]	Singapore	Prospective cohort	1993–1998 (baseline)	Diabetes	Physician-diagnosed diabetes	Fracture	12.2 y	++
Soong et al. [29]	Taiwan	Retrospective cohort	2004–2005 (baseline)	Diabetes	NR	Fracture	1 y	+
Tatsuno et al. [30]	Japan	Cross-sectional	2001–2009	Diabetes Dyslipidemia	Medical history	Fracture	NA	+
Li et al. [31]	China	Cross-sectional	1998–2008	Diabetes	Medical history of diabetes	Osteoporosis	NA	+
El-Heis et al. [32]	Jordan	Cross-sectional	2009–2010	Diabetes	Medical history of diabetes	Osteoporosis	NA	+
Shaw 1993 [33]	Taiwan	Cross-sectional	1988–1989	Diabetes	Medical history of diabetes	Osteoporosis	NA	+
Romana and Li-Yu [34]	Philippines	Case-control	2000–2003	Diabetes type 2	Medical history of diabetes	Osteoporosis	NA	+
Shan et al. [35]	China	Cross-sectional	1997–2005	Diabetes type 2	American Diabetes Association	Osteoporosis	NA	+
Shilbayeh 2003 [36]	Jordan	Cross-sectional	2000–2002	Diabetes type 2	Medical history of diabetes	Osteoporosis	NA	+
Khoo et al. (Ms OS) [37]	Hong Kong	Cross-sectional	2002–2003	Diabetes	Patient questionnaire	BMD	NA	+
Lau et al. (Mr OS) [38]	Hong Kong	Cross-sectional	NR	Diabetes	Patient questionnaire	BMD	NA	+
Chen et al. [39]	China	Cross-sectional	2007–2008	Diabetes type 2	WHO criteria	BMD	NA	+
Anaforoglu et al. [40]	Turkey	Cross-sectional	2005–2006	Diabetes type 2	Physician-diagnosed diabetes	BMD	NA	+
Kim et al. [41]	Korea	Cross-sectional	NR	MetS	NCEP-ATP III criteria	Fracture	NA	+
Kim et al. [42]	Korea	Cross-sectional	2005	MetS	AHA/NHLBI criteria	Osteoporosis	NA	+
Kim et al. [43]	Korea	Cross-sectional	2005–2006	MetS	AHA/NHLBI criteria	BMD	NA	+
Kim et al. [44]	Korea	Cross-sectional	2008–2010	MetS	AHA/NHLBI criteria	BMD	NA	+
Tseng et al. [45]	Taiwan	Cross-sectional	2007	MetS	NCEP-ATP III criteria	BMD	NA	+
Hwang and Choi [46]	Korea	Cross-sectional	2006–2007	MetS Hypertriglyceridemia Hyperglycemia	NCEP-ATP III criteria	BMD	NA	+
Jeon et al. [47]	Korea	Cross-sectional	2006–2009	MetS	AHA/NHLBI criteria	BMD	NA	+
Park et al. [48]	Korea	Cross-sectional	2004–2008	MetS	NCEP-ATP III criteria	BMD	NA	+

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Sanada et al. [49]	Japan	Cross-sectional	2004–2009	MetS	BMD	NA	+
					(1) Body mass index ≥ 25 kg/m ² ; plus one other risk factor: (2) blood pressure ≥ 130 mmHg systolic and/or ≥ 85 mmHg diastolic; (3) triglycerides ≥ 150 mg/dl and/or HDL-cholesterol ≤ 40 mg/dl; and (4) fasting plasma glucose ≥ 110 mg/dl		
Kim et al. [50]	Korea	Retrospective cohort	2007 (baseline)	MetS	NCEP-ATP III criteria	BMD	+
Yamaguchi et al. [51]	Japan	Cross-sectional	NR	Lipids	Normal range: Total-C, 146–233 mg/dl; HDL-C 43–65 mg/dl; TG, 28–147 mg/dl; LDL-C, <130 mg/dl)	Fracture	+

AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; BMD, bone mineral density; HDL, high-density lipoprotein; ICD-9, International Classification of Diseases, Ninth Revision; MetS, metabolic syndrome; NA, not applicable; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; NR, not reported; TG, triglyceride; WHO, World Health Organization.

high triglycerides had a significantly lower risk of fractures (OR 0.51; 95% CI 0.29–0.89) [51]. In contrast, women with high triglycerides had lower LSBMD [46].

Hyperglycemia

There was no significant difference in BMD between subjects with and without hyperglycemia [46] (Appendix Table 2).

Discussion

Evidence presented in this review suggests that diabetes is a risk factor for fracture in Asian men and women. The association between diabetes and fracture was observed in both men and women and for all fracture sites presented in the included studies. In particular, three studies found an association between diabetes and increased hip fracture risk. This association was also consistent for studies carried out in different regions within Asia. Importantly, this included high-quality evidence from prospective cohort studies suggesting a strong association between diabetes and fracture. This confirms the findings of a previous systematic review that found that diabetes was strongly associated with increased risk of hip fracture in US and European populations [14].

In contrast, the present review did not find a consistent association between diabetes and BMD in Asian populations. There was a high degree of heterogeneity between studies, which reported contrasting results. This finding differs somewhat from a previous meta-analysis in predominantly US and European populations, which demonstrated that patients with diabetes have a higher BMD [17]. Another recent meta-analysis reported a similar finding [16], although a high degree of heterogeneity was also noted, for which Asian ethnicity was a significant source. The reasons for greater heterogeneity in Asian populations are unclear. Notably, studies reporting this association in the present review were from diverse regions across Asia. As such, there may be cultural or lifestyle differences that account for the differences in findings. For example, studies have consistently shown that higher socioeconomic development is associated with increased risk of fractures [52]. Dietary calcium and vitamin D levels also differ between regions, with very high levels of vitamin D deficiency in postmenopausal women in Japan and Korea [53]. Genetic differences may also be important. The risk of fracture has heritable elements that are independent of BMD such as differences in bone geometry, size, and height [52,54]. Further prospective, longitudinal studies are needed to explore the interaction between diabetes and other potential risk factors on BMD and fracture in Asian populations. That diabetes may increase fracture risk without negatively affecting BMD appears to be counterintuitive. It has been suggested, however, that diabetes affects aspects of bone quality other than BMD, or other factors that are completely independent of bone metabolism. For example, diabetes may accelerate the formation of advanced glycation end products in bone, which causes oxidative stress and affects bone collagen quality [55–57]. Diabetic patients may also have an increased risk of falls due to diabetic retinopathy or peripheral neuropathy [58,59].

The present review suggests that Asian men with MetS may be at a higher risk of bone loss, a finding supported by a recent meta-analysis [18]. In addition, a lower BMD was reported in men with MetS than in men without MetS in two studies [43,44] with no significant difference reported in a third study [45]. Again, this finding should be interpreted with caution because studies examining this relationship were of cross-sectional design. In contrast, the relationship between MetS and bone loss in Asian women is unclear, with studies showing contrasting results. The

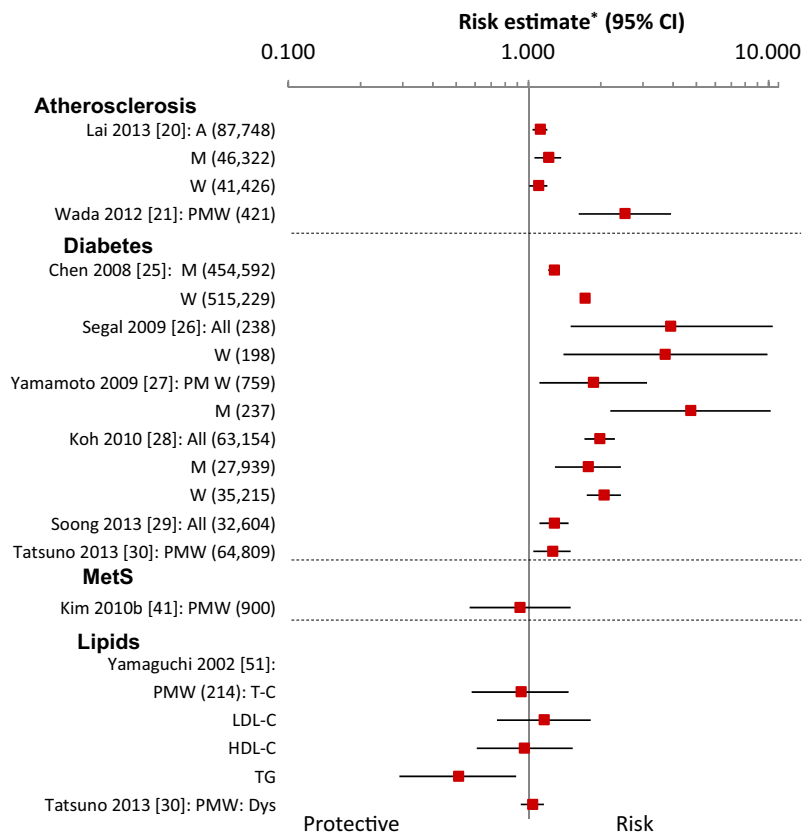


Fig. 2 – Association between metabolic disorders and fracture. A, all patients; Dys, dyslipidemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; M, men; MetS, metabolic syndrome; PMW, postmenopausal women; T-C, total cholesterol; TG, triglyceride; W, women. *Studies presented odds ratio, relative risk, or hazard ratio. Logarithmic scale.

reasons for the impact of sex are yet to be elucidated. Most of the women included in these studies were postmenopausal. Menopause is one of the main risk factors for osteoporosis in part because of decreased estrogen production. It has been postulated that increased adipose tissue associated with MetS is a main source of estrogen in postmenopausal women, which may have a protective effect on bone [60]. In contrast, it has been hypothesized that higher visceral fat may cause greater hormone imbalances in men than in women, which negatively affects bone formation [44]. The effect of higher visceral fat may be particularly enhanced in Asian men because a higher percentage of body fat has been observed in East and South-East Asians than in Caucasians at a given BMI [6,7].

Studies presented in this review found that atherosclerosis may also be associated with increased fracture risk. This finding, however, should be treated with caution because it is based on one cross-sectional and one retrospective study. There was also high heterogeneity in the diagnosis definition of atherosclerosis. Chronically high circulating lipids (which are a primary cause of atherosclerosis) have been hypothesized to increase the risk of osteoporosis. Adipose tissue affects the differentiation of osteoblasts, with increased adipose tissue in bone marrow associated with osteoporosis [61]. Increased oxidative stress through lipid oxidation, as well as pro-inflammatory adipokines, may also inhibit osteoblast differentiation while enhancing osteoclast differentiation [62]. Furthermore, both statins and bisphosphonates inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A reductase pathway (also known as the mevalonate pathway), which regulates cholesterol production as well as contributes to osteoclast regulation [63].

In contrast, one study identified in the present review suggests that triglycerides may have a protective effect for fracture [51]. Although not a focus of the present review, high abdominal fat may be associated with decreased risk of fractures in women and subjects with type 2 diabetes [64,65]. It has been speculated that high body fat and high triglycerides *per se* may have a protective effect, possibly through increased production of estradiol [66], increased mechanical load [50], or a cushioning effect around the skeleton [60].

This review has several limitations. Most of the studies included in the review were cross-sectional design. Therefore, with the exception of diabetes (which included longitudinal cohort studies), the findings of this review should be treated with caution. There was also limited evidence exploring the association between MetS, hyperglycemia or hypercholesterolemia and the risk of fractures in Asian populations. This highlights the need for prospective cohort studies in Asian populations monitoring the development of metabolic disorders, fracture, BMD, and other measures of bone quality (which are potentially predictive of fracture).

Meta-analyses were not undertaken as part of this review because of the high degree of heterogeneity in study design and patient populations. There was heterogeneity in the risk factor diagnosis definitions. In particular, different measures were used to define atherosclerosis, MetS, and high lipid levels. Of 16 studies reporting diabetes, 6 used medical history and 2 relied on self-reporting. This may result in disease misclassification, especially because diabetes is frequently underdiagnosed [67]. Furthermore, 10 studies did not distinguish between type 1 and type 2 diabetes. Although this may affect the strength of

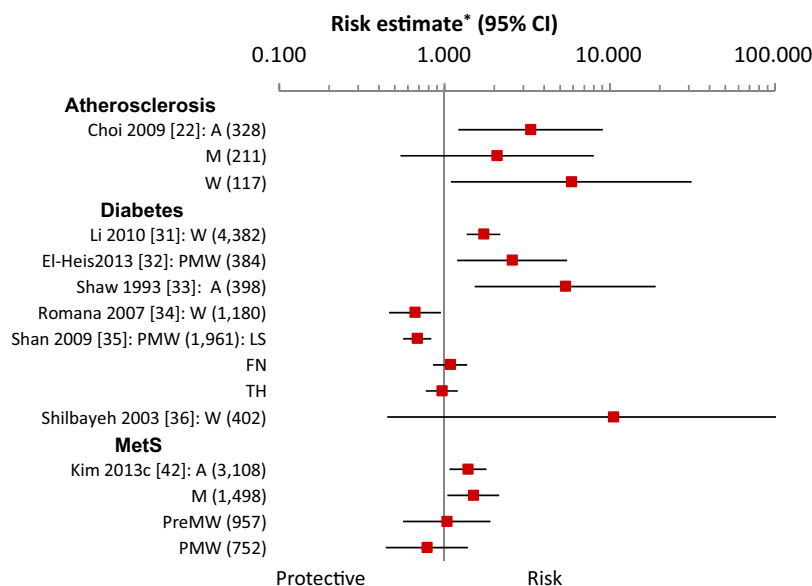


Fig. 3 – Association between metabolic disorders and osteoporosis. A, all patients; FN, femoral neck BMD; LS, lumbar spine BMD; M, men; MetS, metabolic syndrome; PMW, postmenopausal women; TH, total hip BMD; W, women. *All studies presented odds ratio. Logarithmic scale. Choi et al. [22] presented osteoporosis/osteopenia as the predictor and atherosclerosis as the outcome.

association, the impact is expected to be minimal because less than 5% cases of diabetes are type 1 in the Asia-Pacific region [4]. There was also heterogeneity in the outcomes presented (i.e. RR, OR, hazard ratio), method of analysis, and covariates adjusted for in each study. Many of the studies examining MetS and BMD excluded subjects taking osteoporosis medication and disorders known to affect bone metabolism. This was to remove any potential confounders; however, as a result, subjects with more severe disease may be excluded from analysis. Furthermore, important confounders were not always measured and therefore not adjusted for in the analyses (e.g., physical activity, calcium intake, and all relevant medications). In addition, although a sample size cutoff of 200 or more was chosen to allow for dropout, confounding, and missing data for covariates, some studies did not report the number of patients modeled with all covariates. This could be a substantially smaller cohort and thus limit generalizability.

Conclusions

In summary, findings from this review suggest that diabetes is a risk factor for fracture in Asian populations, which is consistent with findings in non-Asian populations [14]. MetS may also be associated with bone loss in Asian men; however, the extent of causality in these observations is yet to be determined. Studies presented in this review suggest that atherosclerosis is associated with increased fractures; however, this finding must be interpreted with caution given the small number of studies and limitations in study design highlighted above. Further prospective cohort studies are needed to investigate the extent and mechanisms of these associations in Asian populations. Nevertheless, these findings highlight the importance of properly managing patients with these risk factors to minimize the risk of fractures. In particular, increased awareness through education and policy prioritization could assist in reducing the risk of fractures in patients with diabetes.

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Supplemental Materials

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