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Association of serum uric acid with bone mineral density and clinical fractures in Chinese type 2 diabetes mellitus patients: A cross-sectional study

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ABSTRACT

Background: We evaluate the associations of serum uric acid (UA) with bone mineral density (BMD) and prevalence of clinical fractures in type 2 diabetes mellitus (T2DM) patients.
Methods: 1562 T2DM patients undergoing BMD measurement and clinical fractures assessment were enrolled andserum UA concentrations were measured.
Results: T2DM patients with osteoporosis had lower serum UA concentrations compared with those with normal BMD values and osteopenia. Serum UA concentration was significantly correlated with BMD values at the lumbar spine, femoral neck, and total hip in postmenopausal women, and serum UA concentration was positively associated with BMD values at the lumbar spine in men. Moreover, patients with clinical fractures had lower serum UA than those without. Multiple logistic regression analysis showed that serum UA concentrations were significantly and inversely associated with the presence of clinical fractures after adjustment for age, BMI, diabetes duration, fasting blood glucose (FBG), Glycated hemoglobin A1c (HbA1c), alkaline phosphatase (ALP), creatinine (Cr), neutrophil to lymphocyte ratio (NLR), diabetic vascular complications [men: OR = 0.996, 95% CI = 0.993–1.000, $P = 0.039$; women: OR = 0.996,95% CI = 0.994–0.998, $P = 0.001$]. The results were not statistically significant when models were further adjusted for BMD values at each site.
Conclusions: Lower serum UA concentrations may be associatedwith lower BMD values and higher prevalence of clinical fractures independent of potential confounders except for BMD values at each site. These findings need to be confirmed by further prospective studies.

1. Introduction

Osteoporosis is a multi-factorial skeletal disease characterized by low bone mass and altered bone quality, and can put patients at an increased risk for abnormal bone strength and fragility fractures [1]. It is estimated that > 200 million people have osteoporosis worldwide, and osteoporosis has therefore become an alarming health problem [2]. Many clinical studies have reported that osteoporosis is one of the chronic complications associated with diabetes mellitus (DM) [1]. Both type 1 and type 2 diabetes mellitus (T2DM) can affect areal bone mineral density (BMD) and the risk of bone fractures [3]. BMD value measured by dual energy X-ray absorptiometry (DXA) is recognized as a major tool to detect osteoporosis and predict fracture risk [4]. Of interest is that most, but not all, epidemiologic studies have found that despite the normal or increased BMD values, T2DM patients have an increased risk for fracture compared to nondiabetic subjects [5, 6], suggesting that increased fracture risk associated with T2DM may be due to impaired bone quality (not revealed from BMD values) and extra-skeletal factors, but the specific mechanisms accounting for diabetes-related bone fracture and the factors for altered BMD values has not been identified clearly, and there are few effective therapies for diabetic osteoporosis. It is therefore an urgent task to seek clinically suitable surrogate markers for diabetic osteoporosis.

Substantial evidence indicates the role of oxidative stress and low circulating antioxidants concentrations in the initiation and progression of osteoporosis, especially type 2 diabetic osteoporosis [7–10]. Serum uric acid (UA), an important endogenous antioxidant, effectively can scavenge superoxide, hydroxyl radicals, and singlet oxygen, as wellas block formation of the strong oxidant peroxynitrite [11]. The antioxidant activityof serum UA is much higher than that of other antioxidants, including vitamins and enzymatic antioxidants [12], with serum UA accounting for approximately 50% of the antioxidant activity

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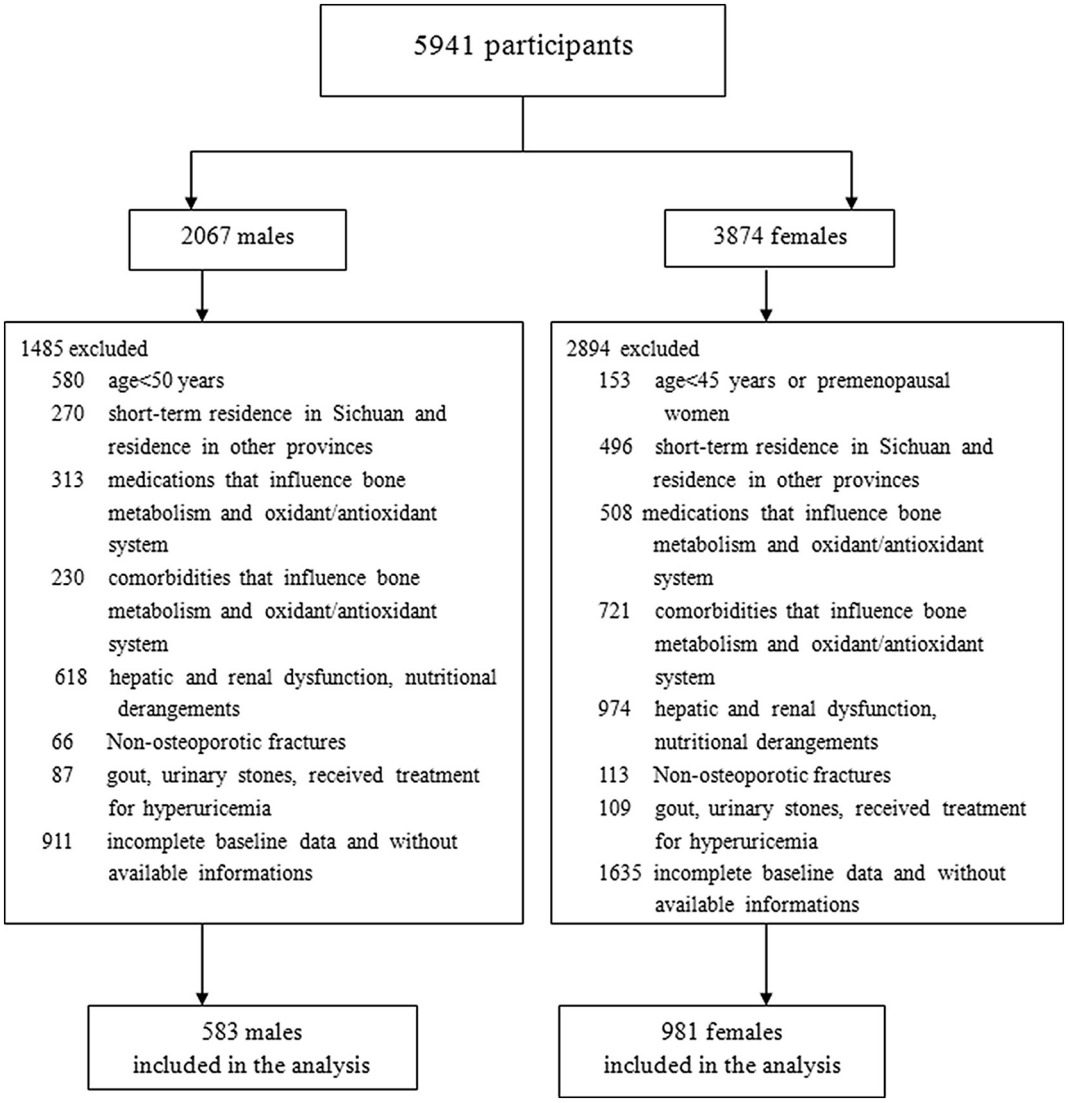

Fig. 1. Flowchart of the study participants.

in human plasma [13]. Moreover, the systemic infusion of serum UA not only increases plasma antioxidant capacity at rest, but also reduces the exercise-associated oxidative stress in healthy subjects [14]. The antioxidant effect of serum UA may potentially protect against osteoporosis. Several studies have demonstrated that serum UA concentrations were positively associated with BMD values at various skeletal sites, T-score and *Z*-score, and inversely with the prevalence of osteoporosis, vertebral and nonvertebral fractures, and bone resorption markers in peri- and postmenopausal women, and young and middle-aged, and elderly men with and without T2DM [10, 15–20], suggesting of a potential protective role of serum UA against osteoporosis. Yet, some recent observational studies have shown the contrary. Sritara et al. and Mehta et al. found that serum UA concentrations were inversely associated with BMD at the femoral neck (FN) after controlling for covariates in females aged 25–54 y, and higherserum UA concentrations were associated with an increased risk of hip fractures in community-dwelling elderly men, respectively [21, 22]. Recent studies reported that serum UA concentration has no relationship with BMD values at various skeletal sites and the onset of new osteoporotic fractures after adjustment for potential confounders in young and middle-aged, and elderly men and pre-menopausal women, and post-menopausal women not treated with estrogen or withT2DM [23–26], and confirmed the conclusion in a rodent model of chronic mild hyperuricemia [25].

Although many studies have reported the relationship between serum UA concentrations, BMD values and bone fractures, the conclusions were inconsistent and controversial. Two investigated the association of serum UA concentrations with BMD values in men aged 19–84 y and postmenopausal women with T2DM, and showed inconsistent conclusions [15, 25], and they did not explore the association of serum UA concentrations with the prevalence of clinical fractures.

2. Materials and methods

2.1. Study population

The population consisted of 5941 patients with T2DM who were initially consecutively enrolled for an education, evaluation, or treatment of diabetes mellitus and osteoporosis at the inpatient clinicof the Endocrinology Department at the Affiliated Hospital of Southwest Medical University during the period between August 2012 and May 2017. The diagnosis of T2DM was based on oral glucose tolerance tests (OGTT) and the 1999 World Health Organization (WHO) criteria. All the patients were being treated with oral medications and insulin injection. Inclusion criteria were: 1) **Previously** confirmed or newly diagnosed T2DM patients; 2) Postmenopausal women aged ≥45 y who