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Original Article

Association between the Metabolic Score of Insulin Resistance Index and Bone Mineral Density: A Cross-Sectional Study

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SUMMARY

Backgrounds: Current literature presents conflicting findings regarding the association between insulin resistance and bone mineral density. While some studies demonstrate a significant correlation, others do not. Furthermore, there is a lack of research investigating the correlation between the metabolic score of insulin resistance index and bone mineral density. Therefore, this study aims to examine the relationship between these two parameters.
Methods: A cross-sectional study was conducted, which included data from five cycles of the National Health and Nutrition Examination Survey with a total of 6769 subjects. Multiple linear regression was utilized to analyze the association between the variables.
Results: After adjusting for potential confounding factors, the results showed a positive correlation between the metabolic score of insulin resistance and total femur (Per-standard deviation [Per-SD]: β = 0.060; Quartile: β = 0.150, both $p < 0.001$), femur neck (Per-SD: β = 0.049; Quartile: β = 0.115, both $p < 0.001$), and lumbar spine (Per-SD: β = 0.040; Quartile: β = 0.108, both $p < 0.001$) bone mineral density, regardless of whether the former was analyzed as a continuous or categorical variable. As the metabolic score of insulin resistance increased, this correlation became more prominent (p for trend < 0.001). Subgroup analyses for gender, age, hypertension, and diabetes all came to conclusions consistent with the above results.
Conclusion: Our study findings indicate a positive correlation between insulin resistance and bone density.

1. Introduction

Osteoporosis is a disease of abnormal bone metabolism characterized by a decrease in the strength of bone tissue, reduced bone density, making them susceptible to fractures.[1] Fractures caused by osteoporosis are prevalent in middle-aged and elderly populations. As the global population ages, the number of people with osteoporosis will continue to rise. The risk of disability and even death from fractures due to osteoporosis is high. Bone mineral density (BMD) is closely related to osteoporosis, and measuring bone density helps assess bone mass trends and risk for osteoporosis and fractures.

Insulin resistance (IR) is a complex metabolic disorder characterized by reduced sensitivity of the body's cells to insulin. IR is associated with a variety of health problems, including diabetes,[2] cardiovascular disease,[3,4] and arterial stiffness.[5] In addition, IR is a critical component of metabolic syndrome. Metabolic syndrome relates to various medical conditions, including elevated blood pressure, hyperglycemia, abdominal obesity, and dyslipidemia. These conditions collectively increase the risk of cardiovascular disease and stroke.[6] Recent in vitro and clinical studies have shown that IR may be related to bone metabolism.[7] Insulin promotes osteoblasts' growth and differentiation and inhibits osteoclast activity. Guo et al. showed that IR was negatively associated with markers of bone turnover in a population with diabetes mellitus.[8] Although research has been conducted on the relationship between IR and BMD, current findings remain inconsistent. While some studies have found a significant correlation between the two factors,[9,10] others have reported no such association.[11,12] Given the conflicting results, further research is warranted to clarify the potential relationship between IR and BMD.

The Metabolic Score of Insulin Resistance (METS-IR) index is a novel marker recently developed to assess IR and is gaining widespread attention and application in clinical settings.[13] The study conducted by Bello-Chavolla et al.[14] demonstrated that the METS-IR index evaluation method exhibits superior diagnostic performance compared to the commonly used HOMA-IR method for assessing IR in clinical practice. The index is calculated based on routine clinical testing indicators, including fasting blood glucose, blood lipids, and body mass index (BMI). These indicators are easily obtainable and offer advantages regarding their accessibility and testing costs. However, studies have not evaluated the relationship between METS-IR and BMD in the general population. Hence, this study aims to examine whether there is a link between the two.

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2. Materials and methods

2.1. Study design and participants

All data in this study were obtained from the NHANES database, which is a publicly available health database collected and maintained by the National Center for Health Statistics in the United States (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm). The survey adopts multistage probability sampling, with every 2 years as a cycle, and about 5,000 people are selected from all over the United States for the survey every year. The database has extensive demographics, questionnaires, physical examinations, and laboratory surveys of the population. Written consent was obtained from all participants before survey implementation, and therefore, no ethical approval was required for this study. We included data from five NHANES cycles (2005–2006, 2007–2008, 2009–2010, 2013–2014, and 2017–2018) because these are the only cycles in which BMD of the femur, femur neck, and lumbar spine was measured at the same time. The selection process of the study population is shown in Figure 1, and a total of 6769 adults were enrolled in this study.

2.2. Dependent and independent variables

BMD as the dependent variable was measured by dual-energy X-ray absorptiometry (Hologic QDR-4500A), and all examinations were performed by trained and certified radiographers. BMD data from three sites were used in this study: femur, femur neck, and lumbar spine. METS-IR, the independent variable, is calculated indirectly from biochemical blood indicators and BMI. BMI was obtained from the body measurement module data. METS-IR is calculated as: ln (2 × fasting glucose [mg/dL] + fasting triglycerides [mg/dL]) × BMI [kg/m^2] / ln (high-density lipoprotein cholesterol [mg/dL]).[14]

2.3. Covariates

To minimize potential confounding factors and ensure reliable results, we considered the influence of potential covariates based on previous relevant literature[12,15] and clinical experience. The study collected general information on various demographic characteristics, including sex, age, race, education, and marital status. Activity status, tobacco use, past medical history, and medication are also included. The information mentioned above was obtained through on-site interviews using standardized questionnaire tools. Furthermore, the study also collected blood test-related indicators, such as serum insulin, calcium, blood uric acid, fasting glucose, and lipid data using the laboratory test module. Blood samples are collected at mobile screening centers, processed, stored and transported to laboratories at each site for testing. Each laboratory has a dedicated technical team for sample processing and a senior medical technologist for quality control, calibration and maintenance.[16] Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg measured on three consecutive occasions on different days, or previous diagnosis of hypertension by a physician, or use of antihypertensive medication.[17] Diabetes was defined as fasting glucose ≥ 126 mg/dL or 2-hour OGTT ≥ 200 mg/dL or glycated hemoglobin ≥ 6.5%, or medical history of diabetes or use of glucose-lowering medication or insulin.

2.4. Statistical analysis

Data were analyzed using R software (http://www.R-project.org) and Empower (http://www.empowerstats.com). A normality test was performed by Shapiro-Wilk and K-S before the sample comparison. Continuous variables were expressed as mean ± standard deviation or median and interquartile range, while categorical variables were expressed as percentages. To enhance the representativeness of the data, we employed 2-year fasting examination weights to adjust the data. In cases of missing data, if the data were continuous variables and the missing data were within 5%, we substituted the mean of the variable; otherwise, they were converted to categorical variables through a specific method. When the missing data were categorical variables and exceeded ten samples, the variable was divided into an "unclear group"; otherwise, it was removed. The difference according to the quartiles of the METS-IR was compared using a one-way analysis of variance for continuous data and chi-squared tests for categorical variables. Multiple linear regression analysis was utilized to examine the relationship between METS-IR and total femur, femur neck, and total spine BMD. The results were presented as β with its 95% confidence intervals (95% CIs). A total of three regression models were generated based on the adjusted covariates. Model 1 was unadjusted, Model 2 was adjusted for sex, age, and race, and Model 3 was adjusted for Model 2 plus education, marital status, smoking, activity, hypertension, diabetes, serum calcium, serum uric acid, blood urea nitrogen, total cholesterol, taking insulin or glucose-lowering drugs, taken prednisone or cortisone, ever had osteoporosis. Additional stratified group analyses were conducted by sex, age, hypertension, and diabetes. p-values below 0.05 were deemed to indicate statistically significant.

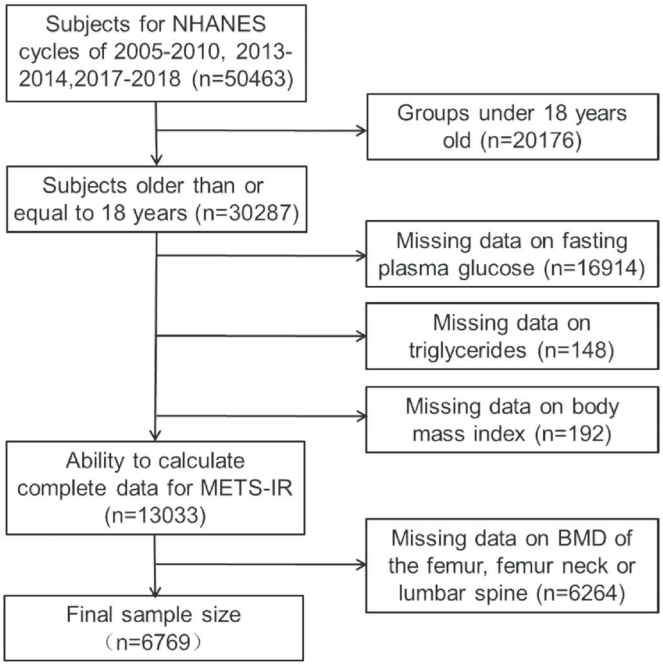

Figure 1. Flow chart for the selection of subjects.

3. Results

3.1. Characteristics of participants

The general characteristics of the subjects are presented in Table 1. Among the 6769 participants, 3452 were male and 3317 female, with a mean age of 47.35 ± 17.46 years. The subjects were categorized into four groups based on the quartiles of METS-IR. Between-group comparisons revealed statistically significant differences across groups concerning sex, age, education, smoking, hyper-

tension, and diabetes, taking insulin or glucose-lowering drugs. As the METS-IR score increased, there was a corresponding rise in fasting insulin, blood uric acid, total cholesterol, fasting glucose, triglycerides, BMI, high-density lipoprotein cholesterol and BMD.

3.2. Association between METS-IR and BMD

The results of the regression analysis are presented in Table 2. These findings demonstrate that METS-IR is positively correlated

Table 1
Characteristics of participants.

Characteristic	METS-IR				p value
	Q1 < 33.84	Q2 33.85–39.97	Q3 33.98–47.14	Q4 ≥ 47.15	
No. of participants	1686	1698	1692	1693	
Gender, n (%)					< 0.001
Male	803 (47.63)	865 (50.94)	861 (50.89)	923 (54.52)	
Female	883 (52.37)	833 (49.06)	831 (49.11)	770 (45.48)	
Age (mean ± SD, year)	46.31 ± 17.68	46.71 ± 17.24	47.15 ± 17.45	49.20 ± 17.33	< 0.001
Race, n (%)					0.169
Mexican American	322 (19.10)	307 (18.08)	335 (19.80)	355 (20.97)	
Non-Hispanic White	722 (42.82)	722 (42.52)	732 (43.26)	751 (44.36)	
Non-Hispanic Black	513 (30.43)	541 (31.86)	483 (28.55)	468 (27.64)	
Other race	129 (7.65)	128 (7.54)	142 (8.39)	119 (7.03)	
Education, n (%)					0.039
Under high school	390 (23.13)	414 (24.38)	418 (24.70)	467 (27.58)	
High school or equivalent	355 (21.06)	351 (20.67)	386 (22.81)	359 (21.20)	
Above high school	821 (48.70)	813 (47.88)	785 (46.39)	779 (46.01)	
Unclear	120 (7.12)	120 (7.07)	103 (6.09)	88 (5.20)	
Marital status, n (%)					0.072
Married/cohabiting	999 (59.25)	1022 (60.19)	991 (58.57)	990 (58.48)	
Widowed/divorced/separated	315 (18.68)	323 (19.02)	332 (19.62)	380 (22.45)	
Never married	312 (18.51)	285 (16.78)	316 (18.68)	271 (16.01)	
Unclear	60 (3.56)	68 (4.00)	53 (3.13)	52 (3.07)	
Smoking, n (%)					0.038
Never	882 (52.31)	884 (52.06)	846 (50.00)	857 (50.62)	
Former	376 (22.30)	339 (19.96)	393 (23.23)	375 (22.15)	
Current	310 (18.39)	355 (20.91)	351 (20.74)	373 (22.03)	
Unclear	118 (7.00)	120 (7.07)	102 (6.03)	88 (5.20)	
Activity, n (%)					0.707
Active	930 (55.16)	965 (56.83)	955 (56.44)	971 (57.35)	
Inactive	755 (44.78)	731 (43.05)	736 (43.50)	722 (42.65)	
Hypertension, n (%)					< 0.001
No	1109 (65.78)	1120 (65.96)	1101 (65.07)	981 (57.94)	
Yes	577 (34.22)	578 (34.04)	591 (34.93)	712 (42.06)	
Diabetes, n (%)					< 0.001
No	1481 (87.84)	1439 (84.75)	1402 (82.86)	1293 (76.37)	
Yes	205 (12.16)	259 (15.25)	290 (17.14)	400 (23.63)	
Taking insulin or glucose-lowering drugs					< 0.001
No	1617 (95.91)	1609 (94.76)	1592 (94.09)	1565 (92.44)	
Yes	69 (4.09)	89 (5.24)	100 (5.91)	128 (7.56)	
Taken prednisone or cortisone					0.344
No	1493 (88.55)	1495 (88.04)	1498 (88.53)	1525 (90.08)	
Yes	70 (4.15)	77 (4.53)	81 (4.79)	74 (4.37)	
Unclear	123 (7.30)	126 (7.42)	113 (6.68)	94 (5.55)	
Had osteoporosis					0.140
No	1476 (87.54)	1495 (88.04)	1501 (88.71)	1505 (88.90)	
Yes	86 (5.10)	81 (4.77)	82 (4.85)	99 (5.85)	
Unclear	124 (7.35)	122 (7.18)	109 (6.44)	89 (5.26)	
Serum calcium (mean ± SD, mg/dL)	9.40 ± 0.35	9.41 ± 0.35	9.41 ± 0.35	9.39 ± 0.34	0.475
Serum uric acid (mean ± SD, mg/dL)	5.30 ± 1.34	5.42 ± 1.37	5.42 ± 1.35	5.58 ± 1.42	< 0.001
Blood urea nitrogen (median (IQR), mg/dL)	12.00 (9.00–15.00)	12.00 (9.00–15.00)	12.00 (10.00–15.00)	13.00 (10.00–16.00)	< 0.001
TC (mean ± SD, mg/dL)	190.68 ± 39.47	193.45 ± 40.31	195.41 ± 41.68	198.34 ± 44.43	< 0.001
Fasting glucose (median (IQR), mg/dL)	98.00 (91.00–106.00)	99.00 (92.00–107.00)	100.00 (93.00–109.00)	101.00 (94.00–114.00)	< 0.001
TG (median (IQR), mg/dL)	93.00 (65.00–132.00)	100.00 (71.00–143.00)	106.00 (73.75–159.00)	117.00 (82.00–178.00)	< 0.001
BMI (mean ± SD, kg/m^2)	21.73 ± 2.18	25.72 ± 1.96	29.01 ± 2.31	34.95 ± 4.55	< 0.001
HDL-C (mean ± SD, mg/dL)	66.74 ± 17.06	56.39 ± 13.59	49.78 ± 11.89	44.00 ± 11.44	< 0.001
Total femur BMD (mean ± SD, g/cm^2)	0.90 ± 0.16	0.96 ± 0.16	1.00 ± 0.15	1.05 ± 0.15	< 0.001
Femurneck BMD (mean ± SD, g/cm^2)	0.79 ± 0.16	0.82 ± 0.15	0.85 ± 0.15	0.90 ± 0.16	< 0.001
Total spine BMD (mean ± SD, g/cm^2)	0.98 ± 0.14	1.02 ± 0.16	1.04 ± 0.14	1.08 ± 0.15	< 0.001

BMD, bone mineral density; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; METS-IR, metabolic score for insulin resistance; METS-IR = In (2 × fasting glucose [mg/dL] + TG [mg/dL]) × BMI [kg/m^2] / In (HDL-C [mg/dL]); SD, standard deviation; TC, total cholesterol; TG, triglycerides.

with BMD for the total femur (β = 0.060; 95% CI: 0.057, 0.064), femur neck (β = 0.049; 95% CI: 0.045, 0.052), and lumbar spine (β = 0.040; 95% CI: 0.036, 0.044). When METS-IR was divided into quartiles, a positive correlation was also observed for both variables. BMD was significantly higher in the highest quartile compared to the lowest quartile in the total femur (β = 0.150; 95% CI: 0.140, 0.161), femur neck (β = 0.115; 95% CI: 0.105, 0.126), and lumbar spine (β = 0.108; 95% CI: 0.098, 0.119).

3.3. Subgroup analysis

Subgroup stratified analyses based on gender, age, hypertension, and diabetes are presented in (Supplement Table 1). After adjusting for covariates, a positive association between METS-IR and BMD persisted across all subgroups. The interaction test between the subgroups mentioned above showed that the interaction between the variables did not show a statistical difference.

4. Discussion

In the current study, we have discovered a positive correlation between IR, as evaluated by the METS-IR index, and the BMD of the total femur, femur neck, and lumbar spine. Our findings suggest that an increase in METS-IR scores was associated with a proportional increase in BMD. To comprehensively address potential confounding variables, we conducted multiple linear regression analyses. Besides general demographic characteristics, we also accounted for lifestyle factors such as smoking and physical activity. Furthermore, we considered the effects of diseases such as hypertension, diabetes, and ever had osteoporosis. Moreover, other blood biochemical indicators were widely considered, including serum calcium, uric acid, blood urea nitrogen, and cholesterol. In addition, we also considered participants' previous medication use, including taking insulin or glucose-lowering drugs, prednisone, or cortisone. Our analyses demonstrated that the results were highly robust and remained consistent despite variable variations, further confirmed by subgroup regression analyses.

Typically, older adults undergo a decline in estrogen levels upon reaching menopause, triggering the activation of osteoclasts in the body, which results in bone loss.[18] However, we observed a distinct response in individuals with IR. That is, BMD increased with higher METS-IR scores, consistent with the findings of Shanbhogue et al.[19] This finding suggests that the usual pattern of BMD may be altered in the context of IR. Notably, a survey of 5,931 older adults revealed that higher glucose and insulin levels were linked to increased BMD and lower rates of fractures.[20] This phenomenon was similarly mirrored in a cohort study of non-diabetic older adults by Napoli et al.[15]

Existing literature has supported a positive relationship between IR and BMD in diabetic patients. A meta-analysis showed that the type 2 diabetic population exhibited higher BMD, yet their fracture risk was increased.[21] Yuan's study further demonstrated that prediabetic and diabetic patients had increased BMD in the hip, femoral neck, and spine.[22] In this study, consistent with prior research,[23] we observed that increasing IR was associated with higher BMD not only in diabetic patients but also in non-diabetic individuals. In addition to the abovementioned findings, we observed a positive association between IR and BMD in either hypertensive or non-hypertensive participants. Future research needs to verify whether this phenomenon is universal and investigate whether BMD is observed in all populations with high IR rather than being limited to individuals diagnosed with diabetes.

Theoretically, higher BMD should correspond with a lower risk of osteoporosis or fractures. However, diabetic patients may exhibit low bone turnover, poor microarchitecture, and increased bone fragility despite having high BMD.[24] These seemingly conflicting results suggest that multiple factors contribute to the reduction of bone biomechanical capacity. IR can disrupt bone homeostasis, leading to an imbalance between osteoblasts and osteoclasts. Studies on mice

Table 2
Relationship between METS-IR index and BMD.

Independent variables	Crude Model		Model I		Model II	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Total femur BMD						
Per-SD increase	0.059 (0.055, 0.062)	< 0.001	0.060 (0.056, 0.063)	< 0.001	0.060 (0.057, 0.064)	< 0.001
Q1	Reference		Reference		Reference	
Q2	0.050 (0.040, 0.061)	< 0.001	0.051 (0.040, 0.062)	< 0.001	0.052 (0.041, 0.062)	< 0.001
Q3	0.093 (0.083, 0.104)	< 0.001	0.094 (0.083, 0.104)	< 0.001	0.094 (0.084, 0.105)	< 0.001
Q4	0.147 (0.136, 0.158)	< 0.001	0.149 (0.138, 0.159)	< 0.001	0.150 (0.140, 0.161)	< 0.001
p for trend	< 0.001		< 0.001		< 0.001	
Femur neck BMD						
Per-SD increase	0.047 (0.043, 0.051)	< 0.001	0.048 (0.044, 0.052)	< 0.001	0.049 (0.045, 0.052)	< 0.001
Q1	Reference		Reference		Reference	
Q2	0.026 (0.015, 0.037)	< 0.001	0.026 (0.016, 0.037)	< 0.001	0.027 (0.016, 0.037)	0.739
Q3	0.060 (0.049, 0.070)	< 0.001	0.060 (0.050, 0.071)	< 0.001	0.061 (0.050, 0.071)	0.027
Q4	0.112 (0.101, 0.123)	< 0.001	0.114 (0.103, 0.125)	< 0.001	0.115 (0.105, 0.126)	< 0.05
p for trend	< 0.001		< 0.001		< 0.001	
Total spine BMD						
Per-SD increase	0.039 (0.035, 0.042)	< 0.001	0.039 (0.036, 0.043)	< 0.001	0.040 (0.036, 0.044)	< 0.001
Q1	Reference		Reference		Reference	
Q2	0.051 (0.040, 0.061)	< 0.001	0.051 (0.041, 0.062)	< 0.001	0.051 (0.041, 0.062)	< 0.001
Q3	0.063 (0.053, 0.074)	< 0.001	0.064 (0.054, 0.074)	< 0.001	0.064 (0.053, 0.074)	< 0.001
Q4	0.105 (0.095, 0.116)	< 0.001	0.107 (0.097, 0.118)	< 0.001	0.108 (0.098, 0.119)	< 0.001
p for trend	< 0.001		< 0.001		< 0.001	

β, partial regression coefficient; BMD, bone mineral density; CI, confidence interval.
Crude Model: no covariates were adjusted. Model 2: gender, age and race were adjusted. Model 3: Model 2 plus education, marital status, smoking, activity, hypertension, diabetes, serum calcium, serum uric acid, blood urea nitrogen, total cholesterol, taking insulin or glucose-lowering drugs, taken prednisone or cortisone, ever had osteoporosis.

lacking insulin receptors in osteoblasts have shown that this disruption can result in reduced bone formation and insufficient numbers of osteoblasts.[25] This hypothesis is supported by a cohort study conducted by Kim et al.,[26] which found an inverse relationship between BMD and trabecular bone scores in a community-based population. Specifically, the study showed that individuals with diabetes exhibited higher lumbar BMD but lower trabecular bone scores. These findings are consistent with the results of a survey conducted by Iki et al.[27] A lower trabecular bone score indicates a bone mass reduction and bone microarchitecture deterioration.[28] Hyperinsulinemia may activate a compensatory mechanism in the body, potentially facilitating bone anabolism. Besides, IR is often accompanied by disruptions in glucolipid metabolism. The resulting hyperglycemic state can inhibit osteoclast activity and delay bone matrix degradation, which may explain the observed higher BMD.[29]

Data indicate a 58% increase in the global incidence of musculoskeletal diseases from 1990 to 2017.[30] These diseases contribute significantly to disability and result in substantial public health expenditures. Therefore, it is essential to identify factors associated with musculoskeletal disorders in order to address existing knowledge gaps. Our study findings revealed that with each standard deviation increase in METS-IR, participants experienced an increase in total femur, femur neck, and lumbar spine BMD within the range of 0.040–0.60 g/cm^2. Furthermore, individuals in the highest quartile of METS-IR exhibited higher bone density, ranging from 0.108–0.150 g/cm^2, compared to those in the lowest quartile. It is worth exploring whether increasing insulin resistance leads to compensatory bone synthesis, and the impact of IR levels on changes in bone microstructure warrants further investigation.

The present inquiry boasts several advantages over prior research. Whereas antecedent studies have centered on the correlation between IR and BMD in patients with diabetes, the current research delves into this association among the general population by conducting a survey on a massive sample from the NHANES database. Moreover, the present study investigates the relationship between IR and BMD across different sites and performs further subgroup analyses. The analysis results demonstrated robustness and revealed a positive correlation between IR and BMD, with higher METS-IR scores corresponding to higher BMD. However, there are some limitations to this study. Firstly, it is a cross-sectional study, so we cannot make causal inferences about the relationship between IR and BMD. Additionally, although we took into account potential confounding factors as much as possible, there may still be unknown factors that may bias the results. Moreover, BMD based on dual-energy X-ray measurements is two-dimensional and cannot assess changes in bone microarchitecture, thus precluding the analysis of the association between IR and such changes.

In conclusion, this study demonstrates a positive association between IR and BMD as determined by METS-IR assessment, with higher METS-IR scores indicating an increase in BMD.

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Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=29.

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