

Relationship of Two-Hour Plasma Glucose and Abdominal Visceral Fat with Bone Mineral Density and Bone Mineral Content in Women with Different Glucose Metabolism Status

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Background: Several studies have reported the relationship of diabetes mellitus (DM) and obesity with bone mineral density (BMD), but the conclusions remain unclear. This study aimed to provide more information for the relationship of plasma glucose and abdominal visceral fat (AVF) with BMD and bone mineral content (BMC) in women with different glucose metabolism status.

Methods: Patients were screened by oral glucose tolerance test (OGTT) and were divided into three groups: normal glucose tolerance (NGT, $n=132$), pre-diabetes mellitus (pre-DM, $n=28$) and newly diagnosed type 2 DM (T2DM, $n=27$) groups. Plasma glucose concentrations, anthropometric measurements, body composition, and BMD were measured. Analysis of variance (ANOVA), Pearson correlation, and multiple linear regression models were used to evaluate the relationship between BMD, plasma glucose, AVF, and other variables.

Results: The percentage of subjects with osteoporosis or low BMD was 29.9%, and 66.7% subjects in T2DM group were significantly higher than that in the pre-DM (28.6%) and NGT (22.7%) groups ($p=0.005$ and $p<0.001$, respectively). Both BMD at femoral neck (FN) and lumbar spine (LS) of T2DM group were lower than those in NGT group ($p=0.009$ and $p=0.003$, respectively), and BMC of T2DM group was lower than those of NGT and pre-DM groups ($p<0.001$). The results of statistical analysis revealed that both two-hour plasma glucose (2-h PG) and age showed negative correlation with BMC, FN BMD, and LS BMD. AVF showed positive correlation with BMC and LS BMD. Furthermore, the lean mass (LM) showed independent positive effects on BMC.

Conclusion: Our findings suggest that 1) Age is a strong negative predictor of bone mass. 2) A direct negative effect of increasing 2-h PG might be more prominent at bone mass in women. 3) A moderate increase in AVF is beneficial to bone mass, while excessive increase might be harmful. 4) LM is a positive predictor of BMC.

Keywords: abdominal visceral fat, abnormal glucose metabolism, two-hour plasma glucose, bone mineral density, bone mineral content

Background

Diabetes mellitus, obesity, and osteoporosis have become chronic epidemic diseases worldwide, and are posing serious threat to the public health. But the relationship of DM and obesity with BMD remains unclear in previous studies.

The effects of T2DM on bones are complicated.¹ T2DM and low body mass index (BMI) have been identified as risk factors for osteoporosis.² Currently, it has been recognized that patients with T2DM were associated with higher risk of

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fractures than non-diabetic patients,³ BMD was associated with glucose metabolism.^{4,5} Another study has also revealed the differences in the blood glucose levels among osteoporosis, low BMD, and normal BMD groups.⁶ However, there was a study showed the detection rates of low BMD and osteoporosis have no significant differences among different glucose metabolism groups.⁷ Meta-analysis results also indicated that abnormal glucose metabolism showed no significant correlation with BMD or bone metabolism.⁸

The effect of obesity on BMD is associated with varied factors, but the relationship between obesity and osteoporosis still remains to be controversial,⁹ and it is inconclusive whether obesity increases or decreases BMD. Research indicated obesity as one of the protective factors of bones,¹⁰ body mass has beneficial effects on the mechanical load during bone formation.¹¹ Epidemiological studies have also confirmed the positive relationship between obesity and bone health.¹² However, there are also different opinions showed that AVF induces OP, excessive fat, especially the visceral fat, might be a risk factor for bone loss, increasing the fractures associated with obesity.^{13–15} In addition, visceral fat affects human metabolism by secreting a variety of fat factors, including the effect on bones, which might be used to explain the complex correlation between adipose tissue and bone tissue.

Hence, we intended to analyze BMD in adult women with different plasma glucose levels and AVF status, to provide more information for the relationship of PG and AVF with BMD and BMC. Sex hormones play a critical role in bone remodeling. In order to reduce the influence of gender differences on the research results, only women were included in this study.

Methods

Subjects

This study involved 187 individuals who are referred to the Physical Examination Centre of the First Hospital of Qinhuaingdao. Inclusion criteria included female individuals aged ≥ 18 years, with Chinese ethnicity.

The medical history of these individuals was collected. The exclusion criteria were as follows: individuals with ongoing inflammation (last longer than three month), cardiovascular disease, tumors, significant liver disease (levels of liver enzymes are elevated more than three times), creatinine clearance of < 30 mL/min, autoimmune diseases (such as rheumatoid arthritis), previous pathological fractures,

smoking, and intake of medicines that could affect bone mass (such as bisphosphonates, calcitonin, estrogens, vitamin D, and glucocorticoids).

OGTT

The subjects were divided into three groups, pre-DM, and T2DM were according to the 1998 Standards of the World Health Organization (WHO).¹⁶ Thus, patients meeting either of the following criteria could be diagnosed as having T2DM: (i) fasting plasma glucose (FPG) ≥ 125 mg/dL (7.0 mmol/L), where fasting is defined as no caloric intake for at least 8 h or (ii) two-hour post-load plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. Additionally, patients meeting either of the following standards were diagnosed as having pre-DM: (i) FPG ≥ 110 mg/dL (6.1 mmol/L) and < 125 mg/dL (7.0 mmol/L); or (ii) two-hour post-load plasma glucose ≥ 140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.1 mmol/L) during an OGTT. Plasma glucose (PG, mmol/L) was tested using an automatic analyzer (7600 series; Hitachi, Tokyo, Japan). T2DM patients were all newly diagnosed and had not received lifestyle interventions or insulin treatment.

Anthropometric Measurements

Anthropometric measurements, including height, weight, neck circumference (NC), waist circumference (WC), hip circumference (HC), and blood pressure, were obtained when the subjects were in light clothing and not wearing shoes. WC was accurately measured at the level of mid-way between the lowest rib and the top of the iliac crest. Blood pressure was measured twice using a mercury sphygmomanometer after 10 min of rest while the subjects were seated, and the average of the two measurements was used for analysis. BMI was calculated by dividing weight (kg) by height squared (m^2).

Body Composition and Bone Density Assessment

AVF was measured using a 1.5-T MRI scanner (Signa; GE Medical Systems, Milwaukee, WI, USA). A single MRI slice at the navel level of L4/L5 intervertebral spaces¹⁷ was obtained using water-suppressed T1-weighted imaging sequences (repetition time = 600 ms, echo time = 13 ms). The AVF area was quantified using the area measurement tool of Advantage Workstation 4.2 (GE Healthcare Technologies, Milwaukee, WI, USA). Abdominal obesity was defined as an AVF area of ≥ 100 cm^2 .¹⁸

The total body LM, FM, bone mineral content (BMC), BMD at FN and LS (L1-L4), and left hip (LH) were assessed using DXA (Hologic-4500 densitometer, Hologic, Inc., Waltham, Massachusetts, USA). DXA was performed by a well-trained professional.

Osteoporosis and low BMD were defined in the present study using the WHO criteria.¹⁹ Specifically, osteoporosis was defined as a T-score ≤ -2.5 at either the FN or the LS, low BMD was defined as those with T-scores between -1.0 and -2.5 at either skeletal site in postmenopausal women. And a Z-score of -2.0 or lower is defined as either “low BMD for chronological age” in premenopausal women.

Statistical Analysis

All analyses were performed using SPSS 13.0 statistical software. All of the numerical variables were normally distributed and reported as means $\pm$ standard deviation. Comparisons were conducted between the three groups using ANOVA. Post hoc tests were conducted by Student–Newman–Keuls (S–N–K) test. Comparison of data prevalence was performed by chi-square analysis. To measure the strength of the association between the two variables, Pearson correlation coefficient was used. Three multiple linear regression models were used to evaluate the relationships between BMD, plasma glucose,

AVF, and other variables (stepwise method). In model 1, age, weight, BMI, fasting plasma glucose (FPG), 2-h PG level from OGTT, WC, HC, AVF, LM, and FM were used as independent variables, and BMC was used as dependent variable. In models 2 and 3, BMC was replaced by BMD at FN and LS, respectively. $P < 0.05$ was considered to be statistically significant. The statistical power was nearly 0.7 processed by PASS 11.0 statistical software.

Declarations

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of the First Hospital of Qinhuangdao (ethical approval number:2018H010). Written informed consent was obtained from all subjects/patients.

Results

Among the study subjects, 29.9% had low BMD or osteoporosis. The prevalence of low BMD or osteoporosis was significantly higher in T2DM (66.7%) than in NGT and pre-DM groups ($p < 0.001$), but was similar between NGT and pre-DM (NGT 22.7% vs pre-DM 28.6%).

The information regarding age, as well as anthropometric, biochemical, and body composition are presented in Table 1. Age was similar among the three groups

Table 1 Clinical, Laboratory, and Anthropometric Characteristics of 187 Subjects and Their Comparisons in Three Groups

Variables	NGT(n=132)	Pre-DM (n=28)	T2DM(n=27)	P value
Age	47.62 $\pm$ 11.04	48.43 $\pm$ 10.00	47.59 $\pm$ 10.93	0.936
Weight(kg)	60.64 $\pm$ 10.72	67.75 $\pm$ 12.16 [#]	64.24 $\pm$ 10.87	0.005
BMI (kg/m ²)	23.04 $\pm$ 3.93	25.86 $\pm$ 3.98 [#]	25.15 $\pm$ 3.67 [#]	<0.001
SBP (mmHg)	109.55 $\pm$ 15.83	123.61 $\pm$ 18.11 [#]	125.50 $\pm$ 16.24 [#]	<0.001
DBP (mmHg)	70.11 $\pm$ 11.01	76.43 $\pm$ 10.06 [#]	77.92 $\pm$ 10.28 [#]	<0.001
FPG (mmol/L)	5.01 $\pm$ 0.53	5.28 $\pm$ 0.61	6.86 $\pm$ 1.59 ^{#&}	<0.001
2-h PG (mmol/L)	6.05 $\pm$ 0.96	9.18 $\pm$ 1.00 [#]	13.72 $\pm$ 3.75 ^{#&}	<0.001
NC (cm)	32.87 $\pm$ 5.85	33.80 $\pm$ 2.59	34.2 $\pm$ 2.15	0.457
WC (cm)	78.27 $\pm$ 9.19	84.26 $\pm$ 9.96 [#]	86.66 $\pm$ 9.24 [#]	<0.001
HC (cm)	96.44 $\pm$ 7.7	100.22 $\pm$ 9.13	97.54 $\pm$ 8.79	0.089
AVF (cm ²)	61.08 $\pm$ 26.92	83.76 $\pm$ 32.93 [#]	99.06 $\pm$ 40.50 ^{#&}	<0.001
FM (kg)	22.78 $\pm$ 8.41	30.47 $\pm$ 11.15 [#]	27.39 $\pm$ 7.85 [#]	<0.001
LM (kg)	36.01 $\pm$ 4.07	37.20 $\pm$ 5.22	35.59 $\pm$ 5.40	0.349
BMC (kg)	2.28 $\pm$ 4.15	2.12 $\pm$ 4.29	1.92 $\pm$ 4.16 ^{#&}	<0.001
FN BMD (g/cm ²)	0.91 $\pm$ 0.13	0.88 $\pm$ 0.11	0.83 $\pm$ 0.13 [#]	0.009
LS BMD (g/cm ²)	1.15 $\pm$ 0.16	1.09 $\pm$ 0.17	1.03 $\pm$ 0.18 [#]	0.003
LH BMD (g/cm ²)	0.99 $\pm$ 0.14	0.99 $\pm$ 0.13	0.95 $\pm$ 0.13	0.201
Low BMD or osteoporosis (%)	22.7	28.6	66.7 ^{#&}	<0.001

Notes: [#]Compared with NGT, $P < 0.05$; [&]Compared with pre-DM, $P < 0.05$.

Abbreviations: NGT, normal glucose tolerance; pre-DM, pre-diabetes mellitus; T2DM, type 2 diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2-h PG, two-hour plasma glucose; NC, neck circumference; WC, waist circumference; HC, hip circumference; AVF, abdominal visceral fat; FM, fat mass; LM, lean mass; BMC, bone mineral content; FN, femoral neck; LS, lumbar spine; LH, left hip; BMD, bone mineral density.

($p=0.936$). BMI, WC, and LM were significantly higher in the T2DM group than in the NGT group ($p<0.001$). BMD at FN and LS in the T2DM group was significantly lower when compared to NGT group ($p=0.009$ and $p=0.003$, respectively). FPG, 2-h PG, AVF were higher, and BMC was lower in T2DM group than in NGT and pre-DM groups ($p<0.001$). Furthermore, BMI, 2-h PG, WC, AVF, LM were significantly higher in the pre-DM group than NGT group ($p<0.001$).

The correlation coefficients between BMC, FN BMD, LS BMD, and other variables in all subjects are shown in Table 2. WC showed positive correlation with BMC ($r=0.233$, $p=0.001$), FN BMD ($r=0.203$, $p=0.001$). LM showed positive correlation with BMC ($r=0.624$, $p<0.001$), FN BMD ($r=0.343$, $p<0.001$), LS BMD ($r=0.269$, $p<0.001$). Age showed negative correlation with BMC ($r=-0.366$, $p<0.001$), FN BMD ($r=-0.403$, $p<0.001$), LS BMD ($r=-0.451$, $p<0.001$). And 2-h PG showed negative correlation with BMC ($r=-0.296$, $p<0.001$), FN BMD ($r=-0.236$, $p=0.001$), LS BMD ($r=-0.287$, $p<0.001$). Although the results of univariate correlation analysis showed no correlation between AVF and BMD or BMC in the overall subjects, AVF showed positive correlation with BMC ($r=0.437$, $p=0.025$) in the T2DM group.

The results of regression analysis showed that LM, age, 2-h PG, and AVF demonstrated an independent association with BMC (Model 1, $R^2 = 0.550$, $F= 45.145$, $p<0.001$) (Table 3). Age, 2-h PG and WC showed independent association with FN BMD (Model 2, $R^2 = 0.346$, $F= 19.569$, $p<0.001$) (Table 4). Age, 2-h PG, and AVF were

independently associated with LS BMD (Model 3, $R^2 = 0.362$, $F= 20.554$, $p<0.001$) (Table 5). Because of the age variable has a significant effect on multivariate analysis, three new regression models that eliminated the variable “age” were operated. The results of these new regression analyses excluded the effect of AVF and WC on BMC or BMD, but still showed negative effects of 2-h PG on BMC and BMD, and LM was still positively correlated with BMC. Hence, age, 2-h PG, AVF, WC, and LM were considered as important determinants of BMC or BMD after adjusting for the age variable in this study.

Discussion

In the present study, there was no significant difference in baseline age among the three groups. Univariate analysis showed that age was negatively correlated with BMC ($r=-0.366$, $p<0.001$), FN BMD ($r=-0.403$, $p<0.001$), and LS BMD ($r=-0.451$, $p<0.001$). After adjusting some influential factors, multivariate regression analysis revealed age was independently correlated with BMC, FN BMD, and LS BMD. Hence, age undoubtedly showed a negative effect on BMD, and this was consistent with the results reported previously. Previous study indicated that bone mass reaching peak in women aged 30~39 years, and the age at 40~59 years is the range at which menopause, obesity, and many other related diseases commonly occur, and so this age is regarded as the beginning of bone aging.^{20,21} As we have known, hormones levels vary with age, both age and hormones levels affect bone metabolism. It was indicated that osteoporosis is an inevitable outcome if humans live long enough.

Table 2 Simple Correlations Between BMC, FN BMD, LS BMD, and Age, Glucose, Body Composition Variables in the Study Subjects

Variables	BMC		FN BMD		LS BMD	
	r	p	r	p	r	p
Age	-0.366	<0.001	-0.403	<0.001	-0.451	<0.001
Weight	0.375	<0.001	0.260	<0.001	0.144	0.053
BMI	0.261	<0.001	0.195	<0.001	0.080	0.283
FPG	-0.071	0.335	0.100	0.172	-0.212	0.004
2-h PG	-0.296	<0.001	-0.236	0.001	-0.287	<0.001
NC	0.034	0.659	-0.051	0.510	-0.032	0.682
WC	0.233	0.001	0.203	0.005	0.062	0.408
HC	0.341	<0.001	0.264	<0.001	0.145	0.052
AVF	0.046	0.565	-0.037	0.649	-0.044	0.591
FM	0.056	0.443	0.099	0.180	-0.038	0.610
LM	0.624	<0.001	0.343	<0.001	0.269	<0.001

Abbreviations: BMC, bone mineral content; FN, femoral neck; LS, lumbar spine; BMD, bone mineral density; BMI, body mass index; FPG, fasting plasma glucose; 2-h PG, two-hour plasma glucose; NC, neck circumference; WC, waist circumference; HC, hip circumference; AVF, abdominal visceral fat; FM, fat mass; LM, lean mass.

Table 3 Multiple Linear Regression Analysis for BMC

Variables	B	Std. Error	Beta	t	p	95% CI
Constant	1283.870	158.266	–	4.971	<0.001	773.506~1794.235
LM	0.050	0.006	0.504	8.491	<0.001	0.038~0.061
Age	–14.541	2.416	–0.355	–6.018	<0.001	–19.316~–9.767
2-h PG	–45.393	8.598	–0.340	–5.280	<0.001	–62.383~–28.403
AVF	2.401	0.924	0.182	2.600	0.010	0.576~4.227

Note: Dependent variable: bone mineral content.

Abbreviations: LM, lean mass; 2-h PG, two-hour plasma glucose; AVF, abdominal visceral fat; CI, confidence interval.

Table 4 Multiple Linear Regression Analysis for BMD at Femoral Neck

Variables	B	Std. Error	Beta	t	p	95% CI
Constant	0.579	0.089	–	8.566	<0.001	0.584~0.934
Age	–0.005	0.001	–0.426	–6.177	<0.001	–0.007~–0.003
2-h PG	–0.010	0.003	–0.260	–3.590	<0.001	–0.015~–0.004
WC	0.03	0.001	0.266	3.151	0.002	0.001~0.006

Note: Dependent variable: bone mineral density at femoral neck.

Abbreviations: 2-h PG, two-hour plasma glucose; WC, waist circumference.

Table 5 Multiple Linear Regression Analysis for BMD at Lumbar Spine (L1-L4)

Variables	B	Std. Error	Beta	t	p	95% CI
Constant	1.357	0.119	–	11.406	<0.001	1.122~1.592
Age	–0.008	0.001	–0.506	–7.134	<0.001	–0.010~–0.006
2-h PG	–0.019	0.004	–0.365	–4.685	<0.001	–0.027~–0.011
AVF	0.001	<0.001	0.241	2.849	0.005	0.000~0.002

Note: Dependent variable: bone mineral density at lumbar spine (L1-L4).

Abbreviations: 2-h PG, two-hour plasma glucose; AVF, abdominal visceral fat.

We collected and analyzed plasma glucose levels data, and revealed that the prevalence of low BMD or osteoporosis was 66.7% in the T2DM group, 28.6% in the pre-DM group and 22.7% in the NGT group. Previous studies showed that T2DM population has a higher BMD, but also has a higher risk of overall fracture and hip fracture when compared with non-diabetic patients.^{3,22,23} However, T2DM demonstrated additional harmful effects, which might be related to high blood glucose levels, change in insulin levels and increased obesity rate. These abnormalities might affect bone metabolism indexes by different mechanisms.²⁴ This study showed that FN BMD (0.83 ± 0.13), LS BMD (1.03 ± 0.18) and BMC (1.92 ± 4.16) in T2DM group were lower than those of FN BMD (0.91 ± 0.13), LS BMD (1.15 ± 0.16), and BMC (2.12 ± 4.29) in NGT group. And the BMC was also lower in T2DM group than pre-DM group (2.28 ± 4.15). These results might be related to the increased plasma glucose levels and duration of the disease.³ Furthermore, the results of statistical analysis revealed that 2-h PG was

negatively correlated with BMC, FN BMD, and LS BMD. Studies on mechanisms of glucose affecting bone mass showed that advanced glycation end-products (AGEs),²⁵ the polyol pathway,²⁶ insulin resistance,²⁷ oxidative stress, inflammation, and the production of ROS, which have adverse effects on bone.²⁸ In short, this study highlighted the significant negative impact of 2-h PG on BMD.

The easy-to-obtain anthropometric parameters, such as weight, BMI, WC, HC, NC, etc., are indicators that represent obesity in some aspects. The above parameters were collected and analyzed, but the results showed only the effect of WC on FN BMD. This might be because that abdominal obesity has more significant effect on bone metabolism among obese people, while WC as an index for evaluating abdominal obesity is more reliable than other parameters.^{29–31} Our data showed that WC in T2DM and pre-DM groups were higher than that in NGT group, and WC was positively correlated with BMC ($r=0.233$, $p=0.001$) and FN BMD ($r=0.203$, $p=0.001$).

Regression analysis also suggested that WC had a positive effect on FN BMD.

Compared with WC, AVF is regarded as a gold standard for evaluating abdominal obesity.³² Data analysis results showed that the AVF area was gradually increased from NGT group, pre-DM group to T2DM, and the differences were statistically significant (99.06 ± 40.50 vs 83.76 ± 32.93 vs 61.08 ± 26.92). Although the results of univariate correlation analysis showed no correlation between AVF and BMD or BMC in the overall subjects, AVF was positively correlated with BMC ($r=0.437$, $p=0.025$) in the T2DM group. Further regression analysis indicated that AVF still demonstrated independent positive effects on BMC and LS BMD. There were studies found that AVF had a negative impact on BMD, it is regarded as a risk factor for bone loss and increased obese fractures.^{12–15} Studies showed that adipose tissue showed a positive effect on bones only through mechanical loading,³³ while the others are more complex non-weight-bearing effects.³⁴ Furthermore, epidemiological studies have found adipose tissue showing a positive correlation with BMD and BMC.^{35–37} In contrast, previous studies found that adipose tissue was positively correlated with BMC,³⁸ but excessive adipose tissue could lead to decreased BMC,³⁹ and adipose tissue at different parts might exert different effects on bone.³³ Our results showed positive effects on BMC and LS BMD, which might be due to that a certain range of increase in AVF might have a positive impact on BMD, while an excessive increased AVF might lead to a negative effect.³³ In addition, the adipose tissue, especially the visceral fat not only affects the homeostasis of the body's energy but also affects other processes including bone metabolism by releasing a variety of adipokines. This might be used to explain the complex correlation between adipose tissue and bone tissue.^{11,23,40}

This study also measured LM data using DXA. LM has been widely reported as a protective factor for BMD due to its mechanical traction on bones.⁴¹ Our results showed that LM alone has positive effect on BMC. Univariate correlation analysis showed positive correlation of LM with BMC ($r=0.624$, $p<0.001$), FN BMD ($r=0.343$, $p<0.001$) and LS BMD ($r=0.269$, $p<0.001$). Moreover, regression analysis also confirmed the correlation between LM and BMC, which was consistent with the results reported previously. Therefore, we confirm that LM is a positive predictor of BMC.

Conclusions

In conclusion, our findings suggest that age is a strong negative predictor of bone mass. We observed a significant negative effect of 2-h PG that was more pronounced at bone mass in women. Thirdly, the effect of AVF on bone mass might be related to the extent of its increase, a moderate increase in AVF is beneficial to bone mass, while excessive increase remains harmful, which needs to be further studied. Lastly, we confirm that LM is a positive predictor of BMC.

However, there were certain limitations in the current study. This study involves a cross-sectional design, limiting our ability to prove the causality. It also involves small population, which limits the statistical power and lacks more comprehensive clinical information (such as family history, physical activity, and dietary habits). In addition, menopausal women were not stratified for analysis due to inclusion of sample size.

Abbreviation

BMD, bone mineral density; BMC, bone mineral content; AVF, abdominal visceral fat; OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2-h PG, two-hour plasma glucose; NC, neck circumference; WC, waist circumference; HC, hip circumference; FN, femoral neck; LS, lumbar spine; LH, left hip; FM, fat mass; LM, lean mass; ANOVA, analysis of variance; S–N–K, Student–Newman–Keuls; CI, confidence interval.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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