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Research article

Association between renal function and bone mineral density in patients with type 2 diabetes mellitus

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ABSTRACT

Background: This study evaluated the association between renal function, assessed by serum creatinine and estimated glomerular filtration rate (eGFR) according to the Cockcroft–Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations, and bone mineral density (BMD) in Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: 1322 patients with T2DM were included, and their basic clinical information, serum biochemical tests, and BMD at the total hip and femur neck were collected. Multivariate adjusted linear regression, smooth curve fitting and a piecewise linear regression model were used to analyze linear and nonlinear associations. Age, BMI, drinking, smoking, systolic blood pressure and diastolic blood pressure, FBG, HbA1C, course of diabetes, hsCRP, TC, TG, HDL-C, LDL-C, Ca, P, PTH, ALP, OC, P1NP, β-CTX and 25(OH)D were adjusted.

Results: After adjusting the variables, no correlation between eGFR CG and eGFR MDRD and femur neck BMD was observed in women, men, or the total population. The eGFR CG and eGFR MDRD had a significant positive association with total hip BMD in men and the total population with T2DM. With a 10-unit decrease in eGFR CG, total hip BMD reduced by 0.012 g/cm^2 in men and 0.010 g/cm^2 the total population. Total hip BMD reduced by 0.014 g/cm^2 in men and 0.022 g/cm^2 in the total population with a 10-unit decrease in eGFR MDRD. There was no correlation between eGFR CG or eGFR MDRD and total hip BMD in female participants.

Conclusion: Impaired renal function was associated with decreased total hip BMD in men and the total population with T2DM. No associated between renal function with femur neck BMD was observed.

Abbreviations: eGFR, estimated glomerular filtration rate; CG, Cockcroft–Gault; MDRD, Modification of Diet in Renal Disease; BMD, bone mineral density; T2DM, type 2 diabetes mellitus.

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1. Introduction

Osteoporosis is known as bone mineral density (BMD) and bone quality reduction, bone micro-structure destruction and fracture risk increase. Numerous investigations have revealed that osteoporosis has a subtle relationship with type 2 diabetes mellitus (T2DM). The incidence of osteoporosis and fracture risk increased in patients with T2DM [1,2]. Patients with T2DM show a disorder in bone mineral metabolism and an increased risk of hip fracture, and the coexistence of diabetic nephropathy aggravate this condition [3,4]. Many patients with T2DM have renal impairment, and this can cause mineral homeostasis disorder that enhance the fragility of the bones [5]. Even mild to moderate decline in renal function was harmful to bone health [6,7]. The combination of diabetes and decreased renal function may further raise the risk of fracture, as well as morbidity and mortality. This suggests that a potentially large population with T2DM may be at risk, which could eventually result in a substantial economic burden.

The relationship between renal function and BMD at various skeletal sites was explored, but the results have been inconsistent [6–14]. Chen et al. reported that renal insufficiency in elderly adults was associated with decreased femoral neck BMD rather than total hip or lumbar BMD [8]. Similar trends were observed in healthy postmenopausal women, with a positive correlation between decreased renal function and femoral neck BMD [6,9]. In an analysis of the older community-dwelling population, there was a linear association between renal function and hip BMD [10]. However, some recent observational studies have reported contradictory results. Fujita et al.discovered that in older Japanese men renal function was not associated with declined BMD and elevated bone turnover after adjustment for potential confounders [12]. Additionally, the compromised renal function is unnecessary and irrelevant as a determinant of osteopenia in the spine or femur neck in healthy people [13].

Most previous studies only included older postmenopausal women whose serum creatinine (SCr) level were assessed and excluded individuals with diabetes. In these research, the clinical assessment of renal function varies. The formulas used to calculate the estimated glomerular filtration rate (eGFR) are utilized differently in Chinese patients with diabetes [15,16]. It is yet unknown if early-stage renal function loss in T2DM patients affects BMD at different skeletal sites. Therefore, it is necessary to identify the association to monitor the effect of the progression of diabetic nephropathy on the bone. Our study fully evaluated renal function by assessing SCr level and the eGFR of the Cockcroft–Gault (CG) formula and the Modification of Diet in Renal Disease (MDRD) formula. The study evaluated the association between renal function and BMD of the femoral neck and total hip in Chinese patients with T2DM.

2. Materials and Methods

2.1. Participants

Inpatients with T2DM admitted to the Department of Endocrinology at Zhongshan Hospital, Fudan University from October 2009 to January 2013 were included. T2DM was defined according to the ADA guidelines [17]. Participants were aged over the age of 18. The exclusion criteria included the following: a history of renal disease, diabetic nephropathy, severe cardiovascular and cerebrovascular diseases, malignant tumor, and endocrine diseases that might influence bone metabolism or a history of medication use, such as such as steroids, estrogen, calcium, vitamin D, calcitonin, bisphosphonate, furosemide, thiazide diuretics. 1322 patients were included. Written informed consent was obtained and the Ethics Committee of Zhongshan Hospital, Fudan University approved the study protocol (Approval No. B2017-172 R).

2.2. Data collection

Basic information, laboratory tests, and BMD of each patient were collected. Basic information included age, gender, diabetes duration, body mass index (BMI), smoking and drinking, and history of hypertension. BMI = weight (kg)/height (m) [2]. Laboratory tests included glucose metabolism indexes, lipid metabolism indexes and renal function. The three different indices measuring renal function were SCr, eGFR CG, and eGFR MDRD. The eGFR was calculated using the formula: eGFR CG (ml/min/1.73 m^2) = (140 − age) × weight (kg)/SCr (mg/dL)/72 × (0.85 for females) × 1.73 m^2/body surface area (BSA), BSA = weight $(kg)^{0.425}$ × height $(cm)^{0.725}$ × 0.007184 [18]; eGFR MDRD (ml/min/1.73 m^2) = 186.3 × SCr $(mg/dL)^{-1.154}$ × (age) $^{-0.203}$ × (0.742 for females) [19]. Serological indexes related to bone metabolism were also determined. Serum samples were collected at 6 a.m. and the same machines and procedures were used for testing. The BMD of each patient was measured by dual-energy X-ray absorptiometry (Hologic-Discovery, USA). The same machine and software were used for all BMD measurements and analysis.

2.3. Statistical analyses

Categorical and continuous variables are expressed as numbers, proportions, and mean ± standard deviation. The chi-squared test was used to analyze categorical variables. One-way analysis of variance and the Kruskal–Wallis test was used for normally distributed continuous and skewed continuous variables, respectively. The linear associations between every 10-unit in renal function and BMD at the femur neck and total hip was analyzed. Covariates were included as potential confounders in the final models if they changed the estimates of renal function on BMD by more than 10% or were significantly associated with BMD [20]. The model I was adjusted for age, BMI, drinking, smoking, blood pressure. The model II was further adjusted for fasting blood glucose (FBG), glycosylated hemoglobin (HbA1C), course of diabetes, high sensitivity c reactive protein (hsCRP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Calcium (Ca), phosphorus(P), parathyroid

hormone (PTH), 25(OH)D levels, osteocalcin (OC), total procollagen type 1 *N*-terminal propeptide (P1NP), alkaline phosphatase (ALP), and *C*-terminal telopeptide of type I collagen (cCTX). We further examined the nonlinear association between renal function and BMD at the femoral neck and total hip. Smooth curve fitting and a piecewise linear regression model were applied to analyze nonlinear associations. In the figure of smooth curve fitting, the horizontal coordinate represents renal function (SCr, eGFR CG, eGFR MDRD), and the ordinate represents BMD at the femur neck and total hip. Both linear and nonlinear correlations between renal function and BMD at the femoral neck and total hip were analyzed separately in male and female patients. Models I and II were assessed by performing linear and nonlinear analyses. The regression coefficients and 95% confidence intervals (CIs) were shown. A $p < 0.05$ is with statistical significance. The logarithmic likelihood ratio test compared the differences between Models I and II. *P* for the logarithmic likelihood ratio test <0.05 suggesting a nonlinear association.

R (http://www.r-project.org) and Empower R (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) were used for statistical analyses.

3. Results

3.1. Demographic characteristic of the participants

1322 patients with T2DM (763 men and 559 women) were included. We described the characteristics of different genders. The ages were 60.56 ± 11.51 years for women and 55.16 ± 12.83 years for men, and the diabetes durations were for 8.44 ± 7.07 and 6.01 ± 6.32 years, respectively. Men were more likely than women to smoke and drink, and more women had a history of high blood pressure and had higher systolic blood pressure values than men. The mean HbA1c, TC, LDL-C, HLD-C, P, PTH, 25(OH)D, UA, SCr, and eGFR CG were lower in women than men. BMD at the total lumbar and femoral neck were lower in women than men. In women and men, the

Table 1
Demographic characteristic of the study population.

Variable	Women	Men	Total	*P*-value
N	559	763	1322	
Age (years)	60.56 ± 11.51	55.16 ± 12.83	57.44 ± 12.57	<0.001
BMI(kg/m2)	24.87 ± 3.60	24.94 ± 3.51	24.91 ± 3.55	0.735
Smoking				<0.001
No	549 (98.21%)	436 (57.14%)	985 (74.51%)	
Yes	10 (1.79%)	327 (42.86%)	337 (25.49%)	
Drinking				<0.001
No	554 (99.11%)	591 (77.56%)	1145 (86.68%)	
Yes	5 (0.89%)	171 (22.44%)	176 (13.32%)	
Hypertension				<0.001
No	252 (45.08%)	440 (57.67%)	692 (52.34%)	
Yes	307 (54.92%)	323 (42.33%)	630 (47.66%)	
Course of diabetes (years)	8.44 ± 7.07	6.01 ± 6.32	7.04 ± 6.75	<0.001
Systolic blood pressure (mmhg)	132.50 ± 16.39	129.94 ± 15.64	131.02 ± 16.01	0.004
Diastolic blood pressure (mmhg)	80.47 ± 9.47	81.62 ± 9.34	81.14 ± 9.41	0.028
FBG (mmol/l)	8.69 ± 3.31	8.74 ± 3.03	8.72 ± 3.15	0.777
HbA1C (%)	9.03 ± 2.21	9.49 ± 2.38	9.30 ± 2.32	<0.001
TC (mmol/l)	4.78 ± 1.38	4.49 ± 1.09	4.62 ± 1.23	<0.001
TG (mmol/l)	2.04 ± 2.23	2.18 ± 2.51	2.12 ± 2.40	0.293
HDL-C (mmol/l)	1.19 ± 0.32	1.05 ± 0.28	1.11 ± 0.31	<0.001
LDL-C (mmol/l)	2.71 ± 0.99	2.57 ± 0.84	2.63 ± 0.91	0.005
P (mmol/l)	1.24 ± 0.20	1.26 ± 0.20	1.30 ± 0.20	<0.001
Ca (mmol/l)	2.22 ± 0.11	2.20 ± 0.11	2.23 ± 0.12	0.793
25(OH)D (nmol/l)	32.00 ± 16.19	37.52 ± 17.68	35.19 ± 17.28	<0.001
PTH(pg/ml)	35.6 ± 14.8	36.80 ± 15.65	38.5 ± 16.7	0.001
ALP (u/l)	75.91 ± 36.16	73.84 ± 28.53	74.72 ± 31.98	0.246
OC(pg/ml)	15.55 ± 7.56	13.18 ± 6.06	14.18 ± 6.83	<0.001
P1NP(ng/ml)	44.40 ± 23.15	38.75 ± 29.18	41.14 ± 26.93	<0.001
β-CTX (ng/ml)	0.46 ± 0.28	0.44 ± 0.28	0.45 ± 0.28	0.110
BUN(mmol/l)	5.47 ± 1.75	5.77 ± 1.96	5.64 ± 1.88	0.004
UA (μmol/l)	284.41 ± 84.70	321.13 ± 90.24	305.66 ± 89.77	<0.001
SCr(μmol/l)	56.27 ± 17.13	74.08 ± 27.45	66.57 ± 25.23	<0.001
eGFR CG (ml/min/1.73 m^2)	100.19 ± 36.88	111.46 ± 40.18	106.75 ± 39.22	<0.001
eGFR MDRD (ml/min/1.73 m^2)	110.93 ± 32.80	111.29 ± 31.03	111.14 ± 31.78	0.838
Femur neck BMD(g/cm2)	0.71 ± 0.13	0.80 ± 0.12	0.76 ± 0.13	<0.001
Total hip BMD(g/cm2)	0.85 ± 0.14	0.95 ± 0.14	0.91 ± 0.15	<0.001

Values are mean ± SD or n (%) unless otherwise specified. A $p < 0.05$ was considered statistically significant.
BMI body mass index; FBG fasting blood glucose; HbA1C glycosylated hemoglobin; TC total cholesterol; TG triglyceride; HDL-C high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; P phosphate; PTH parathyroid hormone; ALP alkaline phosphatase; OC osteocalcin; P1NP procollagen type 1 *N*-terminal propeptide; β-CTX *C*-terminal telopeptide of type I collagen; BUN; UA; SCr serum creatinine; eGFR estimated glomerular filtration rate; CG Cockcroft-Gault; MDRD Modification of Diet in Renal Disease; BMD bone mineral density.

SCr, eGFR CG, and eGFR MDRD were 56.27 ± 17.13 and 74.08 ± 27.45 mg/dL, 100.19 ± 36.88 and 111.46 ± 40.18 ml/min/1.73 m^2, and 110.93 ± 32.80 and 111.29 ± 31.03 ml/min/1.73 m^2, respectively. The BMD of the femoral neck and total hip was 0.71 ± 0.13 and 0.85 ± 0.14 and 0.80 ± 0.12 and 0.95 ± 0.14 g/cm^2 for women and men, respectively (Table 1).

3.2. Linear association between renal function and BMD

For BMD at the femur neck, there was a positive association between eGFR CG and femur neck BMD in women, men, and the total population with T2DM in the crude model. In contrast, only in women SCr level presented a negative correlation with femur neck BMD, and eGFR MDRD presented a positive correlation with femur neck BMD. No statistical significance was found when the models were adjusted for age, BMI, drinking, smoking, blood pressure, FBG, HbA1C, course of diabetes, hsCRP, TC, TG, HDL-C, LDL-C, Ca, P, PTH,25(OH)D, ALP, OC, P1NP, and β-CTX (Table 2).

Similar results were obtained for BMD at the total hip. In the non-adjusted model, with a 10-unit increase in eGFR CG, total hip BMD increased by 0.020 g/cm^2, 0.010 g/cm^2, and 0.011 g/cm^2 in women, men, and the total population, respectively (both $p <$ 0.0001). However, in the multivariate adjusted models, no correlations between SCr level, eGFR CG, eGFR MDRD, and total hip BMD were observed in women, men, or the total population.

3.3. Nonlinear association between renal function and femur neck BMD

Smooth curve fitting was applied to observe the association between renal function and BMD at the femoral neck and total hip (Fig. 1 and Fig. 2). The x-axis represents renal function, and the y-axis represents BMD. A piecewise linear regression model was further utilized to analyze the nonlinear associations (Table 3). The SCr level was negatively correlated with femur neck BMD (both p for log likelihood ratio test <0.05) when SCr levels were <53 and < 43 μmol/l in men and the total population, respectively. With a 10-unit increase in SCr, femur neck BMD reduced by 0.071 g/cm^2 (p = 0.0130, 95% CI: −0.116 to −0.008) in men and 0.062 g/cm^2 (p = 0.0122, 95% CI: −0.107 to −0.013) in the total population after adjusting the variables. However, no nonlinear correlation was found between eGFR CG and eGFR MDRD and femur neck BMD in either women, men, or the total population with T2DM.

For BMD at the total hip, there was no nonlinear correlation between SCr and total hip BMD in either women, men, or the total population. The eGFR CG and eGFR MDRD were positively associated with total hip BMD in men and the total population. Total hip BMD in male T2DM patients decreased by 0.012 g/cm^2 and 0.014 g/cm^2 per 10-unit decrease of eGFR CG when eGFR CG was <180.3 ml/min/1.73 m^2 (p = 0.0234, 95% CI: 0.002–0.013) and per 10-unit decrease of eGFR MDRD when eGFR MDRD was <159.3 ml/min/1.73 m^2 (p = 0.0482, 95% CI: 0.002–0.031) after adjusting the confounding factors. The same trends were observed between eGFR CG

Table 2
Multivariate adjusted linear regression for the relationship between SCr, eGFR CG, eGFR MDRD and BMD at femur neck and total hip.

	Women β (95% CI) p-value	Men β (95% CI) p-value	Total β (95% CI) p-value
Femoral neck			
Non-adjusted			
SCr(per 10-unit)	−0.011 (-0.020, −0.002) 0.0020	−0.003 (−0.003, 0.001) 0.7811	−0.003 (−0.012, 0.002) 0.0851
eGFR CG (per 10-unit)	0.020 (0.011, 0.024) <0.0001	0.013 (0.010, 0.014) <0.0001	0.012 (0.011, 0.015) <0.0001
eGFR MDRD (per 10-unit)	0.011 (0.003, 0.014) <0.0001	0.003 (−0.004, 0.011) 0.1026	0.003 (0.001, 0.014) <0.0001
Model I			
SCr(per 10-unit)	−0.004 (−0.010, 0.014) 0.8515	−0.001 (−0.003, 0.001) 0.9821	−0.003 (−0.004, 0.004) 0.9053
eGFR CG (per 10-unit)	0.003 (−0.004, 0.012) 0.1378	0.004 (−0.005, 0.013)0.0794	0.005 (0.001, 0.012) 0.0125
eGFR MDRD (per 10-unit)	−0.003 (−0.005, 0.001) 0.7817	0.003 (−0.004, 0.005) 0.7451	0.001 (−0.002, 0.004) 0.6412
Model II			
SCr(per 10-unit)	−0.002 (−0.012, 0.011) 0.7999	−0.004 (−0.005, 0.004) 0.5097	−0.003 (−0.005, 0.002)0.6224
eGFR CG (per 10-unit)	0.004 (−0.003, 0.011) 0.0797	0.005 (−0.004, 0.011) 0.0573	0.004 (0.002, 0.013) 0.0124
eGFR MDRD (per 10-unit)	0.001 (−0.001, 0.004) 0.8012	0.003 (−0.002, 0.005) 0.5339	0.001 (−0.002, 0.004) 0.4767
Total hip			
Non-adjusted			
SCr(per 10-unit)	−0.012 (−0.017, −0.010) 0.0006	0.002 (−0.001, 0.003) 0.9892	−0.004 (−0.012, 0.002) 0.1065
eGFR CG (per 10-unit)	0.020 (0.012, 0.024) <0.0001	0.010 (0.010, 0.012) <0.0001	0.011 (0.011, 0.013)<0.0001
eGFR MDRD (per 10-unit)	0.010 (0.001, 0.013) <0.0001	−0.001 (−0.001, 0.003) 0.5703	0.001 (0.001, 0.014) 0.0104
Model I			
SCr(per 10-unit)	−0.002 (−0.011, 0.003) 0.2400	−0.002 (−0.002, 0.001) 0.9474	−0.001 (−0.002, 0.004) 0.5106
eGFR CG (per 10-unit)	0.003 (−0.003, 0.010) 0.4026	0.001 (-0.001, 0.003)0.9110	0.003 (−0.002, 0.003) 0.3692
eGFR MDRD (per 10-unit)	−0.002 (−0.003, 0.001) 0.9707	−0.003 (−0.012, 0.004) 0.1935	−0.002 (−0.002, 0.002) 0.6227
Model II			
SCr(per 10-unit)	−0.002 (−0.010, 0.004) 0.5106	−0.002 (−0.012, 0.003) 0.5484	−0.001 (−0.004, 0.002)0.5428
eGFR CG (per 10-unit)	0.001 (−0.001, 0.013) 0.5246	0.002 (−0.001, 0.010)0.4556	0.003 (−0.002, 0.004) 0.3898
eGFR MDRD (per 10-unit)	0.003 (−0.003, 0.002) 0.9306	−0.001 (−0.003, 0.004) 0.6039	−0.002 (−0.003, 0.002) 0.7697

Data were presented as β (95%CI) p-value; A $p < 0.05$ was considered statistically significant.
Adjusted model I was adjusted for age, BMI, drinking, smoking, systolic blood pressure and diastolic blood pressure.
Adjusted model II was further adjusted for FBG, HbA1C, course of diabetes, hsCRP, TC, TG, HDL-C, LDL-C, Ca, P, PTH, ALP, OC, P1NP, β-CTX and 25 (OH)D.

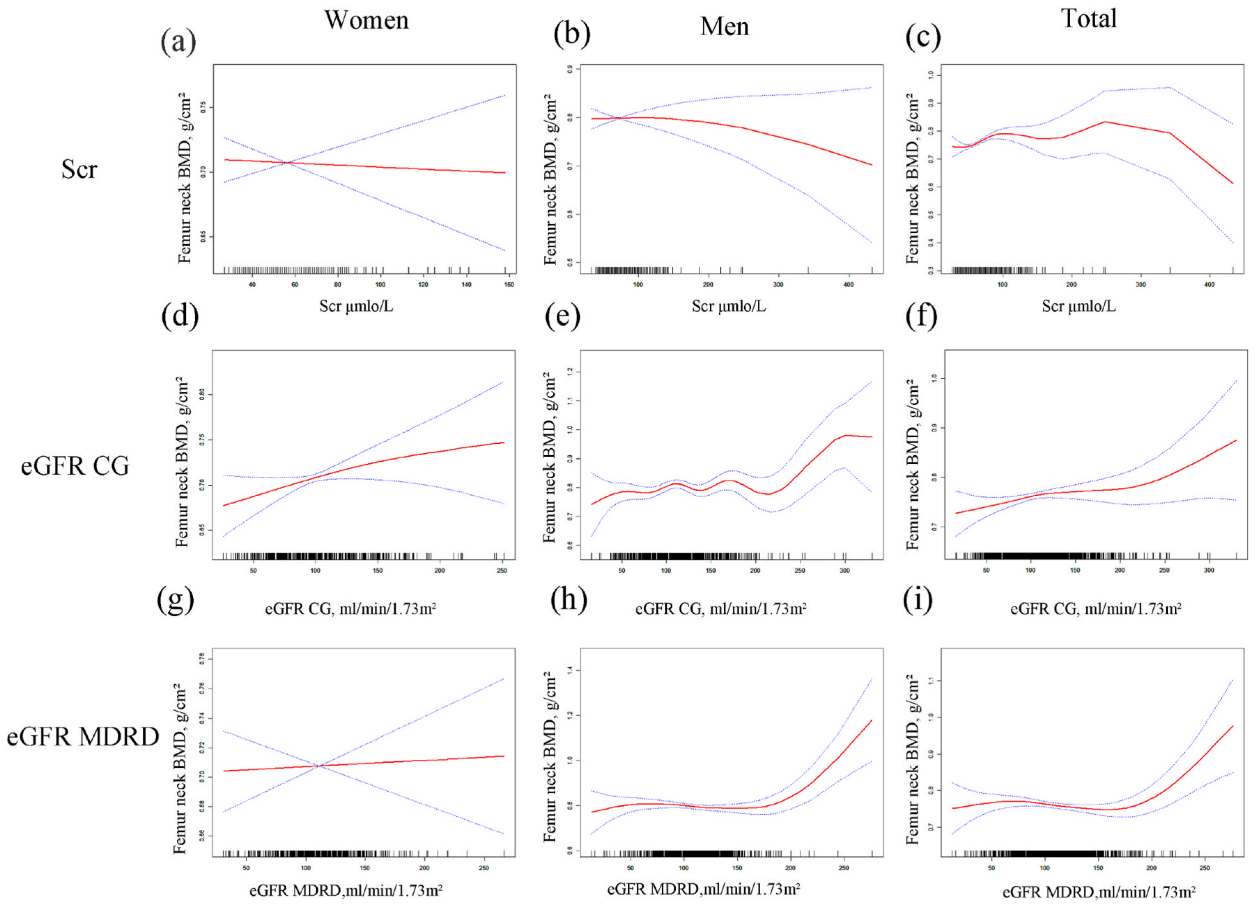

Fig. 1. Smooth curve fitting for the relationship between SCr, eGFR CG, eGFR MDRD and femur neck BMD. Adjusted for age, BMI, drinking, smoking, systolic blood pressure and diastolic blood pressure, FBG, HbA1C, course of diabetes, hsCRP, TC, TG, HDL-C, LDL-C, Ca, P, PTH, ALP, OC, P1NP, β-CTX and 25(OH)D. Smooth curve fitting for the relationship between SCr and femur neck BMD in women (a), men (b) and total (c). Smooth curve fitting for the relationship between eGFR CG and femur neck BMD in women (d), men (e) and total (f). Smooth curve fitting for the relationship between eGFR MDRD and femur neck BMD in women (g), men (h) and total (i).

and eGFR MDRD and total hip BMD in men and the total population. With a 10-unit decrease in eGFR CG, total hip BMD reduced by 0.010 g/cm^2 in the total population ($p = 0.0087$, 95% CI: 0.004–0.022). Total hip BMD was reduced by 0.022 g/cm^2 in the total population with a 10-unit decrease in eGFR MDRD ($p = 0.0305$, 95% CI: 0.003–0.044). Notably, the positive association between eGFR CG and eGFR MDRD and the total hip in the total population was significant when eGFR CG was< 81.7 ml/min/1.73 m^2 and eGFR MDRD was <60 ml/min/1.73 m^2. When the eGFR was higher than that, the association was statistically insignificant. Neither eGFR CG nor eGFR MDRD were found to be correlated with the total hip BMD in women (Table 3).

4. Discussion

This is the first sizeable cross-sectional study to explore the association between renal function, measured by SCr level, eGFR CG and eGFR MDRD, and BMD at the femur neck and total hip in Chinese T2DM patients. This study found that decreased eGFR CG and eGFR MDRD were associated with decreased total hip BMD in men and the total population with T2DM, but not in women. It highlighted that even while renal function in males with T2DM was at a relatively normal level, total hip BMD decreased by 0.12–0.14 g/cm^2 with the decline in renal function (eGFR CG and eGFR MDRD) by approximately 10 ml/min/1.73 m^2. There was no correlation between SCr and total hip BMD in either men or women, or in the total population with T2DM. After adjusting for the variables, a relatively low SCr level was inversely correlated with femur neck BMD in men and the total population. A decline in renal function was not associated with femur neck BMD in Chinese T2DM patients whether they were men, women, or the total population.

It is difficult to estimate renal function accurately in T2DM patients. According to earlier research, almost 20.0% of older Chinese patients with diabetes showed mild kidney damage [16]. The optimal method to assess renal function in Chinese patients is still up for debate. Due to concerns over the reliability of these markers (SCr level, eGFR CG and eGFR MDRD) in Chinese patients with T2DM [15,16], we used all of these common clinical indicators to assess renal function in this investigation. SCr is a commonly used indicator of renal function. But SCr levels cannot accurately predict renal function especially in elderly patients with impaired renal function [21].

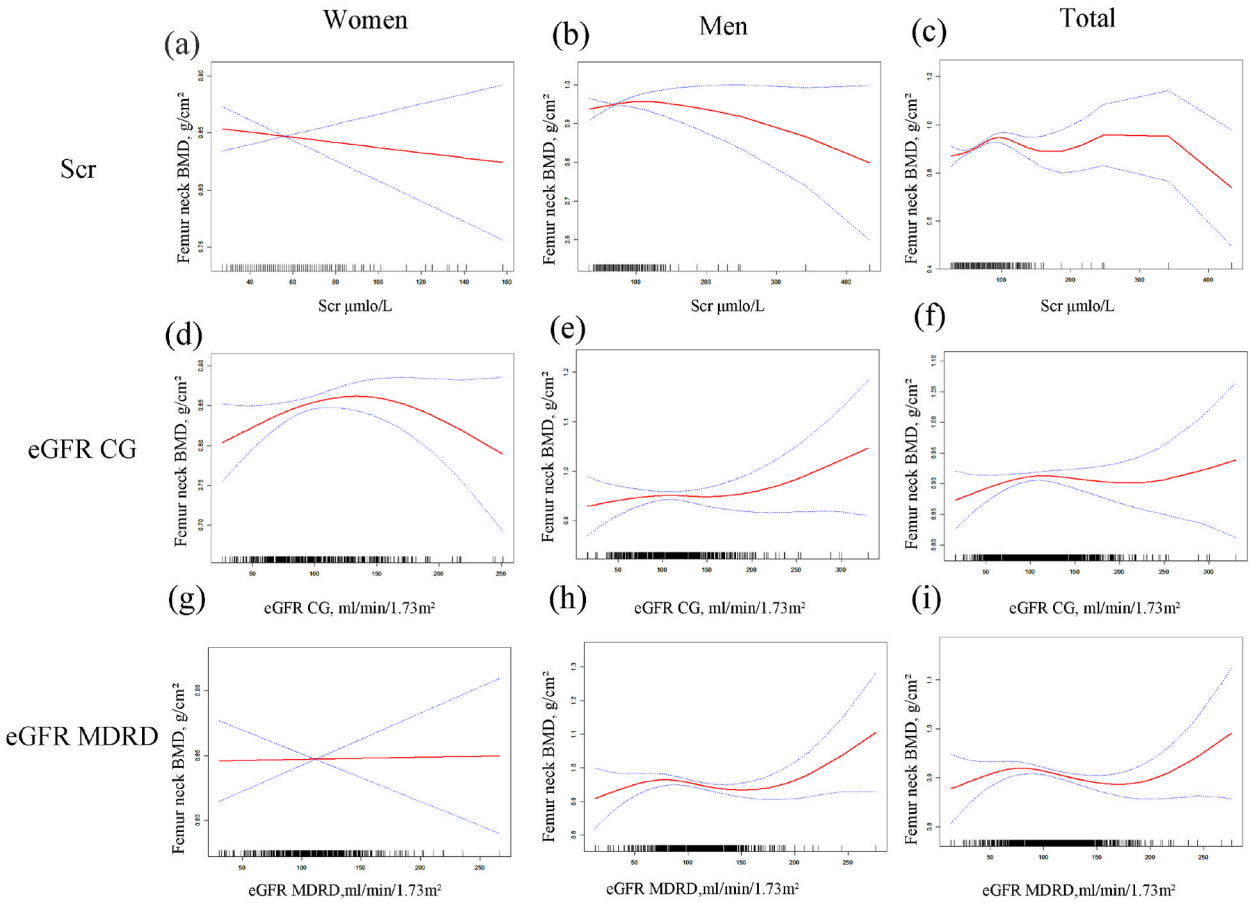

Fig. 2. Smooth curve fitting for the relationship between SCr, eGFR CG, eGFR MDRD and total hip BMD. Adjusted for age, BMI, drinking, smoking, systolic blood pressure and diastolic blood pressure, FBG, HbA1C, course of diabetes, hsCRP, TC, TG, HDL-C, LDL-C, Ca, P, PTH, ALP, OC, P1NP, β-CTX and 25(OH)D. Smooth curve fitting for the relationship between SCr and total hip BMD in women (a), men (b) and total (c). Smooth curve fitting for the relationship between eGFR CG and total hip BMD in women (d), men (e) and total (f). Smooth curve fitting for the relationship between eGFR MDRD and total hip BMD in women (g), men (h) and total (i).

SCr levels are also disturbed by some uncontrollable factors, including diet and the amount of muscle mass. Moreover, studies have demonstrated that eGFR is more accurate for assessing renal function [22]. However, eGFR can vary tremendously depending on choice of equation. In healthy adults and older participants, eGFR was reportedly overestimated and underestimated by the CG and MDRD formulas, respectively [23]. In a retrospective analysis of older people, Garg et al. found that eGFR predicted by CG was always lower than MDRD [24]. CG was inaccurate, especially in individuals who were overweight [25], and MDRD was not the optimal method to evaluate renal function in Chinese patients [26].

Consistent with our conclusion, Jassal et al. [10] reported a positive correlation between early renal dysfunction and hip BMD in men. There was the strongest correlation between renal function and hip BMD when eGFR CG was $<$60 ml/min/1.73 m^2, and eGFR CG was suggested to predict 4-year bone loss. In a longitudinal study of 1477 individuals aged $\geq$65 years, renal dysfunction showed decreased BMD only at the male femoral neck site and PTH was considered to work partially in this association [8]. In female participants, no correlation between the eGFR and BMD at any site were found. We found sex differences that were similar to their results. The reason for this sex-specific association remains unclear. The failure to determine an association between renal function and hip BMD in women likely reflects the multiple causes of decreased BMD (including glucose control and estrogen levels). Indeed, there are many reasons, and the reasons may include abnormalities in calcium and phosphorus metabolism. The HbA1c, serum P, and PTH levels in women were lower than men in our study. Better glucose control may attenuate the impairment of bone metabolism in diabetes. Simultaneously, it can also slow down the progress of injury in the nephrons. In addition, endogenous hormones in the body are crucial to skeletal health, and there are sex differences in hormone content, such as estrogen [27], causing sex differences in bone loss, which might be partially explained by the lack of association between eGFR and hip BMD in female patients. Although some studies have indicated that decreased eGFR was not associated with lower BMD at different sites [12,14], the differences may be partly due to differences in age, gender and weight of the study population, eGFR formula, site of BMD observation, and potential confounding variables. Discordance in BMD at different sites is significantly associated with renal dysfunction [28]. BMD declines at different speeds in different positions in the elderly [29]. Therefore, the difference exists between eGFR and BMD at the femur neck and total hip

Table 3
Non-linear association between SCr, eGFR CG, eGFR MDRD and BMD at femur neck and total hip.

Femoral neck	Women β (95% CI) p-value	Men β (95% CI) p-value	Total β (95% CI) p-value
SCr (per 10-unit)			
Model I	−0.002 (-0.011, 0.010) 0.7999	−0.001 (−0.002, 0.001)0.5097	−0.001 (−0.002, 0.004)0.6224
One line slope			
Model II	3.8	5.3	4.3
Turning point (K)	−0.052 (−0.147, 0.049)0.3204	−0.071 (−0.116, −0.008)0.0130	−0.062 (−0.107, −0.013)0.0122
< K slope 1	−0.003 (−0.012, 0.009)0.9590	−0.001 (−0.002, 0.001)0.8950	−0.003 (−0.003, 0.002)0.9170
> K slope 2	0.315	0.013	0.012
P for logarithmic likelihood ratio test			
eGFR CG (per 10-unit)			
Model I	0.002 (−0.001, 0.008)0.0797	0.002 (−0.003, 0.011)0.0573	0.001 (0.001, 0.006)0.0124
One line slope			
Model II	13.84	18.03	10.19
Turning point (K)	0.010 (0.004, 0.012)0.0199	0.003 (−0.001, 0.012)0.2803	0.012 (0.003, 0.009)0.0127
< K slope 1	−0.002 (−0.013, 0.009)0.6537	0.012 (0.001, 0.017)0.0473	0.002 (−0.003, 0.011)0.1863
> K slope 2	0.113	0.186	0.180
P for logarithmic likelihood ratio test			
eGFR MDRD (per 10-unit)			
Model I	0.001 (−0.003, 0.001)0.8012	0.002 (−0.001, 0.004)0.5339	0.001 (−0.002, 0.004)0.4767
One line slope			
Model II	16.66	15.93	16.26
Turning point (K)	−0.002 (−0.004, 0.001)0.9392	−0.002 (−0.011, 0.004)	−0.002 (−0.002, 0.004)0.2852
< K slope 1	0.014 (−0.008, 0.022)0.4451	0.020 (0.010, 0.043) <0.0001	0.021 (0.007, 0.028)0.0003
> K slope 2	0.458	<0.001	<0.001
P for logarithmic likelihood ratio test	Women β (95% CI) p-value	Man β (95% CI) p-value	Total β (95% CI) p-value
Total hip			
SCr (per 10-unit)			
Model I	−0.001 (−0.010, 0.002)0.5106	−0.002 (−0.011, 0.004) 0.5484	−0.001 (−0.004, 0.004)0.5428
One line slope			
Model II	4.4	8.8	9.3
Turning point (K)	0.020 (−0.033, 0.061)0.5304	0.011 (0.001, 0.019)0.0741	0.003 (−0.002, 0.008)0.2471
< K slope 1	−0.003 (−0.010, 0.004)0.3827	−0.010 (−0.014, −0.001)0.3850	−0.002 (−0.012, 0.003)0.0930
> K slope 2	0.456	0.110	0.079
P for logarithmic likelihood ratio test			
eGFR CG (per 10-unit)			
Model I	0.002 (−0.003, 0.014)0.5246	0.004 (−0.002, 0.008)0.4556	0.002 (−0.001, 0.002) 0.3898
One line slope			
Model II	13.99	18.03	8.17
Turning point (K)	0.002 (−0.002, 0.004)0.9877	0.012 (0.002, 0.013) 0.0234	0.010 (0.004, 0.022)0.0087
< K slope 1	0.011 (−0.002, 0.017)0.1163	−0.011 (−0.020, −0.003)0.0623	−0.001 (−0.003, 0.002) 0.7759
> K slope 2	0.159	0.002	0.012
P for logarithmic likelihood ratio test			
eGFR MDRD (per 10-unit)			
Model I	0.002 (−0.001, 0.002)0.9306	−0.003 (−0.003, 0.001) 0.6039	−0.002 (−0.004, 0.001)0.7697
One line slope			
Model II	9.3	15.93	6
Turning point (K)	0.011 (−0.003, 0.024) 0.3001	0.014 (0.002, 0.031)0.0482	0.022 (0.003, 0.044)0.0305
< K slope 1	−0.001 (−0.012, 0.003) (-0.01, 0.00) 0.5366	−0.002 (−0.010, 0.003) 0.1212	−0.002 (−0.003, 0.003) 0.2512
> K slope 2	0.266	0.026	0.025
P for logarithmic likelihood ratio test			

Data were presented as β (95%CI) p-value; A $p < 0.05$ was considered statistically significant.
Model I, linear analysis; Model II, non-linear analysis. P for logarithmic likelihood ratio test<0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship. Adjusted for age, BMI, drinking, smoking, systolic blood pressure and diastolic blood pressure, FBG, HbA1C, course of diabetes, hsCRP, TC, TG, HDL-C, LDL-C, Ca, P, PTH, ALP, OC, P1NP, β-CTX and 25(OH)D.

in Chinese patients with T2DM.

However, the potential mechanism remains unknown. The kidney produces the 1,25-dihydroxy vitamin D and regulates phosphate and calcium metabolism [5]. They also vary in concentration to regulate different bone-regulating hormones, such as PTH. Renal synthesis of calcitriol decreased, and phosphate levels increased in the relatively early stages of CKD, which in turn leads to a significant increase in PTH level [30,31]. This change contributes to maintaining the serum phosphate and calcium levels within the normal range and maintaining dynamic balance. However, they are not conducive to bone formation, with advancing renal impairment [32], causing cortical bone loss [33]. In addition, deficient 25(OH)D concentration is hypothesized to aggravate secondary hyperparathyroidism. Although the mean PTH level was within the normal range, a slight increase in PTH affects bone metabolism in early CKD. Bezerra et al. reported that aging and hyperparathyroidism caused BMD decline predominantly at the hip, but not the spine, in patients with reduced renal function [34]. Furthermore, changes in BMD and acceleration of bone transformation occurred in the early stage of diabetic nephropathy [35]. Bones are more vulnerable due to vitamin D deficiency and secondary hyperparathyroidism,

in turn, possibly explaining its effect on the association between eGFR and total hip BMD in the early stage of diabetic nephropathy.

This study has notable strengths, including focusing on Chinese patients with T2DM without renal disease. Data about this population are scarce. With 1322 participants, it had a sizable sample size. To our knowledge this is the first population-based study to evaluate the association between renal function and BMD at the femoral neck and total hip in a large sample of Chinese patients with T2DM. Additionally, renal function was assessed by SCr level, eGFR CG, and eGFR MDRD, which are commonly used indicators in clinics. Besides, many important factors were adjusted for in the analysis, such as the course of diabetes and Ca, P, PTH, 25(OH)D, ALP, OC, P1NP, and β-CTX.

The study has some limitations. First, causality cannot be determined between renal function and BMD because it was a cross-sectional study. Further study is indispensable to confirm this association. Second, the population included patients with T2DM; thus, our findings may require caution and be prudent in the application to the general population. Third, some critical confounding factors were not detected, such as menopausal status, female sex, and estrogen level, which may have an impact on bone and affect the results. The average age of women in the study was 60.56 years; thus, they were regarded as postmenopausal, and their estrogen levels were not adjusted in the analysis. Finally, although the two equations were used to calculate eGFR and SCr level for evaluating renal function in this study, the method to evaluate renal function in Chinese patients has limited accuracy [26]. Inulin or radioisotope clearance is recognized as the gold standard. However, it is not easily available in most clinical settings. Data on urine albumin or urine albumin-to-creatinine ratio, which is fast and straightforward to obtain and is applicable for the clinical diagnosis of impaired renal function, were insufficient.

5. Conclusion

This study showed that impaired renal function was associated with decreased total hip BMD in men and the total population with T2DM, but not in women. There was no association between renal function decline and femoral neck BMD in Chinese patients with T2DM. Therefore, hip BMD should be monitored in the early stage of renal function decline in patients with T2DM.

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Author contribution statement

Yangli Ye: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Xilu Yi: Performed the experiments; Analyzed and interpreted the data.
Yao Zhang and Guiping Xu: Performed the experiments; Analyzed and interpreted the data.
Mingxiang Yu: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Xinhua Qu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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