Int Urol Nephrol (2015) 47:1547–1553
DOI 10.1007/s11255-015-1082-1

NEPHROLOGY - ORIGINAL ARTICLE

Relationship between mild-to-moderate chronic kidney disease and decreased bone mineral density in Chinese adult population

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Received: 19 June 2015 / Accepted: 5 August 2015 / Published online: 12 August 2015

Abstract
Background Several studies have shown ethnic differences in bone and mineral metabolism in healthy people and patients with chronic kidney disease (CKD). However, there have been few studies regarding CKD and bone mineral density (BMD) in Chinese population. We aimed to explore the relationship between mild-to-moderate CKD and decreased BMD in Chinese adult population.
Methods A total of 24,002 adults were enrolled in this cross-sectional study. Mild-to-moderate CKD was defined as 30 < estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or eGFR ≥ 60 mL/min/1.73 m^2 with proteinuria greater than 1+. BMD was measured by dual-energy X-ray absorptiometry at the lumbar spine. Either osteopenia or osteoporosis was defined as decreased BMD. Multivariate logistic regression analysis was used to estimate the associations with decreased BMD.
Results The subjects comprised 71.5 % men and 28.5 % women, the age was 49.9 ± 13.9 years. The overall prevalence of CKD was 2.9 %. Decreased BMD was 22.1, 19.9 % had osteopenia, and 2.2 % had osteoporosis. The percentage of patients with decreased BMD, osteopenia and osteoporosis were statistically higher ($P < 0.05$) in CKD patients compared with those of non-CKD participants, which was 29.5 versus 21.9 %, 25.9 versus 19.8 % and 3.6 versus 2.1 %, respectively. The risk for decreased BMD increased with CKD in a simple logistic analysis. However, the correlation disappeared after adjusted for age, sex, smoking, drinking, hypertension, diabetes and obesity.
Conclusions Subjects with worse renal function have significantly lower BMD, but after adjusted for confounders, mild-to-moderate CKD is not independently associated with decreased BMD.

Keywords Chronic kidney disease · Bone mineral density · Absorptiometry · Osteopenia · Osteoporosis

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Introduction

Chronic kidney disease (CKD) is increasing worldwide and to be a global public heath problem [1, 2]. A recent national survey in China indicates that the prevalence of CKD is 10.8 %, and the number of patients with CKD is estimated to 119.5 million [3]. The prevalence of osteoporosis is also

increasing on a global scale. These increases are, in part, related to the increase in aging, obesity, diabetes mellitus and hypertension [3, 4]. CKD-mineral and bone disorder (CKD-MBD) is the term used for the set of changes in bone mineral metabolism as well as its skeletal and cardiovascular complications in CKD patients, such as blood vessel calcifications, fractures and so on. End-stage renal disease (ESRD) is a well-established risk factor for decreased bone mineral density (BMD) and osteoporosis as well as for hip fracture [5–7]. However, the data on the relationship of CKD with BMD are mixed. Data from NHNES III showed that individuals with decreased kidney function had lower BMD in unadjusted models [8]. But, after adjusted for age, sex and race, there was no significant relationship of CKD with BMD. In patients with CKD stages 3–5D with evidence of mineral bone disease, the K/DIGO suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy [9]. However, Yenchek et al. [10] conducted a cohort study and argued against the current KDIGO guideline recommendations and suggested that there may be a role for dual-energy X-ray absorptiometry for screening in CKD.

Several studies have shown ethnic differences in bone and mineral metabolism in healthy people and patients with chronic kidney disease (CKD) [11]. The effect of height, weight and body composition (fat mass, lean body mass, etc.) may result in ethnic difference in bone mass [12]. There have been few studies regarding renal function and BMD with mild or moderate to severe CKD patients in Asia Countries [13–15]. In China, the percentage of mild-to-moderate CKD comprised 98.5 % of all CKD patients [3]. There is little data on the effects of mild-to-moderate renal insufficiency on BMD in Chinese population. Therefore, we aimed to explore the relationship between mild-to-moderate CKD and decreased BMD in Chinese adult population.

Methods

Study population

A total of 24,002 adults who visited the Health Checkup Clinic consecutively in a large tertiary-care university hospital were enrolled in this cross-sectional study. The investigation started in April 2012 and ended in December 2013. Those participants come from all over Jinan to receive a regular paid health examination. Patients with hepatic dysfunction, thyroid diseases, or systemic diseases that might affect bone metabolism were not included. All subjects were free of drugs (such as glucocorticoids, vitamin D, calcium, bisphosphonates and so on.) known to influence bone metabolism until the time of the present study.

The ethics committee of Qianfoshan Hospital approved the study. All participants gave written informed consent prior to data collection.

Blood biochemistry measurements and biometric parameters

Blood was collected by means of venipuncture after an overnight fast of at least 10 h. Routine serum and urinary chemistry determinations were performed by standard automated techniques. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16, 17]. Serum creatinine was measured by means of using the Roche enzymatic method on an automatic biochemistry analyzer (Roche P Modular with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd., www.roche.com). Proteinuria was measured on a morning urine sample using urinary dipstick test. Participants with pyuria were excluded from the analysis of proteinuria due to concern of urinary tract infection. Women during menstruation were asked to receive urine routine test 3 days after menstruation. A dipstick result of trace urine protein or more was defined as proteinuria. eGFR $\geq$ 60 mL/min/1.73 m^2 with proteinuria greater than 1+ or 30 < eGFR < 60 mL/min/1.73 m^2 was defined as mild-to-moderate CKD. CKD stage was categorized based on K/DOQI guidelines [18]: stage 1, normal or increased eGFR $\geq$ 90 mL/min/1.73 m^2; stage 2, mild decreased eGFR (60–89 mL/min/1.73 m^2); stage 3, moderate decreased eGFR (30–59 mL/min/1.73 m^2).

Fasting blood glucose, hemoglobin, serum uric acid, serum total cholesterol, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein (HDL) cholesterol, and triglycerides, glycosylated hemoglobin were also measured by automatic biochemistry analyzer. Total plasma alkaline phosphatase (ALP) was assessed using colorimetric determination.

Sociodemographic characteristics, health history (e.g., hypertension and diabetes), and lifestyle behavior (e.g., smoking and drinking) were obtained by means of questionnaire. The body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square meters). Diabetes was defined as fasting blood glucose $\geq$7.0 mmol/L and/or glycosylated hemoglobin >6.5 % or by the use of hypoglycemic agents or by self-reported history of diabetes. Obesity was defined as a BMI $\geq$ 30 kg/m^2. Blood pressure was measured using a sphygmomanometer, and three measurements were taken at 5-min intervals. The mean of the three readings was calculated, unless the difference between the readings was greater than 10 mmHg, in which case the mean of the two closest measurements

Table 1 Baseline clinical characteristics of participants

	All ($n = 24,002$)	Male ($n = 17,158$)	Female ($n = 6844$)	P value
Age (years)	49.9 ± 13.9	50.3 ± 14.9	48.8 ± 13.2	<0.001
Current smoking (*n*, %)	5962 (24.8)	5956 (37.6)	6 (0.1)	<0.001
Drinking (*n*, %)	9628 (40.1)	9549 (60.3)	79 (1.3)	<0.001
Hypertension (*n*, %)	7753 (32.3)	6303 (36.9)	1450 (21.3)	<0.001
Diabetes (*n*, %)	2692 (11.2)	2251 (14.5)	441 (7.3)	<0.001
BMI (kg/m^2)	25.5 ± 3.5	26.1 ± 3.3	24.1 ± 3.6	<0.001
Blood glucose (mmol/L)	5.6 (5.2–6.1)	5.7 (5.3–6.3)	5.5 (5.1–5.9)	<0.001
Glycosylated hemoglobin (%)	5.4 (5.0–5.8)	5.4 (5.1–5.8)	5.3 (5.0–5.7)	<0.001
Serum uric acid (μmol/L)	343.0 ± 84.9	368.2 ± 79.4	280.1 ± 62.8	<0.001
Hemoglobin (g/L)	142.1 ± 14.4	148.1 ± 10.6	127.1 ± 11.6	<0.001
Serum albumin (mg/L)	46.4 ± 3.6	46.5 ± 3.6	46.0 ± 3.4	<0.001
Total cholesterol (mmol/L)	4.98 ± 0.96	4.97 ± 0.96	5.01 ± 0.98	0.001
Triglycerides (mmol/L)	1.22 (0.85–1.78)	1.32 (0.92–1.93)	0.99 (0.71–1.43)	<0.001
LDL cholesterol (mmol/L)	3.06 ± 0.76	3.06 ± 0.75	3.05 ± 0.79	<0.001
HDL cholesterol (mmol/L)	1.39 ± 0.26	1.35 ± 0.25	1.49 ± 0.27	<0.001
Alkaline phosphatase (U/L)	69.0 (57.2–82.0)	70.0 (59.0–82.9)	65.0 (53.0–80.0)	<0.001
Serum creatinine (μmol/L)	69.9 ± 15.7	75.3 ± 14.0	56.5 ± 11.1	<0.001
Urea nitrogen (mmol/L)	4.64 ± 1.54	4.81 ± 1.56	4.20 ± 1.37	<0.001
Proteinuria (*n*, %)	437 (1.8)	357 (2.1)	80 (1.2)	<0.001
eGFR (mL/min/1.73 m^2)	101.2 ± 15.3	100.0 ± 15.2	104.2 ± 15.2	0.76
Decreased eGFR (*n*, %)	299 (1.2)	232 (1.4)	67 (1.0)	0.02
CKD (*n*, %)	698 (2.9)	555 (3.2)	143 (2.1)	<0.001
BMD (g/cm^2)	0.58 (0.49–0.84)	0.60 (0.53–0.77)	0.49 (0.42–0.94)	<0.001
T-score	−0.27 (−0.90 to 0.39)	−0.30 (−0.93 to 0.32)	−0.17 (−0.86 to 0.52)	<0.001
Decreased BMD (*n*, %)	5300 (22.1)	3836 (22.4)	1464 (21.4)	0.11
Osteopenia (*n*, %)	4784 (19.9)	3530 (20.6)	1254 (18.3)	<0.001
Osteoporosis (*n*, %)	516 (2.2)	306 (1.8)	210 (3.1)	<0.001

To convert serum cholesterol in mmol/L to mg/dL, multiply by 38.67; serum triglycerides in mmol/L to mg/dL, multiply by 88.545; serum creatinine in mg/dL to μmol/L, multiply by 88.4; serum uric acid in μmol/L to mg/dL, multiply by 0.01681

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *CKD*, chronic kidney disease, *BMD* bone mineral density

was used. Hypertension was defined as systolic blood pressure of more than 140 mmHg or diastolic blood pressure of more than 90 mmHg, or both, or patients already being prescribed by antihypertensive medicaments.

Bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry

BMD values were measured by dual-energy X-ray absorptiometry (DEXA; Hologic QDR 2000, Waltham, MA, USA) at the lumbar spine. BMD was automatically calculated from the bone area (cm^2) and bone mineral content (g) and expressed absolutely in g/cm^2. The *T*-score is the number of SD by which a given measurement differs from the mean for a normal young adult reference population. *T*-score was calculated automatically. Osteoporosis was defined as *T*-score of less than −2.5 according to the Word Health Organization definition [19]. Osteopenia was defined as *T*-score of between −1 and −2.5. Either osteopenia or osteoporosis was defined as decreased BMD.

All of the study investigators and staff members completed a training program to learn the methods and procedures of the study.

Statistical analysis

Data were presented as proportions for categorical variables and mean ± SD or median [interquartile range (IQR)] for continuous variables. The significance of differences in continuous variables between groups was tested using *t* test or one-way analysis of variables or nonparametric Mann–Whitney *U* test, as appropriate. The difference in the distribution of categorical variables was tested using Chi-square test. As BMD was skewed distribution, and we used log

Table 2 Differences of BMD between None-CKD and CKD patients

	Non-CKD	CKD	*P* value*	CKD stage 1	CKD stage 2	CKD stage 3	*P* value†
N	23,304	698	–	247	152	299	–
Age (years)	49.6 ± 13.7	59.3 ± 15.0	<0.001	48.8 ± 12.3	63.0 ± 13.3	66.1 ± 13.0	<0.001
Male (*n*, %)	16,603 (71.2)	555 (79.5)	<0.001	200 (81.0)	123 (80.9)	232 (77.6)	0.55
Current smoking (*n*, %)	5770 (27.2)	192 (30.6)	0.06	92 (40.2)	41 (30.1)	59 (22.5)	<0.001
Drinking (*n*, %)	9394 (44.3)	234 (37.3)	0.001	117 (51.1)	48 (35.3)	69 (26.3)	<0.001
Hypertension (*n*, %)	7367 (31.8)	386 (55.8)	<0.001	119 (48.8)	112 (73.7)	155 (52.4)	<0.001
Diabetes (*n*, %)	2463 (11.7)	229 (36.2)	<0.001	94 (42.0)	61 (42.4)	74 (28.0)	0.001
Obesity (*n*, %)	5127 (22.1)	233 (33.7)	<0.001	81 (32.9)	57 (37.7)	95 (32.2)	0.48
eGFR (mL/min/1.73 m^2)	101.9 ± 14.3	76.8 ± 24.6	<0.001	105.3 ± 9.2	78.2 ± 9.0	52.5 ± 6.2	<0.001
Decreased BMD (*n*, %)	5094 (21.9)	206 (29.5)	<0.001	57 (23.1)	48 (31.6)	101 (33.8)	0.02
Osteopenia (*n*, %)	4603 (19.8)	181 (25.9)	<0.001	54 (21.9)	42 (27.6)	85 (28.4)	0.11
Osteoporosis (*n*, %)	491 (2.1)	25 (3.6)	0.005	3 (1.2)	6 (3.9)	16 (5.4)	0.02

BMD bone mineral density, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate

* *P* value, compared CKD patients with non-CKD patients

† *P* value, compared among different stages of CKD patients

transformation of BMD to normalize distribution. Multiple linear regression was performed to assess the association between eGFR and lgBMD. Multivariate logistic regression analysis was used to estimate the associations with decreased BMD. Independent variables included age (continuous), sex, smoking (yes/no), drinking (yes/no), hypertension (yes/no), diabetes (yes/no), obesity (yes/no) and CKD (yes/no). Crude and adjusted odds ratios (ORs) with 95 % confidence interval (CI) were reported.

All analyses were performed by SPSS statistical package, version 16.0 (SPSS, Inc., Chicago, IL, USA). A *P* value of less than 0.05 is considered statistically significant.

Results

Among 24,002 participants in the study, the mean age was 49.9 ± 13.9 years (range 18–91 years), and 71.5 % of them were males. The prevalence of proteinuria was 1.8 %, decreased eGFR was 1.2 %, and the overall prevalence of CKD was 2.9 %. Decreased BMD was 22.1, 19.9 % had osteopenia, and 2.2 % had osteoporosis. Baseline characteristics of the participants stratified by sex were shown in Table 1.

The percentage of CKD stage 1, stage 2 and stage 3 were 35.4, 21.8 and 42.8 % in CKD patients, respectively. Participants with CKD were older, had higher percentage of males, drinking, hypertension, diabetes and obesity compared to participants with non-CKD ($P < 0.05$). We also compared the differences of BMD between CKD and non-CKD participants. The percentage of patients with decreased BMD, osteopenia and osteoporosis were statistically higher ($P < 0.05$) in the CKD patients compared with those of non-CKD, which was 29.5 versus 21.9 %, 25.9 versus 19.8 % and 3.6 versus 2.1 %, respectively. The prevalence of decreased BMD and osteoporosis increased with lower eGFR ($P < 0.05$) (Table 2).

In the multiple regression analysis, eGFR was negatively associated with lgBMD ($P < 0.001$) after adjusted for potential confounders including age, sex, smoking, drinking, hypertension, diabetes and obesity. Among CKD patients, eGFR was associated with lgBMD in crude regression analysis ($P = 0.002$), but the correlation disappeared after adjusted for confounders ($P = 0.41$) (Table 3).

We analyzed the OR of variables associated with decreased BMD. In the simple logistic analysis, age, smoking, drinking, hypertension, diabetes, obesity and CKD were associated with decreased BMD ($P < 0.05$). After adjusted for potential confounders, age, smoking and obesity were associated with decreased BMD, with ORs of 1.07 (95 % CI 1.06–1.07), 1.20 (95 % CI 1.09–1.31) and 0.49 (95 % CI 0.44–0.54), respectively. The risk for decreased BMD increased with CKD in a simple logistic analysis; however, the correlation disappeared after adjusted for confounders (Table 4).

Discussion

CKD is associated with a range of different metabolic bone disease. Osteoporosis and CKD are both common in old age, often coexisting together. Measurement of bone mineral density by DEXA is of limited benefit in predicting fracture risk in patients with severe stage 4–5 CKD but has good value in stage 1–3 CKD [9, 20]. Presently, the diagnosis of osteoporosis can be made in stages 1–3 CKD, as it is

in subjects without CKD, as long as there are no biochemical abnormalities suggesting the presence of CKD-MBD. Our study revealed a higher prevalence of decreased BMD, about 21.9 % in non-CKD population and 29.5 % in mild-to-moderate CKD patients. Subjects with worse renal function have significantly lower BMD; however, the correlation disappeared after adjusted for confounders by known predictors of BMD, such as age, sex, smoking, drinking, hypertension, diabetes, obesity and so on.

In CKD patients, decreasing GFR is associated with increased parathyroid hormone (PTH) secretion and fibroblast growth factor 23 (FGF-23) signaling leading to decreased vitamin D synthesis [21, 22], which is to be associated with bone loss. The biomarkers of mineral metabolism that commonly are used clinically, such as calcium, phosphate, PTH and total ALP, are used widely as surrogate markers of high- or low-turnover bone disease. The main pathological disorder of CKD-MBD is secondary hyperparathyroidism, in which the elevation of PTH can be observed since early stages of CKD [21, 23]. The value of bone biomarkers in predicting bone histomorphometry and identifying fracture risk is limited in CKD patients. Although there are powerful observational data to show that tight mineral metabolism control is associated with improved survival in the dialysis population [24, 25], the relationship between mineral metabolism, for example, PTH and BMD, is conflicting [26–28]. Bone-specific ALP is a glycoprotein found on the surface of osteoblast. It represents biosynthetic activity of these bone-forming cells and, hence, is a sensitive indicator of bone metabolism. It is not cleared by the kidney and serum concentration is not affected by renal dysfunction. A single-center cohort study of 485 HD patients from Japan suggested that bone ALP level may be useful in predicting incident hip fracture [29].

Since ethnic differences in bone and mineral metabolism in healthy people and patients with chronic kidney disease (CKD) are described [11], we can assume that the relationship between CKD and decreased BMD may be different in Chinese Population. We highlight the low prevalence of the diagnosis of osteoporosis by DEXA (1.8 % in males and 3.1 % in females), in contrast with a much higher prevalence of osteoporosis in Korea (6.1 % in males and 16.1 % in females) [13]. BMD in our study was measured only at the lumbar spine and not elsewhere. In one study observed worsening of BMD (*T*-score) at the femur (neck and total) of the stage 4 CKD patients when compared with the stage 3 CKD patients, what did not occur in the lumbar spine [30]. This may explain in part our study could result in underestimation of the prevalence of osteoporosis. In our study, aging and smoking are major risk factors of decreased BMD, while obesity has a protective effect on bone mineral density, which was similar to other

Table 3 Multiple regression analysis for association between eGFR and lgBMD

Variables	Unstandardized coefficients	SE	Standardized coefficients	*P* value
Model 1	−0.001	<0.001	−0.096	<0.001
Model 2	−0.004	<0.001	−0.327	<0.001
Model 3	−0.004	<0.001	−0.321	<0.001
In CKD patients ($n = 698$)				
Model 1	0.001	<0.001	0.119	0.002
Model 2	<0.001	<0.001	0.044	0.32
Model 3	<0.001	<0.001	0.041	0.41

Model 1 was the crude analysis

Model 2 was adjusted for age and sex

Model 3 was adjusted for age, sex, smoking, drinking, hypertension, diabetes and obesity

eGFR estimated glomerular filtration rate, *BMD* bone mineral density, *CKD* chronic kidney disease

Table 4 Multivariate logistic regression analysis for associations of decreased bone mineral density with different variables

Variables	Crude	Age- and sex-adjusted OR[a] (95 % CI)	Multivariable adjusted OR[b] (95 % CI)
Age	1.07 (1.06–1.07)	1.07 (1.06–1.07)	1.07 (1.06–1.07)
Sex	0.95 (0.88–1.01)	1.06 (0.99–1.14)	1.06 (0.92–1.18)
Smoking	1.12 (1.05–1.21)	1.23 (1.13–1.34)	1.12 (1.09–1.31)
Drinking	0.81 (0.76–0.86)	1.05 (0.97–1.14)	1.02 (0.94–1.12)
Hypertension	1.74 (1.63–1.85)	0.93 (0.87–1.0)	1.04 (0.96–1.13)
Diabetes	1.60 (1.46–1.75)	0.91 (0.83–1.01)	1.02 (0.92–1.13)
Obesity	0.60 (0.55–0.65)	0.49 (0.45–0.54)	0.49 (0.44–0.54)
CKD	1.50 (1.27–1.77)	0.80 (0.67–0.96)	0.93 (0.76–1.14)

OR odds ratio, *CI* confidence interval, *CKD* chronic kidney disease

[a] Except for OR of age and sex, all ORs were age and sex adjusted

[b] Model was adjusted for age, sex, smoking, drinking, hypertension, diabetes, obesity, alkaline phosphatase and CKD

studies [13, 31]. The proinflammatory state associated with metabolic syndrome may lead to a reduction in bone mass [32]. Other comorbid disease, such as hypertension [33] and diabetes [34], could be associated with osteoporosis. In our study, we could not conclude an association between either hypertension or diabetes with decreased BMD after adjusted for age and sex.

To our knowledge, this is the largest study testing the association of mild-to-moderate CKD with decreased BMD in Chinese population. However, our study has limitations that deserve mention. First, this study used a convenience sample which was not based on a community-based screening and only one physical examination was used to evaluate CKD in the study. Second, we used a single morning sport urine sample to assess proteinuria, instead of urinary albumin-to-creatinine ratio, which would be more preferable. Third, it was necessary to estimate the figures for patients with a family history of osteoporosis. However, due to the limitation of our questionnaire, we could not evaluate this issue. Finally, the use of cross-sectional design limits making causal relationships between CKD and decreased BMD.

In conclusions, subjects with worse renal function have significantly lower BMD, but after adjusted for confounders, mild-to-moderate CKD is not independently associated with decreased BMD. The management of patients with fragility fractures across the spectrum of CKD should not differ between persons without reductions in eGFR as compared with patients with mild-to-moderate CKD. Further longitudinal studies are required to confirm this issue among Chinese adult population.

Acknowledgments This work was funded by the Natural Science Foundation from Shandong Science and Technology Committee (ZR2010HL002).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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