

# Association between the Geriatric Nutritional Risk Index, bone mineral density and osteoporosis in type 2 diabetes patients

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## Keywords

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## ABSTRACT

**Aims/Introduction:** Low bodyweight and hypoalbuminemia are independently associated with osteoporosis. In this study, the relationship among the Geriatric Nutritional Risk Index (GNRI), bone mineral density (BMD) and osteoporosis in type 2 diabetes mellitus patients was explored, and the GNRI predictive value was evaluated.

**Materials and Methods:** We enrolled 225 men and 192 women with type 2 diabetes mellitus. Their general condition, and laboratory and BMD data were collected. Spearman's partial correlation analysis adjusting for age, body mass index and albumin was used for exploring the association among the GNRI, BMD and bone metabolism markers. Statistical analyses, including multivariate regression analysis and receiver operating characteristic curve analysis, were also applied in this study.

**Results:** On Spearman's partial correlation analysis, GNRI was positively associated with BMD and albumin-corrected calcium ( $r = 0.145\text{--}0.561$ ,  $P < 0.01$ ). For the multivariate regression analysis, we observed that the GNRI was dramatically related to high total lumbar, total hip, femur neck BMD and osteoporosis (odds ratio 0.857 for men and 0.927 for women, all  $P < 0.05$ ). The area under the receiver operating characteristic curve of the GNRI (0.876 for men and 0.704 for women, all  $P < 0.01$ ) was the largest compared with that of albumin and body mass index in osteoporosis prediction.

**Conclusions:** In this study, it was shown that the GNRI was positively correlated with BMD, and inversely correlated with osteoporosis in type 2 diabetes mellitus patients. In addition, compared with body mass index, albumin and age, the GNRI was a more powerful indicator for osteoporosis.

## INTRODUCTION

In recent years, osteoporosis, especially for low-energy fractures, has become prevalent among the aging population, resulting in disability, poor quality of life and even death of patients<sup>1</sup>. In general, for patients with type 2 diabetes mellitus, the risk of osteoporosis is much higher than that in the normal population<sup>2,3</sup>. In addition, the risk still varies greatly from one case to another, even after modulating for age, duration of diabetes and body mass index (BMI)<sup>4,5</sup>. The risk factors of osteoporosis in the normal population have been shown in previous studies<sup>6</sup>; however, because of the particularity of metabolic disease, the risk factors of

osteoporosis in people with type 2 diabetes mellitus might be quite different. Therefore, it is crucial to discuss them more specifically.

Previous studies have shown that low bodyweight and hypoalbuminemia are separately related to lumbar spine osteoporosis for people with diabetes<sup>7,8</sup>. Recently, the Geriatric Nutritional Risk Index (GNRI) has been applied as a simple and available tool to evaluate the results based on serum albumin and the ratio between the actual and ideal bodyweight<sup>9</sup>. For the past several years, a variety of studies have shown and validated the predictive property of the GNRI for patients with pyogenic liver abscess<sup>10</sup>, sepsis institutionalized<sup>11</sup>, hemodialysis<sup>12</sup> and pneumonia<sup>13</sup>. However, the GNRI has rarely been used to assess the nutrient condition of type 2 diabetes mellitus patients. Furthermore, the

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value of the GNRI in predicting osteoporosis in type 2 diabetes mellitus patients has not been explored yet.

Therefore, the present study aimed to determine the relationship between the GNRI and osteoporosis in type 2 diabetes mellitus patients. The predictive properties of the GNRI, albumin, BMI and age for osteoporosis in patients with type 2 diabetes mellitus were ulteriorly assessed.

## METHODS

### Study population

In the present cross-sectional study, the participants were 447 Chinese older adults with type 2 diabetes mellitus (age >50 years, including 255 men and 192 postmenopausal women). The participants visited the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University for evaluating and treating type 2 diabetes mellitus, and were enrolled between January 2017 to December 2017. For the participants, the exclusion criteria were as follows: (i) malignant tumor and severe heart, liver or kidney diseases; (ii) pituitary, thyroid, parathyroid, adrenal and gonadal diseases; (iii) long-term bedridden; (iv) individuals concomitantly taking drugs affecting the bone metabolism, such as calcium, vitamin D and bisphosphonates; and (v) patients without available information. This study obtained approval from the ethics committee of the Second Affiliated Hospital of Wenzhou Medical University (No. LCKY2017-21), and obtained the written informed consent of all participants following the Declaration of Helsinki.

### Clinical assessment and health history

Bodyweight and height were measured with light clothing and without shoes. The body mass index (BMI; kg/m<sup>2</sup>), defined as the bodyweight (kg) per square of height (m<sup>2</sup>), was calculated for each patient. Blood pressure (mmHg) was measured by a mercury sphygmomanometer in the supine position after resting for 5 min. The duration of diabetes was counted by years, starting from the time point the patients was diagnosed with type 2 diabetes based on the medical record, up to carrying out the blood tests and measuring bone mineral density (BMD) values. Smoking and drinking history were considered as never or ever.

### Biochemical indexes

Serum samples were collected at 06.00 hours after overnight fasting (at least 8 h). The glucose metabolism indexes, including fasting blood glucose (FBG) and glycosylated hemoglobin, were measured according to standard methodology. In addition, the levels of lipids in serum, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were analyzed. Furthermore, the bone metabolic indicators, which contained parathyroid hormone, procollagen of type I N-propeptide,  $\beta$ -isomerized C-terminal telopeptides and 25-hydroxy-vitamin were also detected. Additionally, other biochemical markers, such as blood creatinine, uric and calcium, were recorded.

### BMD index

Dual-energy X-ray absorptiometry (Hologic-Discovery, Bedford, MA, USA) was used to measure the BMD value of each patient at three positions: total lumbar, femur neck and total hip. The standard of osteoporosis in the World Health Organization criterion was evaluated by the BMD, the value of which was >2.5 standard deviations below the T-score<sup>14</sup>.

### GNRI

The GNRI was calculated based on the parameters, including height (H; cm), actual bodyweight (kg), ideal bodyweight (kg) and the level of serum albumin (g/L), and the calculation formula is shown as follows<sup>9</sup>:

$$\text{GNRI} = (1.489 \times \text{albumin [g/L]}) + (41.7 \times [\text{weight/WL0}]).$$

The WL0 in the above equation represented the ideal weight, which can be further calculated by the following equations:

$$\text{Men: WL0} = H - 100 - ([H - 150]/4)$$

$$\text{Women: WL0} = H - 100 - ([H - 150]/2.5)$$

### Statistical analysis

The statistical analyses were processed dividedly for men and women. In this study, mean  $\pm$  standard deviation was applied to measure continuous variables, and the proportion was applied to measure categorical variables. The difference of a quantitative variable between two groups was investigated using the independent two-sample *t*-test or the Mann-Whitney *U*-test, and Pearson's  $\chi^2$ -test was used to test for differences in the distribution of a categorical variable. Spearman's partial correlation analysis adjusting for age, BMI and albumin was applied to determine the relationships between GNRI, BMD and bone metabolism markers. Multivariate linear regression analysis was carried out to show the relationship among BMD at the lumbar spine, hip and femoral neck, and other parameters. The hazard ratios of risk factors for osteoporosis in people with type 2 diabetes mellitus was further assessed by sex sub-analysis. Furthermore, the receiver operating characteristic curve was applied to estimate the predictive property of the GNRI for osteoporosis, and the areas under the receiver operating characteristic curve (AUC) were also calculated.

## RESULTS

### Analysis of baseline characteristics

The baseline characteristics of all participants are represented in Table 1. In this study, 447 patients had type 2 diabetes, with the average age ranging from 66.10  $\pm$  9.47 years, and BMI ranging from 24.41  $\pm$  3.66 kg/m<sup>2</sup>. Figure S1 shows the distribution of BMD in type 2 diabetes mellitus patients. The average BMD at the total lumbar, femur neck and total hip of men were higher than those in women (1.073 vs 0.925, 0.827 vs

**Table 1** | Patients characteristics, stratified by sex

|                                   | Total patients (n = 447) | Men patients (n = 255) | Women patients (n = 192) | P     |
|-----------------------------------|--------------------------|------------------------|--------------------------|-------|
| Age (years)                       | 66.10 ± 9.47             | 64.95 ± 9.79           | 67.63 ± 8.82             | 0.003 |
| Diabetes duration (years)         | 8.02 ± 6.82              | 7.64 ± 6.90            | 8.52 ± 6.70              | 0.177 |
| Systolic blood pressure (mmHg)    | 139.44 ± 22.27           | 136.92 ± 21.53         | 142.79 ± 22.84           | 0.006 |
| Diastolic blood pressure (mmHg)   | 77.42 ± 12.56            | 78.26 ± 12.60          | 76.30 ± 12.45            | 0.103 |
| BMI (kg/m <sup>2</sup> )          | 24.41 ± 3.66             | 23.97 ± 3.25           | 25.00 ± 4.07             | 0.003 |
| Smoking (current or ever)         | 28.6%                    | 49.4%                  | 1.0%                     | 0.000 |
| Drinking (current or ever)        | 21.7%                    | 36.9%                  | 1.6%                     | 0.000 |
| Laboratory findings               |                          |                        |                          |       |
| FBG (mmol/L)                      | 8.85 ± 3.18              | 8.53 ± 2.72            | 9.27 ± 3.66              | 0.030 |
| HbA1c (mmol/L)                    | 9.85 ± 2.36              | 10.14 ± 2.55           | 9.46 ± 2.02              | 0.003 |
| TC (mmol/L)                       | 4.47 ± 1.22              | 4.29 ± 1.09            | 4.69 ± 1.35              | 0.001 |
| TG (mmol/L)                       | 1.82 ± 1.57              | 1.65 ± 1.10            | 2.05 ± 2.01              | 0.009 |
| HDL-c (mmol/L)                    | 1.00 ± 0.26              | 0.96 ± 0.25            | 1.06 ± 0.26              | 0.000 |
| LDL-c (mmol/L)                    | 2.58 ± 0.93              | 2.51 ± 0.88            | 2.67 ± 0.99              | 0.087 |
| Albumin (g/L)                     | 37.65 ± 4.67             | 38.26 ± 4.17           | 36.83 ± 4.95             | 0.001 |
| Creatinine (μmol/L)               | 71.98 ± 31.75            | 78.64 ± 30.00          | 63.15 ± 31.92            | 0.000 |
| Uric (μmol/L)                     | 314.19 ± 98.01           | 327.74 ± 101.06        | 296.15 ± 90.96           | 0.001 |
| PTH (pg/mL)                       | 43.60 ± 22.18            | 43.08 ± 21.04          | 44.43 ± 24.10            | 0.739 |
| PINP (ng/mL)                      | 14.95 ± 22.08            | 13.14 ± 19.76          | 17.36 ± 24.67            | 0.045 |
| β-CTX (ng/mL)                     | 0.38 ± 0.24              | 0.35 ± 0.25            | 0.41 ± 0.23              | 0.072 |
| 25(OH)D (ng/mL)                   | 58.42 ± 22.71            | 60.54 ± 20.93          | 55.71 ± 24.66            | 0.155 |
| Calcium (mmol/L)                  | 2.19 ± 0.11              | 2.19 ± 0.11            | 2.19 ± 0.11              | 0.812 |
| GNRI                              | 101.72 ± 9.65            | 101.36 ± 9.30          | 102.22 ± 10.09           | 0.355 |
| BMD                               |                          |                        |                          |       |
| Total lumbar (g/cm <sup>2</sup> ) | 1.009 ± 0.312            | 1.073 ± 0.363          | 0.925 ± 0.201            | 0.000 |
| Femur neck (g/cm <sup>2</sup> )   | 0.788 ± 0.148            | 0.827 ± 0.135          | 0.738 ± 0.149            | 0.000 |
| Total hip (g/cm <sup>2</sup> )    | 0.858 ± 0.162            | 0.896 ± 0.148          | 0.809 ± 0.166            | 0.000 |
| Osteoporosis                      | 15.1%                    | 9.8%                   | 21.9%                    | 0.001 |

Values are mean ± standard deviation or number (%).  $P < 0.05$  was deemed significant (comparison between men and women). 25(OH)D, 25-hydroxy-vitamin; β-CTX, β-isomerized C-terminal telopeptides; BMD, bone mineral density; BMI, body mass index; FBG, fasting blood glucose; GNRI, Geriatric Nutritional Risk Index; HbA1c, glycosylated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; PINP, procollagen of type I N-propeptide; PTH, parathyroid hormone; TC, total cholesterol; TG, triglyceride.

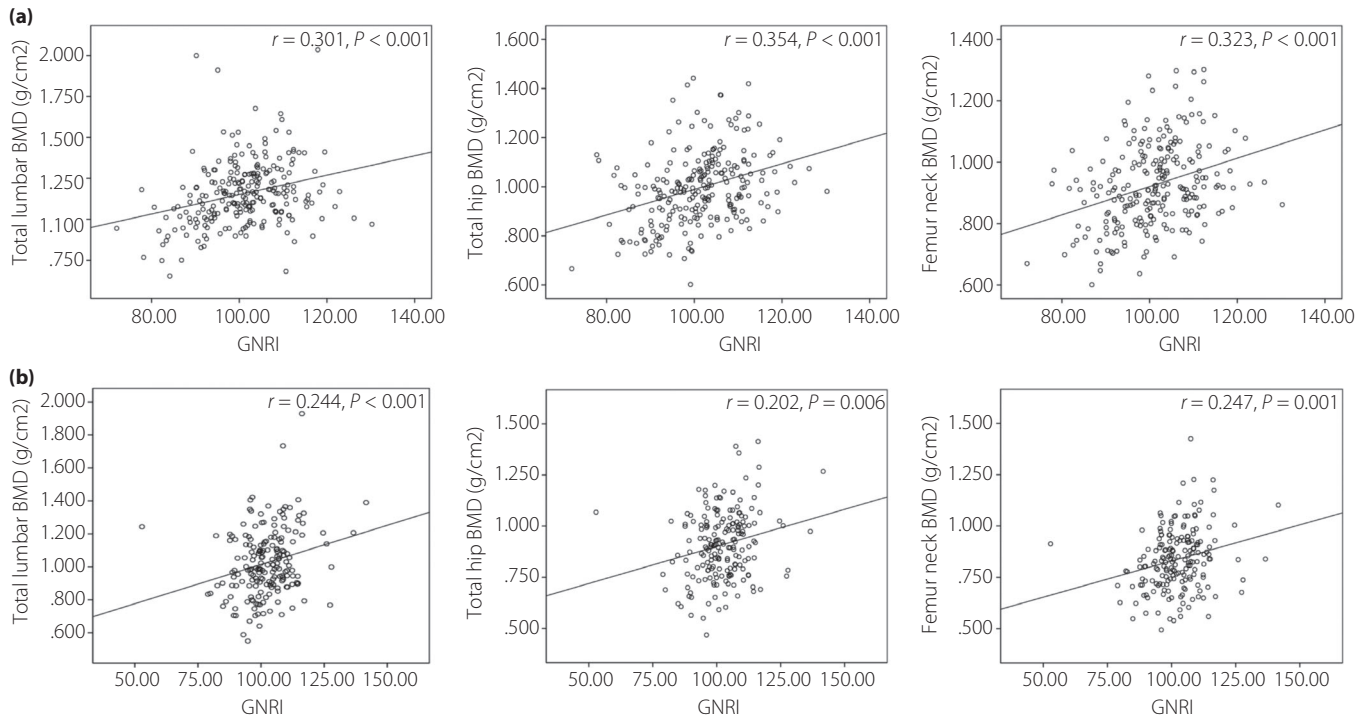
0.738, 0.896 vs 0.809, respectively, and all  $P < 0.01$ ). Compared with women, the levels of FBG, TC, TG, HDL-C, LDL-C, PINH and the incidence of osteoporosis were markedly lower in men. In addition, a history of smoking or drinking was drastically higher among men than that among women.

#### Spearman's partial correlations among GNRI, BMD and bone metabolism markers

The GNRI was found to be positively and significantly associated with BMD at all bone sites (Figure 1). After adjusting for age, BMI and albumin, Spearman's partial correlation analysis showed that GNRI was still related to BMD procollagen of type I N-propeptide and albumin-corrected calcium (Table 2). The Pearson's correlation coefficients ( $r$ ) were 0.341, 0.410, 0.355, 0.278 and 0.145 at total lumbar, total hip, femur neck procollagen of type I N-propeptide and albumin-corrected calcium, respectively, in men, and 0.561, 0.495, 0.538, 0.307 and 0.209 in women, respectively. The GNRI has a negative association with parathyroid hormone ( $r = -0.321$  in men and  $r = -0.315$  in women,  $P < 0.05$ ).

#### Linear regression analyses for BMD

Tables 3 and 4 show multivariate linear regression analysis for BMD between BMI and age. Sex, age and BMI have a great influence on the incidence of osteoporosis. Therefore, we carried out a subgroup analysis of sex, age and BMI. After adjusting for age, diabetic duration, systolic blood pressure, diastolic blood pressure, smoking, drinking, TC, TG, HDL-C, LDL-C, creatinine, uric, glycosylated hemoglobin and FBG, the GNRI was independently correlated with BMD of total lumbar, hip and femoral neck in the group with BMI <24 ( $\beta$  values were 0.314, 0.357 and 0.431 in men, and 0.123, 0.252 and 0.398 in women). In women with BMI >24, the GNRI was independently associated with the BMD of the total lumbar, hip and femoral neck ( $\beta$  values were 0.302, 0.295 and 0.364), but no independent correlation was shown for men. In men aged <65 years men, the GNRI was independently associated with the BMD of the total hip and femoral neck ( $\beta$  values were 0.277 and 0.392, respectively). For women aged <65 years, the GNRI was independently associated with the BMD of the total lumbar, hip and femoral neck ( $\beta$  values



**Figure 1** | Scatter diagrams showing the correlation between the Geriatric Nutritional Risk Index (GNRI) and bone mineral density (BMD).

**Table 2** | Correlation analysis between the Geriatric Nutritional Risk Index, bone mineral density and bone metabolism markers adjusted for body mass index, albumin and age

| Variables                 | Men    |       | Women  |       |
|---------------------------|--------|-------|--------|-------|
|                           | r      | P     | r      | P     |
| Total lumbar BMD          | 0.341  | 0.000 | 0.561  | 0.001 |
| Total hip BMD             | 0.410  | 0.000 | 0.495  | 0.002 |
| Femur neck BMD            | 0.355  | 0.000 | 0.538  | 0.001 |
| PTH                       | -0.321 | 0.011 | -0.315 | 0.048 |
| PINP                      | 0.278  | 0.005 | 0.307  | 0.050 |
| β-CTX                     | 0.031  | 0.825 | -0.130 | 0.436 |
| 25(OH)D                   | 0.049  | 0.725 | -0.062 | 0.713 |
| Albumin-corrected Calcium | 0.145  | 0.025 | 0.209  | 0.018 |

were 0.227, 0.290 and 0.369, respectively). In men aged >65 years, the GNRI was independently associated with the BMD of the total lumbar, hip and femoral neck (β values were 0.280, 0.335 and 0.277, respectively). In women aged >65 years, the GNRI was independently associated with the BMD of the total lumbar (β values were 0.296).

**Logistic regression analyses for osteoporosis in participants**

The relationship between the GNRI and osteoporosis was analyzed by logistic regression method, and the results are shown in Table 5. Although adjusting for age, diabetes duration, TC, TG, HDL-C, LDL-C, creatinine, uric, glycosylated hemoglobin

**Table 3** | Geriatric Nutritional Risk Index was independent association with bone mineral density based on the cross-categorization of body mass index and sex

|              | 18.5 ≤ BMI < 24 |        | BMI ≥24 |       |
|--------------|-----------------|--------|---------|-------|
|              | β               | P      | β       | P     |
| <b>Men</b>   |                 |        |         |       |
| Total lumbar | 0.314           | 0.013  | 0.083   | 0.536 |
| Total hip    | 0.357           | 0.004  | 0.072   | 0.590 |
| Femur neck   | 0.431           | <0.001 | 0.05    | 0.711 |
| <b>Women</b> |                 |        |         |       |
| Total lumbar | 0.123           | 0.282  | 0.302   | 0.042 |
| Total hip    | 0.252           | 0.049  | 0.295   | 0.047 |
| Femur neck   | 0.398           | 0.005  | 0.364   | 0.037 |

and FBG reduced the odds ratio, the relationship between GNRI and osteoporosis were still significant (odds ratio 0.860 in men and 0.927 in women, P < 0.05).

**Predictive property of the GNRI for osteoporosis**

In Figure 2, the predictabilities of the GNRI, albumin, BMI and age for osteoporosis were uncovered by the receiver operating characteristic curves. Compared with albumin, BMI and age, the AUC of the GNRI was the highest and statistically significant (0.876 for men and 0.704 for women). The optimal cut-off of the GNRI for predicting osteoporosis was 98.2, with sensitivity of 72.1% and specificity 95.8% in men. The optimal

**Table 4** | Geriatric Nutritional Risk Index was independently associated with bone mineral density based on the cross-categorization of age and sex

|              | Age <65 years |       | Age ≥65 years |       |
|--------------|---------------|-------|---------------|-------|
|              | B             | P     | β             | P     |
| Men          |               |       |               |       |
| Total lumbar | 0.194         | 0.112 | 0.280         | 0.044 |
| Total hip    | 0.277         | 0.021 | 0.335         | 0.017 |
| Femur neck   | 0.392         | 0.001 | 0.277         | 0.045 |
| Women        |               |       |               |       |
| Total lumbar | 0.227         | 0.043 | 0.296         | 0.048 |
| Total hip    | 0.290         | 0.028 | 0.219         | 0.136 |
| Femur neck   | 0.369         | 0.006 | 0.125         | 0.424 |

cut-off of GNRI for predicting osteoporosis was 99.5, with sensitivity of 69.8% and specificity 69.0% in women.

## DISCUSSION

In the present study, it was reported that GNRI was initially used for estimating the risk of malnutrition-related complications in the aging population<sup>15</sup>, and has been applied as a reliable indicator for a variety of diseases<sup>16–18</sup>. According to previous studies, the GNRI was adopted in this work, and the results showed that the GNRI was positively related to the BMD of the total lumbar, femur neck and total hip, and inversely related to osteoporosis in type 2 diabetes mellitus patients. In addition, compared with albumin and BMI, the predictability of the GNRI for osteoporosis was more powerful. Because of the simplicity of the GNRI to assess nutriture merely based on blood albumin, bodyweight and height, the GNRI is a convenient method to estimate nutriture and osteoporosis in type 2 diabetes mellitus patients. In addition, nutritional

supplementation might be an effective method to reduce the incidence of osteoporosis.

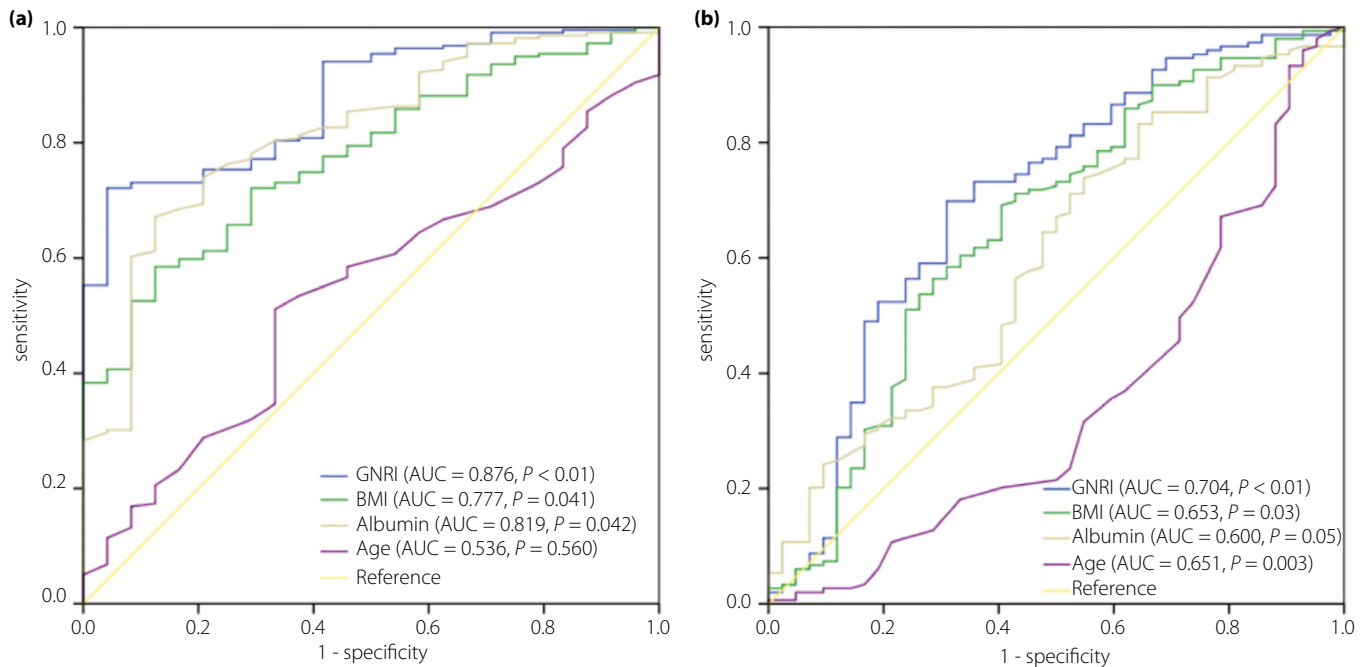
The nutriture of the patients with type 2 diabetes mellitus was negatively impacted, despite the relevant ingestion<sup>19</sup>. Diabetes accelerates the loss of muscle strength, quality and serum albumin<sup>20</sup>, which draws attention to the protein and energy balance in nutrition. It was shown in our work that a low GNRI was a significant risk factor for reduced BMD and osteoporosis in type 2 diabetes mellitus patients. To our knowledge, this is the first time that the direct association among GNRI and BMD, osteoporosis in type 2 diabetes mellitus patients has been shown. Therefore, GNRI might be a convenient and reliable indicator for the BMD status in patients with type 2 diabetes mellitus. The GNRI of the participants was  $101.72 \pm 9.65$ , which showed that the nutritional status was not severe. After grouping the patients into three different groups according to the GNRI, the GNRI at a low status was related to a low level of BMD and serum calcium. Accordingly, it has been partially proven that malnutrition plays a role in the low level of BMD in patients with a low GNRI.

We also observed a sexual dimorphism between GNRI and osteoporosis. No correlation between GNRI and BMD was found in the group with BMI >24 kg/m<sup>2</sup>. A discordant association between BMI and sexual hormones in men and women might partially explain our finding. Testosterone and sex hormone-binding globulin levels decreased in men with increased BMI, whereas a favorable association was shown between BMI and serum estrogen concentrations in postmenopausal women<sup>21,22</sup>. Karim *et al.* suggested that these associations can be explained by the increased fat mass with increased peripheral aromatization after menopause. Another putative mechanism is increased plasma levels of leptin. A recent meta-analysis showed that high levels of leptin were positively associated with BMD in postmenopausal women.

**Table 5** | Logistic regression analysis for osteoporosis

| Variables         | Men   |                       |       | Women |                       |       |
|-------------------|-------|-----------------------|-------|-------|-----------------------|-------|
|                   | SE    | Odds ratio (95% CI)   | P     | SE    | Odds ratio (95% CI)   | P     |
| Age               | 0.035 | 0.994 (0.928, 1.063)  | 0.853 | 0.026 | 1.058 (1.004, 1.114)  | 0.033 |
| Diabetes duration | 0.049 | 1.005 (0.913, 1.106)  | 0.922 | 0.036 | 1.011 (0.943, 1.085)  | 0.754 |
| TC                | 0.012 | 1.691 (0.142, 2.009)  | 0.246 | 0.965 | 0.633 (0.096, 4.197)  | 0.636 |
| TG                | 1.148 | 0.126 (0.007, 2.293)  | 0.162 | 0.343 | 1.076 (0.550, 2.107)  | 0.830 |
| HDL-c             | 3.486 | 0.029 (0.000, 26.819) | 0.309 | 1.474 | 4.889 (0.272, 8.739)  | 0.282 |
| LDL-c             | 2.404 | 0.168 (0.002, 18.669) | 0.458 | 1.080 | 1.354 (0.163, 11.236) | 0.779 |
| Creatinine        | 0.015 | 0.995 (0.966, 1.024)  | 0.715 | 0.008 | 0.998 (0.982, 1.015)  | 0.848 |
| Uric              | 0.005 | 1.002 (0.993, 1.011)  | 0.714 | 0.003 | 1.003 (0.997, 1.010)  | 0.294 |
| HbA1c             | 0.137 | 1.071 (0.819, 1.400)  | 0.616 | 0.119 | 0.957 (0.758, 1.208)  | 0.711 |
| FPG               | 0.138 | 0.909 (0.693, 1.191)  | 0.489 | 0.054 | 1.032 (0.929, 1.147)  | 0.560 |
| GNRI              | 0.048 | 0.860 (0.783, 0.944)  | 0.002 | 0.031 | 0.927 (0.872, 0.985)  | 0.014 |

FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-c, High-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; SE, standard error; TC, total cholesterol; TG, triglyceride.



**Figure 2** | (a) Receiver operating characteristic analysis of the Geriatric Nutritional Risk Index (GNRI), body mass index (BMI), albumin and age for osteoporosis among men. (b) Receiver operating characteristic analysis of GNRI, BMI, albumin and age for osteoporosis among women. AUC, area under the curve.

As serum albumin and bodyweight were applied to develop the GNRI, it reflected the nutriture and enabled comprehensive assessment of the above variables. As a consequence, the GNRI value – the integration of both serum albumin and BMI – was a complementary indicator improving the diagnostic accuracy and reducing the limitations. As shown in Figure 2a,b, the AUC of GNRI was the largest compared with that of BMI and serum albumin, which was also statistically significant.

The relationship between nutrition and bone mass in chronic obstructive pulmonary disease<sup>23</sup>, chronic kidney disease<sup>24</sup>, non-alcoholic fatty liver disease<sup>25</sup> and cardiovascular disease<sup>26</sup> has been well developed. As a consequence, it has been proven that GNRI can be applied as a convenient and reliable indicator for the BMD conditions of patients with the above diseases. In addition, it has been shown that there is a dramatically inverse relationship between GNRI and BMD in rheumatoid arthritis patients<sup>27</sup>. As the association is caused by protein that originates from animals and plants<sup>28</sup>, it is crucial to guarantee the intake of enough protein from the diet.

There are several plausible mechanisms that might explain why the GNRI may be associated with osteoporosis. First, previous studies have shown that the intestinal absorption of calcium is upregulated by the high intake of protein<sup>29,30</sup>. Consistent with this, a positive relationship between the GNRI and calcium was represented in both men and women ( $r = 0.400$  for men and  $0.423$  for women). The role of calcium supplementation in the treatment of osteoporosis has been

extensively studied<sup>31</sup>. Second, supplementing protein in the diet can effectively increase muscle strength and body coordination. Furthermore, bones and joints can be protected by the enhanced muscularity<sup>32,33</sup>. Third, several studies have shown that the high intake of protein might contribute to the increased serum IGF-I level<sup>34</sup>. Yakar *et al* showed that low levels of insulin-like growth factor-1 in mice contributed to reduced bone strength<sup>35</sup>. Furthermore, another study proved that low insulin-like growth factor-1 levels played a role in increasing the risk of fracture for postmenopausal women, independent of BMD<sup>36</sup>. Therefore, high calcium, increased muscularity and high insulin-like growth factor-1 might provide evidence about the mechanisms of the significant relationship between the GNRI and osteoporosis. In the present study, based on the logistic regression analyses, the odds ratio for osteoporosis was 0.857 in men and 0.927 in women.

However, there were some limitations in the present work. First, the causality of the GNRI and BMD was difficult to evaluate in this cross-sectional study. As the present study was based on the former data, several key parameters could not be further analyzed, affecting the selection of controls. Second, all the serum samples were collected only once from the participants, and BMD at each position was also collected once, leading to the deviations in the GNRI and BMD. Third, some relevant parameters that affected the results might have been neglected in the present study, such as the menopausal status, estrogen level, dietary habits, physical activity and previous fractures.

In conclusion, a low GNRI was significantly associated with osteoporosis and low levels of BMD in type 2 diabetes mellitus patients. Compared with serum albumin and BMI, the predictive ability of GNRI for osteoporosis was superior. In summary, GNRI can be applied to evaluate the appropriate nutritional intervention.

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## DISCLOSURE

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1** | Distribution of bone mineral density (BMD).