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Original Research Article

Prevalence and determinants of abnormal bone metabolism among Han Chinese diabetes patients: A cross-sectional study

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Abstract

Purpose: *To determine the prevalence and determinants of abnormal bone metabolism among Han Chinese diabetes patients.*
Methods: *Epidemiological characteristics, anthropometry, densitometry, clinical parameters, and pathological examinations of 335 Han Chinese type 1 and type 2 diabetes patients were analyzed in relation to bone densitometry.*
Results: *A total of 86 patients (25 %) were normal (T-score or Z-score of -1 or higher), while 259 patients (75 %) had abnormal bone metabolism (T-score or Z-score less than -1). Among the 259 patients with abnormal bone metabolism, 15 (4 %) had fracture-liable fragility (T-score or Z-score below -3), 112 (32 %) had osteoporosis (T-score or Z-score below -2.5), while 132 (39 %) had osteopenia (T-score or Z-score between -1 to -2.5). Age > 50 years (p = 0.0411), female sex (p = 0.0391), low body mass index (p = 0.0331), long duration of diabetes (p = 0.0291), low waist-to-hip ratio (p = 0.0336), treatment with metformin or Chinese traditional medicine or insulin (p = 0.0395), abnormal levels of pathological parameters (p = 0.0397), and HbA1c ≥ 7 (p = 0.0123) were independent risk factors for abnormal bone metabolism.*
Conclusion: *Han Chinese individuals have a risk of abnormal bone metabolism in the diabetic state. Older people, women, patients who took metformin or Chinese traditional medicine or insulin treatment, individuals with abnormal pathological parameters, and those with HbA1c ≥ 7, had reduced bone mineral density. Body mass index and waist-to-hip ratio were protective against abnormal bone metabolism.*

Keywords: *Abnormal bone metabolism, Densitometry, Diabetes, Insulin, Metformin, T-score, Z-score, Bone mineral density*

INTRODUCTION

The metabolic disease diabetes is most common among older population [1]. The Chinese population has the highest prevalence of diabetes [2]. Type 1 and type 2 diabetes are associated with abnormal bone metabolism through several mechanisms of action [3].

Diabetes compromises bone microstructure by diminishing osteoblast differentiation, increasing osteoblast apoptosis, and enhancing osteoclast-mediated bone resorption [4]. Generally, long duration of intake of anti-diabetic therapies, for example, metformin and insulin, are also associated with bone fracture [5]. Some other independent factors are also associated with abnormal bone metabolism in diabetic patients, for example, postmenopausal women with diabetes have diminished bone mineral density [6]. Moreover, the nutritional supply to bones is compromised in diabetes patients because of the damage to microcirculation, leading to abnormal bone metabolism [7]. Infections may develop in diabetic patients, following bone fracture [1].

Unlike Caucasians, most Chinese diabetic patients are on Chinese traditional medicines for diabetes due to ancient knowledge and practices [8]. In Chinese traditional medicine therapy for diabetes, there are no vitamin D and calcium supplements [9]. For example, the prevalence of type 2 diabetes in Chinese population is above 11 %, and the rate of diagnosis of metabolic disease in Chinese population over 50 years patients is about 21 % [1].

Therefore, there is an obvious lack of supplementation of vitamin D and calcium in Chinese diabetic patients. This may also be responsible for abnormal bone metabolism in Chinese diabetic patients. The objective of this study was to evaluate the prevalence and determinants of abnormal bone metabolism among Han Chinese diabetes patients.

METHODS

Ethical approval and consent to participate

The protocol designed for the study was approved by the First Hospital of Huzhou Review Board and the Chinese Diabetes Society (approval no. CPU1514). The study was done in line with the law of China and the 2008 Declarations of Helsinki. Being a retrospective study, patients' consent was waived by the Institutional Review Board.

Inclusion criteria

Only Han Chinese patients with type 1 and type 2 diabetes were included in the analysis.

Exclusion criteria

Patients with incomplete data were excluded from the analysis.

Collection of data

Epidemiological characteristics (age, duration of diabetes, and gender); anthropometric measures (body mass index (BMI) and waist-to-hip ratio), and clinical parameters (medical history, Hb1Ac, and treatment patterns) were analyzed. Other data collected included pathological examinations such as total serum calcium and total serum phosphate which were evaluated spectrophotometrically in an automated analyzer. Levels of vitamin D and calcitriol were measured using radioimmunoassay kits (IDS Immunodiagnostic Systems, Boldon, UK).

Vitamin D level lower than 5 ng/mL was considered indicative of severe deficiency. Vitamin D levels of 5 – 15 ng/mL were considered indicative of mild deficiency, while values of 16 – 30 ng/mL were taken as indicative of vitamin D insufficiency [10]. The standard values for calcitriol were 19.6 – 54.3 ng/L. Data on bone densitometry was obtained using dual-energy X-ray absorptiometry (Lunar Prodigy Primo, GE Healthcare Lunar, Madison, WI, USA) for densitometry of the lumbar spine, total hip, femoral neck, and distal radius. The *T*-scores and *Z*-scores were evaluated. The *T*-score is the standard deviation from the mean bone mineral density for a young healthy population, while *Z*-score is an indication of the standard deviation from the mean bone mineral density for a population of the same age, sex, and race [11].

The World Health Organization criteria were used to define osteoporosis and osteopenia. In this respect, *T*-scores between -1 to -2.5 were considered as indicative of osteopenia, -2.5 or below was considered evidence of osteoporosis, and below -3 was considered as fragility liable to fracture. A *Z*-score below -3 was considered as indicative of fragility liable to fracture, *Z*-score below -2.5 was considered indicative of osteoporosis, and *Z*-scores ranging from -1 to -2.5 were suggestive of mild osteopenia [10,12].

Based on bone densitometry, the Han Chinese diabetes patients were divided into 5 groups viz: normal bone mass, osteopenia, osteoporosis, and fragility liable to fracture groups. Patients with *T*-score or *Z*-score of -1 or more, were considered normal patients, while those with *T*-score or *Z*-score less than -1 were considered diabetic patients with abnormal bone metabolism [13].

Statistical analysis

The InStat 3.01 GraphPad Software (San Diego, CA, USA) was used for statistical analysis.

Kolmogorov and Smirnov method was used to check the linearity of data. Unpaired *t*-test was used for comparison of linear continuous data with equal standard deviation (SD), while Fisher's exact test or Chi-square test for independence (χ^2-test) was used for constant data. Mann-Whitney test was used for non-linear data. Unpaired *t*-test with Welch correction was used for linear continuous data with unequal SDs. Bartlett test was used to check the linearity of SDs. Multivariate analysis was performed to determine the association between pathological, epidemiological, anthropometric, and clinical parameters with abnormal bone metabolism. Kruskal-Wallis' test or one-way analysis of variance (ANOVA) was performed for subgroup analysis. Tukey or Dunn's multiple comparisons test was used for *post hoc* analysis. Differences were considered significant at $p < 0.05$.

RESULTS

Study population

Data from 349 Han Chinese type 1 and type 2 diabetes patients at the First Hospital of Huzhou, Huzhou, Zhejiang Province, China, and the referring hospitals were included in this study. The data of 14 out of the 349 patients were incomplete. Therefore, these patients were excluded from the analyses. A total of 86 Chinese diabetic patients (25 %) were normal (*T*-score or *Z*-score -1 or more), while 259 of the patients (75 %) had abnormal bone metabolism (*T*-score or *Z*-score less than -1). A breakdown of the pathologies in the 259 Han Chinese diabetic patients with abnormal bone metabolism revealed that 15 patients (4 %) had fracture-liable fragility grades (*T*-score or *Z*-score below -3), 112 patients (32 %) had osteoporosis (*T*-score or *Z*-score below -2.5), while 132 (39 %) had osteopenia (*T*-score or *Z*-score between -1 to -2.5).

Characteristics

Female, older patients, diabetics with lower BMI, patients with longer duration of diabetes, lower waist-to-hip ratio, and subjects on metformin, insulin, and/ or Chinese traditional medicine(s), had abnormal bone metabolism (*T*-score or *Z*-score less than -1). In contrast, patients on sitagliptin had normal bone metabolism (*T*-score or *Z*-score -1 or more). Educational status, type of diabetes, and co-morbidities did not affect abnormal bone metabolism. The details of levels of epidemiological, anthropometric, and clinical parameters in the Han Chinese type 1 and type 2 diabetes patients are presented in Table 1.

Table 1: Scores on epidemiological, anthropometric, and clinical parameters of Han Chinese type 1 and type 2 diabetes patients

Parameter		**Normal bone metabolism**	**With abnormal bone metabolism**	**Statistics**
Bone densitometry		***T-score or Z-score -1 or more***	***T-score or Z-score less than -1***	
Number of diabetes patients		*86*	*259*	*P-value*
Age (years, (interquartile range))		51(39–61)	54 (43–67)	<0.0001
Sex	Male	60 (70)	133 (51)	<0.0001
	Female	16 (30)	126 (49)	
Body mass index (kg/m^2, (interquartile range))		25 (25–29)	23 (21–29)	<0.0001
Duration of diabetes (months, (interquartile range)		15 (5–25)	42 (22–62)	<0.0001
Educational status	Uneducated	35 (41)	93 (36)	0.7139
	Undergraduate	30 (35)	95 (37)	
	Graduate or more	21 (24)	71 (27)	
Waist-to-hip ratio (interquartile range)		0.97 (0.89–1.05)	0.94 (0.79–0.99)	<0.0001
Co-morbidities	Hyperlipidemia	1 (1)	8 (3)	0.4602
	Cardiac diseases	1 (1)	8 (3)	0.4602
	Diabetic foot ulcer	2 (2)	8 (3)	0.999
	Retinopathy	1 (1)	4 (2)	0.999
Diabetes treatment(s)	Metformin	8 (9)	64 (25)	0.002
	Metformin+glimepiride	7 (8)	55 (21)	0.0056
	Insulin	5 (6)	59 (23)	0.0002
	Chinese traditional medicine(s)	25 (29)	61 (24)	0.0278
	Sitagliptin	41 (48)	20 (8)	<0.0001
Diabetes type	Type 1	8 (9)	31 (12)	0.5614
	Type 2	78 (91)	228 (88)	

Categorical variables are presented as frequency (percentages) and continuous non-linear variables are presented as interquartile (range).

In the subgroups of patients with abnormal bone metabolism, the prognostic values of the epidemiological, anthropometric, and clinical parameters of Han Chinese type 1 and type 2 diabetes patients were also the same, i.e., bone metabolism worse if T-score and/ or Z-score decreased. A subgroup analysis of patients with abnormal bone metabolism is shown in Table 2.

Pathological examinations

All 259 patients with abnormal bone metabolism had vitamin D deficiency, lower total serum calcium and phosphate levels, lower standard serum calcitriol levels, and higher levels of HbA1c, than normal group. The results of pathological examinations of patients are presented in Table 3.

Determinants of abnormal bone metabolism

The independent risk factors for abnormal bone metabolism were age more than 50 years, female sex, lower BMI, longer duration of diabetes, lower waist-to-hip ratio, intake of metformin or Chinese traditional medicine or insulin treatment(s), HbA1c ≥ 7, and abnormal pathological parameters. The details of the epidemiological, anthropometric, clinical, and pathological parameters associated with abnormal bone metabolism are presented in Table 4.

DISCUSSION

The prevalence of abnormal bone metabolism among Han Chinese diabetes patients in the current study was 75 %. The results of the prevalence of abnormal bone metabolism among diabetic patients in the current study are in line with the results obtained in a previous retrospective study on the Chinese population [1], but are at variance with findings in a cross-sectional study of an Indian population [13]. China and India have numerous differences in race, geographical location, and lifestyle, amongst other factors. The climate in China, eating habits of the Han Chinese population, poor availability of good medical care for diabetic patients in China, and long-term medical expenses for diabetes treatment in China may be responsible for the high prevalence rate of abnormal bone metabolism among Han Chinese diabetes patients [14]. Moreover, a cross-sectional study of the Indian population also reported higher incidences of osteoporosis among diabetes patients [13]. This study has demonstrated that Han Chinese individuals have risk of abnormal bone metabolism if they are diabetic. An age of more than 50 years was associated with abnormal bone metabolism. The results of the association of age with abnormal bone metabolism are in line with the findings in a retrospective study on the Chinese population [1] and a meta-analysis [14]. However, the results are different from the findings in a cross-sectional study on the Indian population [13]. Human bone mass declines with age [14]. Calcium absorption from the gut declines due to age [1]. In addition, in old age, the synthesis of 1,25-$(OH)_2D3$ decreases in the kidneys [15]. This study has demonstrated that Han Chinese diabetes patients have the risk of abnormal bone metabolism if aged more than 50 years.

The female sex was associated with abnormal bone metabolism. The association of sex with abnormal bone metabolism is in line results of a retrospective study on the Chinese population [1], a meta-analysis [14], and also with findings in another report [11]. Altered serum calcium and serum phosphate levels in diabetic females are responsible for abnormal bone metabolism in females [16]. Han Chinese diabetes women have risk of abnormal bone metabolism. The duration of diabetes was associated with abnormal bone metabolism. The results of the association of the duration of diabetes with abnormal bone metabolism are in line with the results reported in a retrospective study on the Chinese population [1], and a retrospective analysis on the European population [10]. Insulin function gradually declines in diabetes patients, thereby decreasing bone turnover which affects osteoclast activity and bone resorption [17,18]. This study has demonstrated that Han Chinese diabetes patients have the risk of abnormal bone metabolism if they had a longer duration of diabetes.

Body mass index and waist-to-hip ratio were associated with abnormal bone metabolism. The association of the body mass index and waist-to-hip ratio with abnormal bone metabolism is consistent with the results obtained in a retrospective study on the Chinese population [1], results of prospective study [19], and results from a meta-analysis [20]. However, they are at variance with the findings in a cross-sectional study of an Indian population [13]. A high body mass index and waist-to-hip ratio increase the mechanical stress of bones, thereby increasing bone formation [1]. High-fat content leads to high vitamin D content which, apart from increasing calcium absorption, is a precursor for other hormones, thereby increasing bone resorption [20,21]. Thus, body mass index and waist-to-hip ratio are protective factors against abnormal bone metabolism.

Table 2: Epidemiological, anthropometric, and clinical parameters of Han Chinese type 1 and type 2 diabetes patients with abnormal bone metabolism

Parameter		Fragility for fracture	Osteoporosis	Osteopenia	Statistics
Bone densitometry		***Z-score or T-score below -3***	***-2.5 or below T-score or Z-score***	***Between -1 to -2.5 T-score or Z-score***	
Number of diabetic patients		*15*	*112*	*132*	*P-value*
Age (years, (interquartile range))		60 (53–67)	56 (45–67)	51(43–62)	<0.0001
Sex	Male	5 (33)	67 (60)	61(46)	0.0376
	Female	10 (67)	45 (40)	71(54)	
Body mass index (kg/m^2, (interquartile range))		22 (21–23)	23 (21–25)	24 (21–29)	<0.0001
Duration of diabetes (months, (interquartile range))		58 (55–62)	50 (40–62)	29 (22–43)	<0.0001
Educational status	Uneducated	7 (47)	50 (45)	36 (27)	0.0165
	Undergraduate	7 (47)	37 (33)	51 (39)	
	Graduate or more	1 (6)	25 (22)	45 (34)	
Waist-to-hip ratio		0.81(0.79–0.86)	0.94 (0.81–0.99)	0.94 (0.88–0.98)	<0.0001
Co-morbidities	Hyperlipidemia	1 (6)	3 (3)	4 (3)	0.7026
	Cardiac diseases	1(6)	3 (3)	4 (3)	0.7026
	Diabetic foot ulcer	1 (6)	4 (4)	3 (2)	0.5998
	Retinopathy	1 (6)	2 (2)	1 (1)	0.2051
Diabetes treatment(s)	Metformin	4 (27)	25 (22)	35 (27)	0.7388
	Metformin+glimepiride	3 (20)	20 (18)	32 (24)	0.4744
	Insulin	4 (27)	28 (25)	27 (20)	0.6543
	Chinese traditional medicine(s)	3 (20)	29 (26)	29 (22)	0.73
	Sitagliptin	1 (6)	10 (9)	9 (7)	0.8173
Diabetes type	Type 1	2 (13)	11 (10)	18 (14)	2
	Type 2	13 (87)	101 (90)	114 (86)	

Categorical variables are presented as frequency (percentages) and continuous non-linear variables are presented as interquartile (range)

Table 3: Results of pathological examinations of Han Chinese type 1 and type 2 diabetes patients

Parameter	Normal	With abnormal bone metabolism	Statistics
Bone densitometry	***T-score or Z-score -1 or more***	***T-score or Z-score less than -1***	
Number of diabetes patients	*86*	*259*	*P-value*
Total serum calcium (mg/dL)	10(9–12)	9(8.5–11)	0.04211
%HbA1c	6.5(6–8)	9.5(7.5–13)	0.0321
Total serum phosphate (mg/dL)	2(2–3)	1(1–3)	0.0214
Serum vitamin D (ng/L)	17(15–27)	7(5–17)	0.0322
Serum calcitriol (ng/L)	21(15–32)	20(15–25)	0.0234

Variables are presented as interquartile range

Table 4: Multivariate analysis for association between abnormal bone metabolism and epidemiological, anthropometric, clinical, and pathological parameters

Parameter	**Odds ratio**	**95 % confidence interval**	***P*-value**
Age (≥50 years* *vs*.<50 years)	1.0211	0.9511–1.1141	0.0411
Sex (female* *vs*. male)	1.1242	0.9321–1.2214	0.0391
Body mass index (lower* *vs*. higher)	1.3211	0.9122–1.3211	0.0331
Duration of diabetes (longer* *vs*. shorter)	1.4222	0.9011–1.5114	0.0291
Waist-to-hip ratio (lower* *vs*. higher)	1.3241	0.9112–1.4211	0.0336
Diabetes treatment(s) (metformin or Chinese traditional medicine or insulin* *vs*. sitagliptin)	1.1541	0.9223–1.2111	0.0395
Pathological parameters (abnormal* *vs*. normal)	1.1622	0.9331–1.2231	0.0397
HbA1c (≥7* *vs*. <7)	1.5321	1.1123–1.8541	0.0123

An odd ratio of more than 1 and a *p-value* less than 0.05 were considered significant. *Significant parameter for abnormal bone metabolism.

Treatment using metformin, Chinese traditional medicine, and/or insulin treatment(s) was associated with abnormal bone metabolism. The results of the association of antidiabetic medication(s) with bone metabolism in the current study, are in line with the report in a randomized controlled trial [5]. Chinese traditional medicine is used in practice in the raw form. There are so many phytochemical compounds in raw drug(s). Moreover, calcium and vitamin D supplements are not given when Chinese traditional medicine is used for treatment of diabetes [22]. Metformin affects skeletal health, and exogenous insulin is osteoanabolic [5]. However, studies have demonstrated the safety of Sitagliptin [5]. Further research is required to evaluate the effects of diabetes treatment on abnormal bone metabolism.

HbA1c ≥ 7 was associated with abnormal bone metabolism. The association of HbA1c with abnormal bone metabolism is in line with a previous report in a prospective study [17]. Han Chinese diabetes patients with HbA1c ≥ 7 have risk of abnormal bone metabolism.

Limitations of this study

The sample size was small. Generally, type 1 diabetes patients have a 2–7-fold higher risk of osteoporotic fracture than normal persons [23]. However, in the current study, abnormal bone metabolism was not associated with the type of diabetes. Another limitation is the small number of type 1 patients included in the current study. Regional factor was not evaluated in this study because a study has already reported its insignificance in a meta-analysis [14]. The study did not discriminate between premenopausal and postmenopausal women. A study has reported that postmenopausal women with diabetes have diminished bone mineral density [6]. The sample size was small. Hospital sample was used for the study. A population-based survey was not available. A possible justification for this is that pathological and bone densitometry parameters are available only with the hospital samples.

CONCLUSION

Han Chinese individuals have a risk of abnormal bone metabolism in the diabetic state. In this population, age more than 50 years, female sex, longer duration of diabetes, use of metformin, Chinese traditional medicine, and/ or insulin; and HbA1c ≥ 7, are associated with higher risk of abnormal bone metabolism. However, higher body mass index and waist-to-hip ratio are protective factors against abnormal bone metabolism.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors have read and approved the manuscript for publication. Jianxiang Zhu was project administrator, contributed to supervision, literature review, validation, and methodology of the study. Zengbing Xia contributed to investigation, literature review, software, resources, and methodology of the study. Jikang Min contributed to conceptualization, literature review, formal analysis, data curation, and methodology of the study. Wenlin Hu contributed to literature review, software, validation, visualization, and methodology of the study. Heng Li contributed to literature review, methodology, supervision, formal analysis, and data curation of the study. Chao Mei contributed to visualization, methodology, formal analysis, and literature review of the study, and drafted, and edited the manuscript for intellectual content. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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