Introduction

Osteoporosis and type 2 diabetes mellitus (T2DM) are two highly prevalent conditions of late life and quite often coexist. Osteoporosis and a high falls risk can often occur together as a result of advancing age, which may result in severe fractures, leading to disability, poor quality of life, hospitalizations and higher mortality. Low bone mineral density (BMD) in older adults is known to be associated with higher incidences of osteoporotic fractures. While the relation of T2DM with BMD remains inconsistent across studies, the fracture risks in individuals with T2DM has been suggested to increase. Osteoporosis has been shown to predict fracture risks in individuals with T2DM. Furthermore, individuals with T2DM have even worse fracture outcomes than those with normal bone mineral density (BMD).
blood glucose. However, strategies to reduce fracture risks appear underutilized in older adults with T2DM, possibly due to challenges in identifying the high-risk individuals. Thus, it is crucial to identify those at risk of osteoporosis in this population and implement preventive strategies accordingly so as to avoid the negative consequences of osteoporosis.

The influential factors for osteoporosis include age, sex, serum vitamin D concentrations, lifestyle factors, chronic inflammation, and nutritional risk. Poor neuromuscular function is a risk factor for fracture risk. Many mechanisms have been assumed to contribute to diabetic osteoporosis, such as poor glycemic control, defects in insulin secretion or insulin action, low serum vitamin D concentrations, increased proinflammatory cytokines. Additionally, older adults with T2DM may have an additional risk of undernutrition, as a result of overly restrictive eating patterns to control blood sugar. Serum albumin and prealbumin are among widely used nutritional biomarkers. However, prealbumin has been suggested to be the earliest laboratory indicator of nutrition and is a much preferred biomarker for malnutrition compared with albumin. Previous studies have reported conflicting results on the association of hypoalbuminemia with osteoporosis. Few observational studies have suggested an independent association of osteoporosis with lower levels of serum albumin, while others have reported no such association. Nonetheless, the relationship between osteoporosis and prealbumin has been rarely investigated (to our knowledge, only two studies). A recent study has shown reduced prealbumin to be associated with BMD in postmenopausal women. While another study has shown such an association in patients undergoing chronic peritoneal dialysis. In addition, the association of osteoporosis with prealbumin in individuals with T2DM has not yet been examined.

Therefore, the objective of our study was to investigate whether the levels of prealbumin in older adults with T2DM with osteoporosis differed from those in older adults with T2DM without osteoporosis and whether low prealbumin was an independent risk factor for osteoporosis in this population.

**Materials and methods**

**Study participants**

This cross-sectional study was conducted using the geriatric T2DM database of Xuanwu Hospital, Capital Medical University, China. In total, 603 older adults with T2DM aged over 60 years were recruited by the Department of Endocrinology from July 2016 to August 2017. Among which, 22 of them refused to participate in the study, and 24 could not cooperate with the protocol due to disability. A total of 557 participants aged >60 years who met the 1999 World Health Organization (WHO) diagnosis and classification criteria of T2DM were included in the database. The exclusion criteria for our current study were:

(1) Conditions affecting bone metabolism and nutritional status, including thyroid disease, parathyroid disease, Cushing’s syndrome, rheumatoid arthritis, acute inflammatory diseases, autoimmune disease, cancer, stage 4 to 5 chronic kidney disease, chronic liver disease.

(2) Medical treatment that could significantly affect bone metabolism, including glucocorticoid drugs, thiazolidinedione, calcitriol drugs.

(3) No information on laboratory results or dual-energy X-ray absorptiometry (DEXA) parameters.

Thus, a total of 370 participants were included in this study (Figure 1). The participants were divided into two groups: (1) those with osteoporosis (n = 121), and (2) those without osteoporosis (n = 249).

The study obtained ethical approval from the Research Ethics Boards at Xuanwu Hospital of Capital Medical University, China (approval number: CTR-IPR-2019002). Written informed consent was obtained from all participants on provision of a complete study description.

**Selection of risk factors**

Participants were assessed for their potential risk factors for osteoporosis based on past literature such as serum vitamin D concentrations, lifestyle factors, chronic inflammation, nutritional risk and poor neuromuscular function (markers
described below in detail) and included in our analyses.

Clinical and anthropometric information
Information on demographic data, lifestyle habit, disease history and medication records were obtained from all participants. The height and weight of each were measured while the participants were wearing lightweight clothing without wearing shoes. The body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m²).

Biochemical measurements
Blood samples of the participants were drawn in the morning after a 10-hour overnight fast. Fasting blood glucose (FBG), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (CRE), albumin, prealbumin, fasting blood insulin (FINS), and fasting blood C peptide were detected by automatic biochemical analyzer (BioTek Instrument, Inc., Beijing, China). A low serum prealbumin level was defined as <170 mg/l.24 The homeostasis model assessment (HOMA) formula was used for calculating the insulin resistance (IR) index (HOMA-IR). HOMA-IR = fasting insulin (μIU/ml) × fasting glucose (mmol/l)/22.5. Hemoglobin A1c (HbA1c) was detected by high-performance liquid chromatography. Serum 25-hydroxyvitamin D3 [25(OH)D3] was determined by double antibody radioimmunoassay (DiaSorin, Stillwater, MN, USA and Linco Research, St. Charles, MO, USA). Serum levels of highly sensitive C-reactive protein (hs-CRP) were determined by an immunoturbidimetry assay (Kanto Chemical Co Inc, Tokyo, Japan). Serum levels of interleukin (IL)-6 were detected using an enzyme-linked immunosorbent assay kit (Beijing Biolab Science and Technology Co. Ltd., Beijing, China). The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation.25 The hemoglobin (Hb) level was determined using a CELL DYN 3200 hematology analyzer (Abbott Laboratories, Abbott Park, IL, USA). According to the WHO diagnostic criteria, anemia was defined as Hb levels <13 g/dl for men and <12 g/dl for women.26

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**Figure 1.** Flow chart on the selection of participants.
Assessment of osteoporosis and appendicular muscle mass

Both body composition parameters and the BMD (g/cm²) were determined by DEXA (LUNAR iDXA, USA). A single experienced technologist performed all the scans. BMD was measured at the lumbar spine 2–4, femoral neck and total hip. The BMD T-score was calculated from the sex-matched BMD data in young adults derived in China. According to the criteria recommended by WHO in 1994, osteoporosis was diagnosed by a T-score $< -2.5 \times$ standard deviation (SD) at any site on the lumbar spine, femoral neck, or total hip. Appendicular skeletal muscle (ASM; kg) was calculated as the sum of arm and leg skeletal muscle mass. Skeletal muscle index (SMI) was calculated as ASM divided by height squared (m²) and was the indicator of relative ASM. Low muscle mass was defined as SMI $< 7.0$ kg/m² for men and $< 5.4$ kg/m² for women.

Muscle strength and gait speed measurements

Hand grip strength was measured three times on each side using the Jamar® Hydraulic Hand Dynamometer (Patterson Medical, Warrenville, IL, USA). The maximal grip strength of six measures was used in the analyses. Low grip strength was defined as $< 26$ kg for men and $< 18$ kg for women, as per the consensus report of the Asian Working Group for Sarcopenia.

For the assessment of gait speed, participants were instructed to walk at their usual walking speed for a 6-meter distance. Trained staff recorded time for the 6-meter walk (seconds) to the nearest 0.01 s by using a stopwatch. Overall, two timed trials were conducted to derive the gait speed (m/s) and the best (i.e. fastest) performance was used for the present analysis. Low gait speed was defined as a gait speed $< 0.8$ m/s.

Statistical analyses

All statistical analyses for this study were performed using SPSS version 17.0. Normally distributed data were reported as the mean ± SD, while variables with skewed distribution were expressed as median (interquartile range). Comparisons for categorical variables were performed via Chi-square tests, while the unpaired Student’s t test or the Mann–Whitney U test was used for continuous variables. The correlations between prealbumin level and IL-6, hs-CRP were analyzed using a Pearson’s correlation or Spearman’s rank correlation coefficient. Binary logistic regression was carried out to examine the association between prealbumin and osteoporosis. The results of the regression modeling were presented as odds ratios (ORs) and their 95% confidence intervals (CIs). The variables in the logistic regression model included age, sex, BMI, anemia, low grip strength, low SMI and low prealbumin. A two-sided p value was determined and $p < 0.05$ was considered to be statistically significant.

Results

A total of 176 males and 194 females with a mean age of 67.60 ± 5.78 years were included in this study (Table 1). Of the 370 participants in the study, 21.59% (38/176) of men and 42.78% (83/194) of women were classified as having osteoporosis. The mean T2DM duration of the participants was 14.44 ± 8.71 years. The mean

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**Table 1.** The demographics of the participants with and without osteoporosis.

|                      | Total n = 370 | Without osteoporosis n = 249 | Osteoporosis n = 121 | p value |
|----------------------|--------------|------------------------------|----------------------|---------|
| Age (years)          | 67.60 ± 5.78 | 66.59 ± 6.22                 | 67.79 ± 7.73         | 0.137   |
| Sex                  |              |                              |                      |         |
| Male                 | 176 (47.57%) | 138 (59.42%)                 | 38 (31.40%)          | <0.001  |
| Female               | 194 (52.43%) | 111 (44.58%)                 | 83 (68.60%)          |         |
| Diabetes duration (years) | 14.44 ± 8.71 | 15.18 ± 9.21                 | 13.74 ± 7.51         | 0.111   |
HbA1c was 8.43 ± 1.81%. The prealbumin levels were significantly lower in persons with osteoporosis than those without osteoporosis (235.40 ± 60.66 versus 261.34 ± 55.28, respectively), and so were the BMI and Hb levels (p < 0.001). The proportion of participants with prealbumin levels below the normal range was significantly higher in individuals with osteoporosis compared with those without osteoporosis (16.53% versus 4.42%, respectively; Table 2). The mean BMI of the participants was 25.81 ± 3.66 kg/m². Participants with osteoporosis had a lower ASM and grip strength (p < 0.001; Table 3).

Results of the logistic regression model for the association of prealbumin and risk factors associated with osteoporosis are shown in Table 4. Anemia (yes or no), low grip strength (yes or no), and low SMI (yes or no), as well as age, sex, BMI, and low prealbumin level (yes or no), were included in the multivariate logistic regression model. We found that low prealbumin (OR: 3.85, 95% CI: 1.54–6.34) was significantly associated with an increased risk of osteoporosis. Female, low BMI and low grip strength were the associated risk factors for osteoporosis in older adults with T2DM.

Discussion
In this study, we found that low levels of prealbumin were associated with an increased risk of osteoporosis in older adults with T2DM. The association remained significantly independent...
of several confounders such as age, sex, BMI, metabolic parameters, muscle mass and grip strength. It is undeniable that nutrition plays an extremely important role in bone health. Albumin and pre-albumin are the widely used biomarkers of

### Table 3. Anthropometry and body composition measurements of the participants with and without osteoporosis.

|                          | Total n = 370 | Without osteoporosis n = 249 | Osteoporosis n = 121 | p value |
|--------------------------|---------------|-----------------------------|----------------------|---------|
| BMI (kg/m²)              | 25.81 ± 3.66  | 26.36 ± 3.26                | 24.70 ± 3.74         | <0.001  |
| ASM (kg)                 | 19.30 ± 4.13  | 20.13 ± 3.94                | 17.43 ± 3.68         | <0.001  |
| SMI (kg/m²)              | 7.03 ± 1.03   | 7.21 ± 0.99                 | 6.59 ± 0.96          | <0.001  |
| Low SMI (n, %)           | 51 (13.78%)   | 22 (8.83%)                  | 29 (23.96%)          | <0.001  |
| Grip strength (kg)       | 29.86 ± 10.04 | 31.88 ± 9.87                | 26.68 ± 9.38         | <0.001  |
| Low grip strength (n, %) | 49 (13.24%)   | 21 (8.43%)                  | 28 (23.14%)          | <0.001  |
| Low gait speed (n, %)    | 47 (12.70%)   | 29 (11.65%)                 | 18 (14.87%)          | 0.382   |
| BMD (g/cm²)              |               |                            |                      |         |
| Lumbar spine 2–4         | 1.126 ± 0.252 | 1.200 ± 0.180               | 0.959 ± 0.134        | <0.001  |
| Right femoral neck       | 0.883 ± 0.156 | 0.940 ± 0.131               | 0.767 ± 0.138        | <0.001  |
| Right total hip          | 0.952 ± 0.158 | 1.004 ± 0.134               | 0.814 ± 0.125        | <0.001  |

ASM, appendicular skeletal muscle mass; BMD, bone mineral density; BMI, body mass index; SMI, skeletal muscle mass index.

Low grip strength was defined as <26 kg for men and <18 kg for women. Low muscle mass was defined as SMI <7.0 kg/m² for men and <5.4 kg/m² for women.

### Table 4. Logistic regression models for risk factors associated with osteoporosis.

|                          | Model 1a Unadjusted OR 95% CI P value | Model 2b Adjusted OR 95% CI P value |
|--------------------------|--------------------------------------|-------------------------------------|
| Low prealbumin           | 4.36 1.88–7.10 0.001                 | 3.85 1.54–6.34 0.004                |
| Age                      | / 1.01 0.97–1.05 0.639               | / 0.97–1.05 0.639                   |
| Female                   | / 2.98 1.75–5.08 0.000               | / 1.75–5.08 0.000                   |
| BMI                      | / 0.88 0.81–0.95 0.001               | / 0.81–0.95 0.001                   |
| Low grip strength        | / 1.77 1.17–3.58 0.045               | / 1.17–3.58 0.045                   |
| Anemia                   | / 1.22 0.66–2.66 0.525               | / 0.66–2.66 0.525                   |
| Low SMI                  | / 1.19 0.60–2.37 0.620               | / 0.60–2.37 0.620                   |

BMI, body mass index; CI, confidence interval; OR, odds ratio; SMI, skeletal muscle mass index.

Low grip strength was defined as <26 kg for men and <18 kg for women. Low muscle mass was defined as SMI <7.0 kg/m² for men and <5.4 kg/m² for women.

aModel 1: unadjusted.
bModel 2: adjusted by age, sex, BMI, anemia, low grip strength, low SMI.
nutrition. A number of studies have concluded that hypoalbuminemia is associated with osteoporosis,20,21 but these findings remain contradictory.22,32 In the NHANES database, Afshinnia20 reported an independent association of osteoporosis with hypoalbuminemia at the femoral neck, total femur, and lumbar spine in the general population of the United States. However, in the Rancho Bernardo study, Lunde and colleagues22 failed to show such an association. The discrepancy in the results of these studies may be due to a different selected population and methodological limitations including low sample size, lack of enough confounders and narrow range of variables. To our knowledge, studies investigating the association of prealbumin and osteoporosis are sparse. A recent study has found reduced prealbumin to be associated with BMD in women with osteoporosis.23 Another study reported that albumin and prealbumin to be related predictors of BMD in patients undergoing chronic peritoneal dialysis.19 However, in our study, low levels of prealbumin but not albumin were found to be significantly associated with osteoporosis in older adults with T2DM. The possible explanation for such findings could be as suggested before, that prealbumin is a more sensitive nutritional marker than albumin for assessing nutritional status because of its short half-life. Prealbumin is known to be a good marker of visceral protein status and affected earlier by acute variations in protein balance.33 The association between prealbumin and osteoporosis might be explained by the nutrition risk in older people with osteoporosis. Proper osseous metabolism is significantly affected by calcium, vitamin D, proteins, magnesium and other vitamins.34 Nutrition risk induces osteoporosis and fragility fracture.12

The mechanism underlying the association between hypoalbuminemia with osteoporosis is unclear. Albumin and prealbumin are not only markers of nutritional status but also belong to the negative acute-phase reactants, the concentrations of which fall during inflammation.35 Inflammation plays a potential role in both the normal bone remodeling process and the pathogenesis of osteoporosis. Numerous proinflammatory cytokines have been implicated in the regulation of osteoblasts and osteoclasts.10 For example, IL-6 promotes osteoclast differentiation and activation. Hs-CRP is regarded as a sensitive marker of systemic inflammation and its production in the liver is regulated by IL-1, IL-6 and tumor necrosis factor (TNF)-α.36 The association between hs-CRP levels and BMD has been observed in several studies.11 Hypoalbuminemia is the result of inflammation which reduces the effective use of dietary protein and augments catabolism of the key somatic protein.37 Consistent with previous studies, our present study demonstrated that prealbumin was inversely correlated with hs-CRP and IL-6 (p < 0.001). However, although there was an increased trend for serum levels of hs-CRP and IL-6 in individuals with osteoporosis, the result did not reach statistical significance. The results are different from previous studies.10 The discrepancies could be mainly associated with selection bias of the study populations. Hypoalbuminemia may directly suppress osteogenesis and activate osteoclasts via nuclear factor (NF)-κB, which is considered a potent mediator of inflammatory osteolysis; or it may be indirectly linked with NF-κB-mediated osteoclastogenesis via cytokines such as the receptor activator of NF-κB ligand, TNF-α, IL-1, and oxygen radicals.21,38 Indeed, further studies are required to help better understand the pathophysiological link between osteoporosis and albumin metabolism.

Anemia, BMI and muscle mass are commonly used indicators of nutritional status. Thus, we also performed Hb, BMI and muscle mass measurements to assess nutritional status. Previous studies showed that Hb and anemia status were associated with BMD and risk of fracture in the general population.39 In addition, previous studies suggested that the impairment of muscle status (i.e. muscle mass and muscle strength) is associated with a deterioration in bone mass.13 In our study significant differences were found according to BMI, Hb, and DEXA parameters (ASM, SMI) between participants with and without osteoporosis. However, low grip strength but not low SMI was found to be associated with osteoporosis. The possible explanation could be that muscle strength does not depend solely on muscle mass and may decline more with age than muscle mass.40,41 Many mechanisms have been assumed to contribute to diabetic osteoporosis. One of them is that metabolic alterations in T2DM can trigger disorders of calcium homeostasis, skeletal metabolism, and bone mass.42 Some studies have reported BMD to decrease more severely in T2DM individuals with poor glycemic control.15
The explanation for this may be that a higher concentration of advanced glycation end-products as a result of higher glucose levels in collagen may reduce bone strength and stimulate apoptosis of osteoblasts, thereby contributing to deficient bone formation.\textsuperscript{43,44} Another mechanism is that a defect in the insulin secretion or insulin action in individuals with diabetes can lead to diabetic osteopenia due to a deficiency in the anabolic activation of insulin.\textsuperscript{16} For instance, one previous study indicated that there was a positive correlation between the levels of insulin secretion and BMD in older Japanese adults with T2DM.\textsuperscript{6} Our study showed that there was no significant difference according to HbA1c, FINS, and HOMA-IR between the individuals with T2DM with and without osteoporosis. One of the reasons for such findings could be that the study was performed in older adults with T2DM under fairly controlled and stable conditions.

Our study showed that low levels of prealbumin were associated with a higher risk of osteoporosis which has tremendous clinical implications, given the rapid aging of populations worldwide. Comprehensive clinical evaluation of prealbumin in older adults with T2DM might be helpful for the early identification of those at high risk of osteoporosis. Early recognition of osteoporosis and initiation of therapy for osteoporosis with bone-active agents might prevent bone loss and thus improve patient outcomes. Such findings could play an extremely important role in reducing the increasing burden of osteoporosis in older people with T2DM; however, our study had some limitations. First, this study is cross-sectional; thus, a causal pathway from low levels of prealbumin to osteoporosis cannot be definitively proven. Therefore, follow-up studies should be conducted in the future. Second, our study consisted of individuals selected only from Xuanwu Hospital. Hence, the present study population may not be representative of the general T2DM population and the results of our study are not generalizable to other populations. Third, dietary habits and medications that potentially affect osteoporosis and albumin/prealbumin levels were not included in the models.

In conclusion, our study demonstrated that low levels of prealbumin were associated with an increased risk of osteoporosis in older adults with T2DM. Further longitudinal studies are warranted to clarify the association of prealbumin levels and the development of osteoporosis.

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