Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 11, pp. 1284-1288
DOI: 10.1097/GME.0000000000001396

Association of bone mineral density with a first-degree family history of diabetes in normoglycemic postmenopausal women

Lijuan Yang, MD, Xiang Hu, MD, PhD, Hailing Zhang, MD, Wei Pan, MD, Weihui Yu, MD, PhD, and Xuejiang Gu, MD, PhD

Abstract

Objective: A first-degree family history of diabetes (FHD) contributes to increased risks of metabolic and cardiovascular diseases. Bone is an insulin-resistant site and an organ susceptible to microvascular complications. The goal of the present study was to investigate the association of FHD with bone mineral density (BMD) in postmenopausal women.

Methods: In all, 892 normoglycemic postmenopausal women were divided into subgroups of participants with or without a first-degree FHD. BMD was measured using dual-energy x-ray absorptiometry. Fasting plasma insulin and glucose levels were measured, and insulin resistance was evaluated using the Homeostasis Model Assessment—Insulin Resistance (HOMA-IR) index.

Results: The BMD of the lumbar spine and femoral neck were much higher in the participants with a first-degree FHD than in those without an FHD (all $P < 0.05$). Lumbar spine BMD and femoral neck BMD were both positively associated with HOMA-IR ($P = 0.041$ and $P = 0.005$, respectively). Multiple stepwise regression analysis showed that a first-degree FHD was an independent factor that was positively associated with lumbar spine BMD (standardized $\beta = 0.111$, $P = 0.001$) and femoral neck BMD (standardized $\beta = 0.078$, $P = 0.021$). A first-degree FHD was associated with increased BMD, insulin resistance, and hyperinsulinemia.

Conclusions: Our study indicated that normoglycemic postmenopausal women with a first-degree FHD exhibit increased BMD with insulin resistance and hyperinsulinemia. A first-degree FHD was an independent factor associated with elevated BMD in Chinese women after menopause.

Key Words: BMD – First-degree FHD – Insulin resistance.

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of osteoporotic fracture.[1,2] However, few studies have suggested that T2DM is associated with accelerated bone loss.[3-6] Strong evidence has revealed normal to high bone mineral density (BMD) in most patients with T2DM.[1,7-10] Insulin resistance is linked to BMD, thus possibly explaining these paradoxical findings. Even after adjustment for BMI, BMD was still increased in patients with T2DM, which suggests that increased BMD might be attributed to hyperinsulinemia.[9,11,12] Some clinical studies have shown that BMD was elevated or normal in the status of hyperinsulinemia, including metabolic syndrome,[13] nonalcoholic fatty liver disease,[14] polycystic ovary syndrome,[15] and even in individuals with impaired glucose tolerance, who had a lower fracture risk compared with that of healthy controls.[11] Therefore, bone could change throughout the evolution of the disease from prediabetes to overt diabetes. Hyperinsulinemia may be the dominant factor that affects the skeleton in the early phase of diabetes. Skeletal fragility is associated with the progressive β-cell dysfunction that occurs with disease evolution, the accumulation of advanced glycosylation end products,[16] microvascular complications,[17] and muscle dysfunction.[18] Because T2DM individuals are at increased risk of fracture, understanding the early pathophysiology of altered BMD may be critical for the development of preventive strategies for diabetic osteoporosis.

Insulin resistance and β-cell dysfunction,[19] diabetes,[20,21] adipocyte dysfunction,[22] and endothelial function[23] have been identified in individuals with a first-degree family history of diabetes (FHD), even in the absence of diabetes. To date, however, no data have been published that demonstrated whether BMD is altered in individuals with a first-degree FHD.

Therefore, the goal of the present study was to explore BMD in normoglycemic postmenopausal women with a first-degree FHD and the relationship between insulin resistance and bone mass. All of the participants enrolled in this study were normoglycemic for the purpose of attenuating the impact

Received March 18, 2019; revised and accepted May 16, 2019.

From the Department of Endocrine and Metabolic Diseases, the First Affiliated Hospital of Wenzhou Medical University, Ouhai District, Wenzhou, Zhejiang Province, China.

L.Y. and X.H. contributed equally to this work.

Funding/support: National key R&D Program of China (2016YFC1305202); Wenzhou Science & Technology Bureau (Y20170047).

Financial disclosure/conflicts of interest: None reported.

Address correspondence to: Xuejiang Gu, MD, PhD, Department of Endocrine and Metabolic Diseases, the First Affiliated Hospital of Wenzhou Medical University, Ouhai District, Wenzhou 325000, Zhejiang Province, China. E-mail: guxuejiang@wmu.edu.cn

of abnormal glucose metabolism, chronic complications of diabetes, and diabetes therapies on BMD.

METHODS

Participants

In all, 892 normoglycemic postmenopausal women were enrolled. Based on the 1999 World Health Organization criteria, individuals with impaired glucose regulation or diabetes were not included in the present study. Individuals currently undergoing therapy for osteoporosis (eg, bisphosphonate or hormonal agents) and individuals with chronic renal failure, liver cirrhosis, thyroid disease, rheumatoid arthritis, or any type of cancer were excluded.

A first-degree FHD was defined as having one or more first-degree relatives with diabetes (parents, siblings, or offspring).

The Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University preapproved this study, and all participants provided written informed consent before participation.

Measures

Body weight and height were measured to the nearest 0.1 cm and 0.1 kg, respectively, with standard methods. Body mass index (BMI) was calculated as follows: BMI = weight (kg)/height^2 (m^2).

Blood serum samples, which were obtained from the antecubital vein, were collected between 6:00 and 9:00 AM after 10 to 12 hours of fasting. The biochemical indices included fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting serum insulin (FINS), serum lipid profiles (triglycerides [TGs], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]), serum uric acid (SUA), creatinine, and C-reactive protein (CRP). The estimated glomerular filtration rate (eGFR) was calculated with age, sex, and serum creatinine. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated as follows: HOMA-IR = FINS (mU/L) × FPG (mmol/L)/22.5.

All participants included in our study had undergone dual-energy x-ray absorptiometry (DXA; *Prodigy primo*, GE Inc., Madison, WI) for the assessment of BMD (grams per square centimeter) of the femoral neck and lumbar spine (L1-L4). Well-trained and qualified technicians performed standardized daily quality control of the DXA instruments using spine phantom; accurate and reliable data were generated. The coefficient of variation (CV) for repeated measurement by the DXA operator of the lumbar spine and femoral neck was <1.0%.

Analysis

The SPSS 16.0 statistical package for the social science (SPSS Inc., Chicago, IL) was used for statistical analysis. The normality of the data distribution was determined by the one-sample Kolmogorov-Smirnov test. Data were expressed as the mean ± standard deviation or median, with the interquartile range according to a normal or skewed distribution, respectively. Comparisons between the two groups were carried out by an unpaired Student's *t* test for normally distributed variables or the Mann-Whitney *U* test for variables with a skewed distribution. Spearman's correlation coefficient analyses were conducted to assess the relationships of BMD with indices of HOMA-IR and other metabolic parameters. Multiple stepwise regression analysis was performed to identify independent factors affecting BMD. The threshold of statistical significance was set at 0.05 for two-tailed *P* values.

RESULTS

Clinical characteristics of study participants

In all, 892 normoglycemic postmenopausal women were enrolled in the present study (age range: 51-74 years, median 55.00 [53.00-59.50] years), including 147 participants with a first-degree FHD and 745 participants without an FHD. In the postmenopausal women, participants with a first-degree FHD had greater body weight and higher FIN, HOMA-IR, and HbA1c values than those without an FHD (all $P < 0.05$). Individuals with and without a first-degree FHD did not differ significantly with respect to the other variables (all $P > 0.05$; Table 1)

BMD in participants with and without a first-degree FHD

In postmenopausal women, the BMD of the femoral neck and lumbar spine were much higher in participants with a first-degree FHD than in those without an FHD (0.890 [0.810-0.950] vs 0.85 [0.800-0.930], $P < 0.05$; 1.077 ± 0.146 vs 1.034 ± 0.112; $P < 0.01$, respectively; Fig. 1).

TABLE 1. *Characteristics of the study participants (N = 892)*

Variable	A first-degree FHD	
	−(n = 745)	+(n = 147)
Age (y)	55.00 (53.00-59.50)	55.00 (53.00-59.00)
Weight (kg)	56.73 ± 6.98	58.45 ± 7.58[a]
Height (cm)	156.47 ± 5.11	157.13 ± 4.80
BMI (kg/m^2)	22.87 (21.48-24.83)	23.69 (21.30-25.84)
FPG (mmol/L)	5.20 (4.90-5.50)	5.20 (4.90-5.60)
HbA1c (%)	5.50 (5.30-5.80)	5.60 (5.40-5.80)[a]
FINS (pmol/L)	49.00 (35.45-65.75)	56.60 (40.70-72.50)[b]
HOMA-IR	1.60 (1.13-2.23)	1.85 (1.33-2.42)[b]
TG (mmol/L)	1.28 (0.91-1.76)	1.20 (0.89-1.74)
LDL-C (mmol/L)	3.13 ± 0.79	3.11 ± 0.80
HDL-C (mmol/L)	1.44 (1.25-1.69)	1.42 (1.23-1.67)
SUA (umol/L)	281.76 ± 5.68	287.05 ± 5.85
CRP (mg/L)	0.68 (0.35-1.57)	0.78 (0.33-1.43)
eGFR	100.60 (94.90-105.00)	101.10 (94.20-105.70)
Menopausal period (y)	5.00 (3.00-9.50)	5.00 (3.00-9.00)
Lumbar spine BMD (g/cm^2)	1.034 ± 0.112	1.077 ± 0.146[b]
Femoral neck BMD (g/cm^2)	0.850 (0.800-0.930)	0.89 (0.810-0.950)[a]

BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FHD, family history of diabetes; FINS, fasting serum insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; TG, triglyceride.
Data are means ±SD, median (interquartile range).
[a] $P < 0.05$ versus participants without an FHD in corresponding group.
[b] $P < 0.01$ versus participants without an FHD in corresponding group.

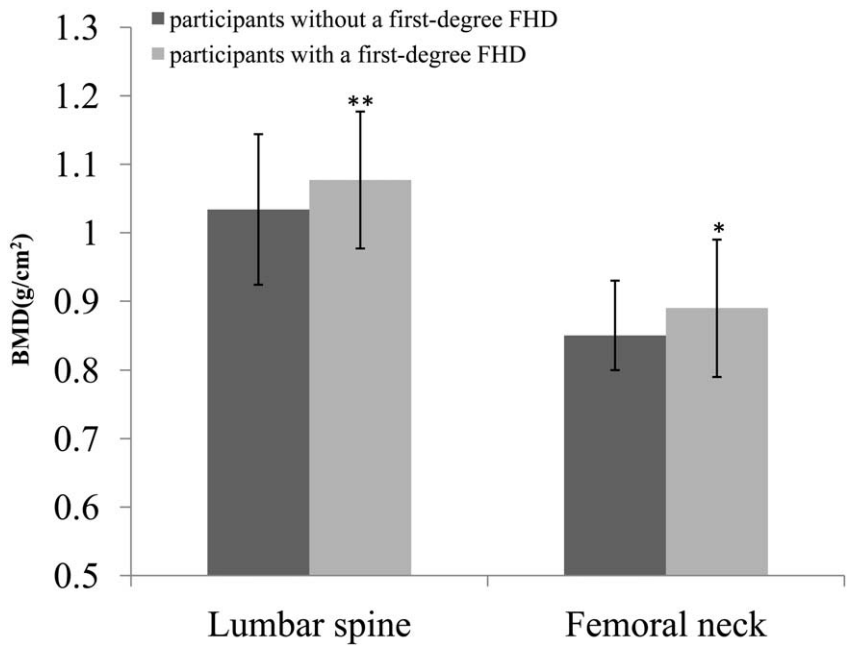

FIG. 1. Group comparisons of BMD between participants with a first-degree FHD and those without an FHD. BMD is expressed as median values with interquartile ranges. $P^{*} < 0.05$; $P^{**} < 0.01$. BMD, bone mineral density; FHD, family history of diabetes.

Spearman's correlation analyses of BMD

In postmenopausal women, lumbar spine BMD was positively associated with HOMA-IR, menopausal period, and eGFR (all $P < 0.05$), but negatively associated with age (all $P < 0.001$). Femoral neck BMD was positively associated with BMI, HOMA-IR, TGs, menopausal period, and eGFR (all $P < 0.05$), but negatively associated with age (all $P < 0.001$). Additional detailed results are displayed in Table 2.

TABLE 2. *Spearman's correlation analyses of BMD*

	Lumbar spine		Femoral neck	
Variables	*r*	*P*	*r*	*P*
Age	−0.307	<0.001	−0.197	<0.001
BMI	0.054	0.122	0.118	0.001
HbA1c	0.018	0.591	0.027	0.414
HOMA-IR	0.068	0.041	0.094	0.005
TG	0.014	0.677	0.026	0.043
LDL-C	−0.007	0.823	0.002	0.952
HDL-C	−0.043	0.203	−0.050	0.136
SUA	0.043	0.19	0.056	0.094
CRP	−0.001	0.969	0.062	0.067
Menopausal period	−0.307	<0.001	−0.197	<0.001
eGFR	0.227	<0.001	0.159	<0.001
A first-degree FHD	0.089	0.008	0.083	0.013

BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FHD, family history of diabetes; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; TG, triglyceride.

Multiple stepwise regression analysis of BMD

Upon defining BMD as a dependent variable, multiple regression analysis took into account variables including a first-degree FHD, age, BMI, HbA1c, HOMA-IR, TGs, HDL-C, LDL-C, SUA, eGFR, menopausal period, and CRP as independent variables. The results showed that a first-degree FHD was an independent factor positively associated with lumbar spine BMD (standardized $\beta = 0.112$, $P = 0.001$) and femoral neck BMD (standardized $\beta = 0.075$, $P = 0.029$) (Table 3).

DISCUSSION

To our knowledge, this was the first study to examine the association of femoral neck and lumbar spine BMD with a first-degree FHD, and also with related factors. In the present study, individuals with a first-degree FHD exhibited higher BMD than those without an FHD. HOMA-IR was positively associated with BMD in postmenopausal women. Moreover, a first-degree FHD, HOMA-IR, and SUA were identified as independent positive factors associated with BMD.

Increased BMD has been noted not only in individuals with T2DM, but also in individuals with impaired glucose tolerance.[1,7-10] Nevertheless, there are no studies reporting BMD in a population of individuals with a first-degree FHD. Bone is influenced in the early phase of diabetes, and hyperinsulinemia is the dominant factor. However, the association between insulin resistance and bone mass is not clear. HOMA-IR was negatively associated with total body, femoral neck, and lumbar spine areal bone mineral density in South Korean men.[24] Insulin resistance was inversely associated with

TABLE 3. *Multiple linear stepwise regression analysis of BMD*

	Lumber spine					Femoral neck			
Independent variables	B	Standardized β	T	*P*	Independent variables	B	Standardized β	t	*P*
A first-degree FHD	0.036	0.112	3.336	0.001	A first-degree FHD	0.020	0.075	2.193	0.029
Age	−0.008	−0.316	−9.384	<0.001	BMI	0.003	0.085	2.449	0.015
SUA	0.000	0.083	2.456	0.014	Menopausal period	−0.004	−0.178	−4.715	<0.001
HOMA-IR	0.014	0.103	3.059	0.002	HOMA-IR	0.010	0.091	2.603	0.009
					SUA	0.000	0.101	2.810	0.005
					eGFR	0.001	0.085	2.198	0.028

BMI, body mass index; eGFR, estimated glomerular filtration rate; FHD, family history of diabetes; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance; SUA, serum uric acid.

lumbar spine aBMD in menopausal Chinese-Singaporean women without diabetes.[25] HOMA-IR was positively correlated with the total hip and lumbar spine BMD in White women without diabetes.[26] HOMA-IR was positively associated with lumbar spine aBMD in individuals in the United States.[27] Therefore, differences in sex, age, and race affect the relationship between insulin resistance and BMD. Consistent with the latter two findings, the present study demonstrated that the lumbar spine BMD and femoral neck BMD were positively associated with HOMA-IR in postmenopausal women and that individuals with a first-degree FHD were more likely to have a high HOMA-IR. The present study revealed for the first time a significant increase in BMD in normoglycemic individuals with a first-degree FHD, supporting the concept that the protective effects on the skeleton occur before the onset of glucose metabolism abnormalities. Based on these clinical associations, we suggest that the elevated BMD in individuals with a first-degree FHD could be attributed to insulin resistance.

Both positive and negative associations between SUA and BMD have been reported. Multiple studies have supported the view that SUA had a positive relationship with BMD that could be explained by indices of body fat deposition.[28-30] The results of the present study were consistent with these findings. However, it is not certain whether a positive association between BMD and uric acid is still observed in individuals with hyperuricemia.

The potential mechanisms underlying the contribution of a first degree FHD to BMD remained to be determined. Until now, there has been no direct evidence supporting the contribution of genetic factors to the alteration in BMD in individuals with an FHD. However, individuals with a first-degree FHD inherit susceptibility to insulin resistance,[19] which may further lead to high BMD. Insulin has an anabolic effect on bone. Osteoblasts have insulin receptors, and insulin stimulates the proliferation of these cells in vitro.[31] In normoglycemic but insulin-resistant offspring of parents with T2DM, insulin-stimulated AKT phosphorylation on Ser473 was suppressed, resulting in an approximately 60% reduction in AKT activation.[32] Phosphorylation of the insulin receptor atThr308, Ser473, and especially Tyr 1150/1151 was significantly decreased in the bones of mice fed a high-fat diet (HFD) when compared with the phosphorylation of the receptors of the mice fed a normal diet.[33] An in vivo study revealed that HFD-fed mice developed obesity and glucose intolerance, and also insulin resistance not only in the liver, muscle, and fat but also in the bone. However, by compromising insulin signaling in osteoblasts, HFD feeding inhibited both arms of bone remodeling. The bone volume was increased in HFD-fed mice. Additionally, insulin not only reduced osteoprotegerin expression in osteoblasts via FoxO1 phosphorylation, leading to osteoblastogenesis and bone resorption but also regulated osteoblast differentiation by suppressing the Runx2 inhibitor Twist2.[34] Therefore, on the basis of these studies, it was warranted to hypothesize that insulin resistance may be responsible for the high BMD in individuals with a first-degree FHD. One of the mechanisms of the positive correlation between BMD and SUA is oxidative stress due to the decrease in osteoclastogenesis and the promotion of osteoblast differentiation, leading to increased bone formation.[31] However, experimental studies do not seem to support a protective role of UA on bone health. Therefore, further research is needed to address all these issues in more detail.

The present study has some limitations. First, our study is limited by the cross-sectional design, which did not allow any inference of causality. Further clinical and basic research studies are necessary to verify our findings and reveal the relevant genetic factors. Second, osteocalcin and P1NP should be assessed, which would provide insight into bone formation in relation to insulin resistance. Third, BMD measurements underestimate skeletal fragility in individuals with type 2 diabetes and those in the early stage of diabetes. Thus, healthcare providers and bone strength should be considered. Fourth, future studies are needed to examine the changes in BMD with the evolution of the disease from prediabetes to overt diabetes. Additional work to further characterize the observation of the T-score is warranted.

CONCLUSIONS

In conclusion, the BMD of the lumbar spine and femoral neck was significantly higher in menopausal women with a first-degree FHD than in those without an FHD, even among individuals with normal blood glucose levels. There was a significant positive correlation between BMD and HOMA-IR. A first-degree FHD was found to be an independent factor associated with increased BMD.

REFERENCES

1. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes: a meta-analysis. *Osteoporos Int* 2007;18:427-444.
2. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 2007;166:495-505.
3. Schwartz AV, Ewing SK, Porzig AM, et al. Diabetes and change in bone mineral density at the hip, calcaneus, spine, and radius in older women. *Front Endocrinol (Lausanne)* 2013;4:62.
4. Keegan TH, Schwartz AV, Bauer DC, Sellmeyer DE, Kelsey JL; The Fracture Intervention Trial. Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the fracture intervention trial. *Diabetes Care* 2004;27:1547-1553.
5. Khalil N, Sutton-Tyrrell K, Strotmeyer ES, et al. Menopausal bone changes and incident fractures in diabetic women: a cohort study. *Osteoporos Int* 2011;22:1367-1376.
6. Schwartz AV, Sellmeyer DE, Strotmeyer ES, et al. Diabetes and bone loss at the hip in older black and white adults. *J Bone Miner Res* 2005;20:596-603.
7. Looker AC, Eberhardt MS, Saydah SH. Diabetes and fracture risk in older U.S. adults. *Bone* 2016;82:9-15.
8. Ma L, Oei L, Jiang L, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur J Epidemiol* 2012;27:319-332.
9. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: The Health, Aging, and Body Composition Study. *J Bone Miner Res* 2004;19:1084-1091.
10. Kao WH, Kammerer CM, Schneider JL, Bauer RL, Mitchell BD. Type 2 diabetes is associated with increased bone mineral density in Mexican-American women. *Arch Med Res* 2003;34:399-406.
11. de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos Int* 2005;16:1713-1720.
12. Oei L, Zillikens MC, Dehghan A, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. *Diabetes Care* 2013;36:1619-1628.
13. Peng Xue. Ping Gao. Yukun Li. The association between metabolic syndrome and bone mineral density: a meta-analysis. *Endocrine* 2012;42:546-554.
14. Mantovani A, Dauriz M, Gatti D, et al. Systematic review with meta-analysis: non-alcoholic fatty liver disease is associated with a history of osteoporotic fractures but not with low bone mineral density. *Aliment Pharmacol Ther* 2019;49:375-388.
15. Yuksel O, Dokmetas HS, Topcu S, Erselcan T, Sencan M. Relationship between bone mineral density and insulin resistance in polycystic ovary syndrome. *J Bone Miner Metab* 2001;19:257-262.
16. Yamamoto M. Insights into bone fragility in diabetes: the crucial role of bone quality on skeletal strength. *Endocr J* 2015;62:299-308.
17. Shanbhogue VV, Hansen S, Frost M, Brixen K, Hermann AP. Bone disease in diabetes: another manifestation of microvascular disease? *Lancet Diabetes Endocrinol* 2017;5:827-838.
18. Trierweiler H, Kisielewicz G, Jonasson TH, Petterle RR, Moreira CA, Borba VZC. Sarcopenia: a chronic complication of type 2 diabetes mellitus. *Diabetol Metab Syndr* 2018;10:25.
19. Stadler M, Pacini G, Petrie J, Luger A, Anderwald C; RISC Investigators. Beta cell (dys)function in non-diabetic offspring of diabetic patients. *Diabetologia* 2009;52:2435-2444.
20. Wagner R, Thorand B, Osterhoff MA, et al. Family history of diabetes is associated with higher risk for prediabetes: a multicentre analysis from the German Center for Diabetes Research. *Diabetologia* 2013;56:2176-2180.
21. Cederberg H, Stancakova A, Kuusisto J, Laakso M, Smith U. Family history of type 2 diabetes increases the risk of both obesity and its complications: is type 2 diabetes a disease of inappropriate lipid storage? *J Intern Med* 2015;277:540-551.
22. Hu X, Pan X, Ma X, et al. Contribution of a first-degree family history of diabetes to increased serum adipocyte fatty acid binding protein levels independent of body fat content and distribution. *Int J Obesity* 2016;40:1649-1654.
23. Goldfine AB, Beckman JA, Betensky RA, et al. Family history of diabetes is a major determinant of endothelial function. *J Am Coll Cardiol* 2006;47:2456-2461.
24. Shin D, Kim S, Kim KH, Lee K, Park SM. Association between insulin resistance and bone mass in men. *J Clin Endocrinol Metab* 2014;99:988-995.
25. Kalimeri M, Leek F, Wang NX, et al. Association of insulin resistance with bone strength and bone turnover in menopausal Chinese-Singaporean women without diabetes. *Int J Environ Res Public Health* 2018;15:pii: E889.
26. Shanbhogue VV, Finkelstein JS, Bouxsein ML, Yu EW. Association between insulin resistance and bonestructure in nondiabetic postmenopausal women. *J Clin Endocrinol Metab* 2016;101:3114-3122.
27. Srikanthan P, Crandall CJ, Miller-Martinez D, et al. Insulin resistance and bone strength: findings from the study of midlife in the United States. *J Bone Miner Res* 2014;29:796-803.
28. Pirro M, Mannarino MR, Bianconi V, et al. Uric acid and bone mineral density in postmenopausal osteoporotic women: the link lies within the fat. *Osteoporos Int* 2017;28:973-981.
29. Yan P, Zhang Z, Wan Q, et al. Association of serum uric acid with bone mineral density and clinical fractures in Chinese type 2 diabetes mellitus patients: a cross-sectional study. *Clin Chim Acta* 2018;486:76-85.
30. Ishii S, Miyao M, Mizuno Y, et al. Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. *Osteoporos Int* 2014;25:1099-1105.
31. Keertik F, Ryan C, Riddle. et al. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. *Cell* 2010;142:309-319.
32. Morino K, Petersen KF, Dufour S, et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J Clin Invest* 2005;115:3587-3593.
33. Liu JM, Rosen CJ, Ducy P, Kousteni S, Karsenty G. Regulation of glucose handling by the skeleton: insights from mouse and human studies. *Diabetes* 2016;65:3225-3232.
34. Wei J, Ferron M, Clarke CJ, et al. Bone specific insulin resistance disrupts whole body glucose homeostasis via decreased osteocalcin activation. *J Clin Invest* 2014;124:1-13.

