

# Study on the Correlation between Adiponectin and Bone Mineral Density in Postmenopausal Women from Guangxi Zhuang Autonomous Region

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## Abstract

**Objectives:** To explore the relationship between adiponectin (APN) and bone mineral density in this Zhuang ethnic group, thus providing a basis underpinning the prevention and treatment of osteoporosis (OP). **Methods:** Zhuang women over 50 years old in Guangxi Zhuang Autonomous Region were included in the study. The broadband ultrasound attenuation (BUA) was adopted as the reference to calculate the T value. Quantitative ultrasonic bone density was measured on the right. Body composition measuring instrument was used to measure weight, fat, and muscle mass. Plasma APN level was detected by ELISA and blood lipids were detected by enzymatic method. **Results:** Plasma APN level was found with significant differences in the normal bone mineral density group, bone mineral density reduction group, and osteoporosis group ( $P < 0.05$ ). The elevation of APN predicted a BUA decrease ( $\beta = -0.176$ ,  $P = 0.001$ ) when the partial correlation coefficient of APN is  $-0.210$ . Elevated APN was an independent risk factor for bone mineral density reduction ( $OR = 1.191$ , 95%  $CI$ : 1.004 - 1.407,  $P = 0.04$ ) and OP ( $OR = 1.1337$ , 95%  $CI$ : 1.137 - 1.572,  $P < 0.001$ ). **Conclusion:** Increased APN in postmenopausal women of Zhuang is an independent risk factor for OP. The application of APN in the OP screening and prevention of middle-aged and ageing Zhuang women still needs further research.

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## Keywords

Postmenopausal, Osteoporosis, Adiponectin, Broadband Ultrasound Attenuation

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## 1. Introduction

Osteoporosis (OP) refers to a systemic bone disease characterized by decreased bone mass, deteriorated bone microstructure, and susceptibility to fragility fractures (World Health Organization, WHO) [1]. In 2018, the prevalence of OP has increased in China, affecting more than one-third of people aged 50 years or older [2]. Of them, postmenopausal women suffer the most [3].

Adiponectin (APN) is an adipokine (5 - 15 µg/mL) secreted by adipocytes, accounting for about 0.05% of plasma proteins [4]. Early studies found that APN is mainly involved in glucose metabolism [5]. Further research suggested that it plays a part in the metabolism of multiple organs, such as the cardiovascular system, liver, brain, muscles, and bones [6]. Postmenopausal changes in hormone levels in middle-aged and ageing women can impact bone metabolism and lipid metabolism [7] [8]. In postmenopausal women, the rapid accumulation of body fat goes along with the rapid loss of bone mass [9]. Xinyan Bi *et al.* found that APN is a hormone derived from adipocytes that may affect bone metabolism, possibly mediated by sex hormones [10]. Xiaojie Wang *et al.* suggest that the pathological evaluation value of APN in primary osteoporosis and its correlation analysis with bone metabolism indicators [11]. During this process, however, the role of APN in Zhuang women, which is the most widely distributed adipokine, remains unclear.

According to a previous study, the body fat percentage of postmenopausal Zhuang women was significantly lower than that of other groups [12]. It was speculated that the low body fat percentage of postmenopausal Zhuang women might lead to higher APN levels, but the correlation between the increased APN levels and bone mineral density in these women remained unknown. Therefore, through analyzing the correlation of APN, body fat composition, and lipid metabolism indexes with bone mineral density, this study is designed to explore the effect of APN on the bone mineral density of Zhuang women. In addition, this part has not been studied yet and has certain clinical significance, filling the existing research gap.

## 2. Materials and Methods

### 2.1. Subjects

From July 2016 to December 2016, Zhuang women over 50 years old, were enrolled by cluster random sampling from different townships in Guangxi Zhuang Autonomous Region, including those from Debao County, Tiandeng County,

Daxin County, Wuming County, and Yizhou City. Inclusion criteria were as follows: 1) Three generations or above (including three generations) in a family were all native Zhuang people with permanent residence in the locality. 2) The period after natural menopause was more than 2 years. 3) The subjects did not suffer from bone metabolic diseases or significant nutritional and metabolic diseases. 4) They had never taken drugs that could affect bone metabolism or estrogen levels. 5) There was no oophorectomy or other pathological factors. Exclusion criteria were as follows: 1) Those who did not sign the informed consent form. 2) No blood samples were provided. 3) Samples with missing data. This study had been approved after the medical ethics review by Youjiang Medical University for Nationalities (No. 2015030101), and all participants had given their informed consent.

## 2.2. Measurement of Bone Mineral Density and Subject Grouping

QUS (OSTEOSPACE, France) was used to measure the medial and lateral sides of the right heel to obtain calcaneal broadband ultrasound attenuation (BUA), where the unit of measurement was dB/MHz. DXA is a method that is easy to operate, fast to measure, and has low measurement costs. The basic principle of QUS is to emit ultrasound waves from one side of the bone to the other, receive ultrasound waves that attenuate in amplitude after passing through the bone and soft tissue, measure the ultrasound frequency attenuation (BUA) parameter closely related to bone density, and use it to calculate bone density. This value could reflect the changes in bone mineral density (BMD). The T value represented the peak BUA bone mass of Zhuang women: (*Sample measurement of BUA* - peak BUA of normal population)/standard deviation of peak BUA of normal population. According to the diagnostic criteria of the World Health Organization, conditions with a T-score of  $-2.5$  or lower were classified as OP, conditions with a T-score between  $-1.0$  and  $-2.5$  as bone loss, and those with a T-score of above  $-1.0$  as normal [13]. DXA is that this method is easy to operate, fast to measure, and has low measurement costs.

## 2.3. Measurement of Body Composition

Body weight was measured using a body composition analyzer (TANITA, MC-180, Japan), while the total fat mass, upper limb fat mass, lower limb fat mass, and visceral fat mass were determined by bioelectrical impedance analysis, where the unit of measurement was kilograms (kg). Body fat percentage (%) was calculated by the ratio of fat mass to body mass. Body height (m) was measured using a Martin height meter. All the above operations were carried out by trained practitioners. Body mass index (BMI) was calculated by dividing weight (kg) by height (m) squared.

## 2.4. Determination of Plasma APN and Blood Lipid Components

After introducing heparin to 5 ml of fasting venous blood, plasma was separated.

The Human Adiponectin Platinum ELISA Vers.2 Kit (eBioscience) was used to measure APN levels according to the manual's instructions. Blood lipid indices like total cholesterol (TC), triglycerides (TG), high-density lipoprotein Cholesterol (HDL-C), low-density lipoprotein Cholesterol (LDL-C), and very low-density lipoprotein Cholesterol (VLDL-C) were determined using an enzymatic method on a Roche 702 automatic biochemical analyzer.

## 2.5. Statistical Methods

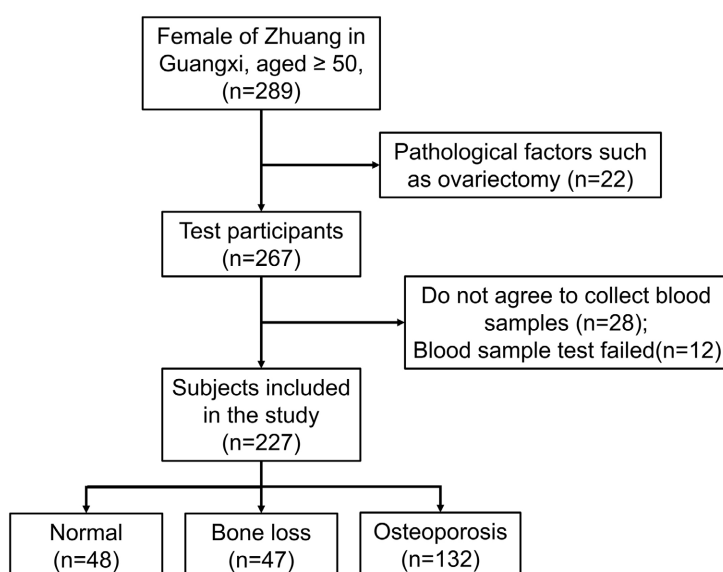
Data analysis was performed using SPSS v26.00 (SPSS Inc., Chicago, IL, USA). Normally distributed data were represented by mean  $\pm$  standard deviation, and Welch's ANOVA test was adopted for comparison among groups; Pearson correlation was used to analyze the linear relationship between APN and BUA; a stepwise linear regression model was employed to analyze factors influencing BUA; multivariate Logistic regression analysis was used to analyze the predictors of OP. The test standard was  $\alpha = 0.05$ , and differences with  $P < 0.05$  were considered statistically significant.

## 3. Results

According to the inclusion criteria, a total of 227 subjects were included in our study and then divided into three groups based on the diagnostic standard of OP and the peak bone mass reference previously established by our team. The normal bone mass group included 48 instances, the bone loss group included 47 cases, and the OP group included 132 cases (**Figure 1**).

### 3.1. Baselines of the Involved Population

The baselines of the subjects have been shown in **Table 1**. Significant differences in BUA values were observed among these three groups ( $P < 0.001$ ). Compared



**Figure 1.** Flow chart of the analysis of the selected samples.

**Table 1.** Baseline characteristics of different groups.

	Total	Normal	Bone loss	OP	Pvalue
Subjects, n	227	48	47	132	
BUA, dB/MHz	54.67 ± 8.26	67.14 ± 4.55	57.90 ± 1.55**	49.00 ± 4.03***	<0.001
T-value	-2.66 ± 2.21	0.61 ± 1.20	-1.73 ± 0.71**	-4.19 ± 1.07***	<0.001
Age, yr	65.13 ± 10.55	56.12 ± 6.50	63.09 ± 10.03**	69.14 ± 9.71***	<0.001
Height, m	1.49 ± 0.07	1.53 ± 0.07	1.50 ± 0.07	1.48 ± 0.06**	<0.001
Weight, kg	52.07 ± 9.07	56.89 ± 7.25	53.23 ± 10.04	49.91 ± 8.60***	<0.001
BMI, kg/m <sup>2</sup>	23.23 ± 3.27	24.33 ± 2.71	23.36 ± 3.25	22.78 ± 3.40 <sup>#</sup>	0.019
Body fat rate, %	28.60 ± 7.41	29.66 ± 6.65	28.28 ± 7.46	28.31 ± 7.68	0.277
APN, µg/mL	15.77 ± 3.11	14.04 ± 2.80	15.31 ± 2.90*	16.51 ± 3.03***	<0.001
Fat mass					
Total, kg	15.44 ± 6.11	17.46 ± 5.27	15.73 ± 6.66	14.61 ± 6.05 <sup>#</sup>	0.019
Visceral, kg	1.94 ± 1.21	2.08 ± 1.01	1.97 ± 1.30	1.88 ± 1.24	0.616
Upper limb, kg	1.40 ± 0.71	1.64 ± 0.63	1.47 ± 0.83	1.29 ± 0.68 <sup>#</sup>	0.010
Lower limb, kg	6.02 ± 1.71	6.93 ± 1.49	6.14 ± 1.91*	5.65 ± 1.59**	<0.001
Blood lipid					
TC, mmol/L	4.96 ± 1.28	4.68 ± 1.43	5.13 ± 1.15	5.01 ± 1.26	0.185
TG, mmol/L	1.60 ± 1.44	1.72 ± 1.82	1.86 ± 1.86	1.46 ± 1.03	0.130
HDL-C, mmol/L	1.46 ± 0.41	1.36 ± 0.42	1.51 ± 0.40	1.46 ± 0.42	0.222
LDL-C, mmol/L	2.80 ± 1.03	2.57 ± 1.08	2.82 ± 1.01	2.87 ± 1.01	0.199
VLDL-C, mmol/L	0.74 ± 0.65	0.67 ± 0.46	0.87 ± 0.77	0.67 ± 0.46	0.131

Data are reported as mean ± SEM or n (%). Compared between the bone loss group and the normal group, the OP group and the normal group: \* $P < 0.05$ , \*\* $P < 0.001$ ; Compared between the osteoporosis group and the bone loss group: <sup>#</sup> $P < 0.05$ , <sup>##</sup> $P < 0.001$ . OP: osteoporosis group; BUA: Broadband Ultrasound Attenuation; BMI: Body Mass Index; APN: Adiponectin; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; VLDL-C: Very Low-Density Lipoprotein Cholesterol.

with the normal bone mass group, there were no significant differences in the visceral fat mass, TC, TG, LDL-C, HDL-C, and VLDL-C between the bone loss group and the OP group ( $P > 0.05$ ), while the differences in age, height, weight, BMI, fat mass, upper limb fat mass, lower limb fat mass and APN were statistically significant ( $P < 0.05$ ). Of them, the inter-group difference in age was significantly different ( $P < 0.001$ ) (Table 1).

### 3.2. Relationship between APN and BUA

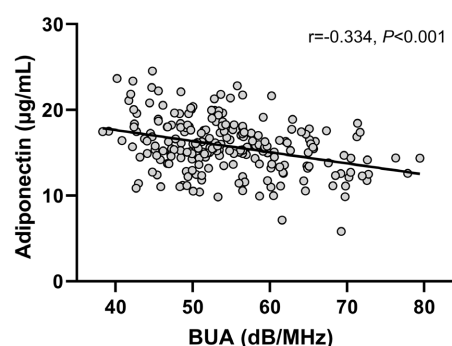
The relationship between APN and BUA has been shown in Figure 2. Pearson correlation analysis demonstrated that APN and BUA were negatively correlated ( $r = -0.344$ ,  $P < 0.001$ ) and that the negative correlation remained after adjustment for age and BMI ( $r = -0.213$ ,  $P = 0.001$ ).

### 3.3. Predictors of BUA

After including APN in the linear regression equation with BUA as the dependent variable (Table 2, Model 1), the results showed that APN was a predictor of BUA ( $P < 0.001$ ), and the partial correlation coefficient was  $-0.344$ . After including age, BMI, and APN in the linear regression equation, where BUA was set as the dependent variable (Table 2, Model 2) and APN as the independent variable, the difference turned out to be statistically significant ( $\beta = -0.176$ ,  $P = 0.001$ ), and the partial correlation coefficient of APN was  $-0.210$ .

### 3.4. Risk Factor Analysis of APN for OP

Multivariate Logistic regression analysis was conducted with the normal bone mass group, the bone loss group, and the OP group (assigned as 0, 1, and 2, respectively) as dependent variables. Age, BMI, and APN were taken as covariants, and the normal bone mass group was taken as the reference. The estimated parameter values have been shown in Table 3. The results showed that increased APN was an independent risk factor for bone loss ( $OR = 1.191$ , 95% CI: 1.004 - 1.407,  $P = 0.04$ ) and OP ( $OR = 1.1337$ , 95% CI: 1.137 - 1.572,  $P < 0.001$ ), and that the influencing effect of APN was greater than that of BMI.



**Figure 2.** Relationship between APN and BUA. APN: Adiponectin; BUA: Broadband Ultrasound Attenuation.

**Table 2.** Independent predictors of the BUA.

	BUA		$r$	$R^2_{\text{adj}}$	Residual
	$\beta$	$P$			
Model 1 <sup>①</sup>					
APN	−0.344	<0.001	−0.344	0.115	13596.18
Model 2 <sup>②</sup>					
Age	−0.540	<0.001	−0.566		
BMI	0.159	0.003	0.200	0.412	8952.32
APN	−0.176	0.001	−0.210		

<sup>①</sup>The dependent variable: APN; <sup>②</sup>The dependent variable variables: Age, BMI, and APN. BUA: Broadband Ultrasound Attenuation; APN: Adiponectin; BMI: Body Mass Index.

**Table 3.** Possible effects of APN on osteoporosis in multiple Logistic regression analysis.

	B	wald	P	OR	95%CI of OR
Model 1 <sup>①</sup>					
Age	0.134	15.924	<0.001	1.143	1.070 - 1.221
BMI	-0.098	1.765	0.184	0.906	0.784 - 1.048
APN	0.175	4.197	0.040	1.191	1.008 - 1.407
Model 2 <sup>②</sup>					
Age	0.196	35.278	<0.001	1.217	1.140 - 1.298
BMI	-0.146	4.251	0.039	0.864	0.752 - 0.993
APN	0.290	12.407	<0.001	1.337	1.137 - 1.572

<sup>①</sup>Bone loss vs Normal; <sup>②</sup>Osteoporosis vs Normal. The dependent variable: Age, BMI, and APN. APN: Adiponectin; BMI: Body Mass Index.

#### 4. Discussion

The Zhuang ethnic group is the most populous ethnic group in Guangxi Zhuang Autonomous Region, China. Studying the relationship between APN and bone density in the Zhuang population can provide certain clinical value for the screening and prevention of osteoporosis in women in this ethnic minority area.

Our study analyzed the correlation of bone mineral density with body fat content and relevant lipid metabolism indexes in postmenopausal women. It was found that age, BMI, and APN were negatively correlated with bone mineral density. Of them, increased APN was an independent risk factor for OP in these women, and age exerted the greatest effect as an independent risk factor. Although fat mass in different parts appeared to be lower in the OP population, the fat mass could not be used to predict the changes in bone mineral density (data not shown). TC, TG, LDL-C, HDL-C, and VLDL-C, as markers of lipid metabolism, showed no significant correlation with the changes in bone mineral density.

In recent years, related studies have reported on the correlation between APN and bone mineral density in postmenopausal women. And most of them have evidenced the predictive effect of increased APN levels for decreased bone mineral density in women. The study by Ansari *et al.* that included 175 postmenopausal Arab women found a significant inverse correlation between APN and total BMD [9]. According to the study by TANNA *et al.*, APN was negatively associated with bone mineral density in OP women ( $P = 0.043$ ), and serum APN in women with fractures (20.8 µg/ml) was significantly higher than that in women without fractures (18.5 µg/ml,  $P = 0.018$ ) [14]. In a study including 256 postmenopausal women, Wang *et al.* suggested a negative correlation between APN and BMD [15], which was corroborated by another study including 271 postmenopausal women (42 - 97 years) [16]. Such an inverse correlation between APN and bone mineral density may remain to work in certain pathologi-

cal states and different genders. For example, serum APN levels were negatively correlated with bone mineral density in patients with knee OA [17]. In obese people, APN and estradiol levels were found in significant inverse correlation with the bone mineral density in the hip and spine [18]. However, some studies did not verify any correlation between APN and bone mineral density [19]. In the study by Stojanovic *et al.* APN levels were significantly positively correlated with total BMD, lumbar spine BMD and femoral neck BMD ( $r = 0.618$ ,  $r = 0.521$ ,  $r = 0.567$ ;  $P < 0.01$ ) [20]. The *in vitro* study conducted by Zhu *et al.* indicated that short-term caloric restriction-induced bone loss by increasing APN [21].

Nevertheless, most animal and cell studies did not support the results above. In the study by Madel *et al.* that was based on adipocyte-deficient mice, it was found that APN could block podosome formation through AMPK activation, thereby inhibiting the activity of mature osteoclasts in mice and reducing bone loss [22]. Wu *et al.* found that APN could promote osteogenesis in hPDLs via the p38 pathway [23]. Based on their animal experiment, Liu *et al.* demonstrated that APN receptor activation has a pro-osteogenic, anti-adipogenic, and anti-osteoclastogenic effect in young mice [7]. This may be related to the different effects of APN on osteoblasts and osteoclasts and its indirect promotion of osteogenesis by enhancing insulin signaling. Here, the different effects of APN on osteoblasts and osteoclasts may be associated with different APN receptors on the cell surface. Jonathan *et al.* further pointed out that the signaling effect of APN in bone homeostasis was correlated with different ages and diseases [24]. Higher bone mineral density and a reduced number of *TRAP5b*-positive osteoclasts were observed in advanced-age (56-week) transgenic mice overexpressing AdipoR1, while these changes were not reported in young mice aged 8 or 32 weeks [25]. This difference may be associated with the regulation of apoptosis by APN. In addition, Ju Zhang *et al.* have found that APN overexpression facilitates bone fracture healing in osteoporosis [26]. APN overexpression promoted bone formation in OVX mouse BMSCs and bone fracture ends by regulating the balance between osteogenesis and adipogenesis [26].

AdipoRon, a small-molecule compound APN receptor agonist, can slightly inhibit the proliferation of pre-osteoblasts and pre-osteoclasts and promote cell migration of mesenchymal stromal cells, although it does not affect the viability of mesenchymal stromal cells. Besides, AdipoRon can facilitate the osteogenic differentiation of pre-osteoblasts and mesenchymal cells. Furthermore, AdipoRon can significantly inhibit osteoclastogenesis through its direct impact on pre-osteoclasts and its indirect inhibition of RANKL in osteoblasts. After treatment with AdipoRon, mesenchymal stem cells demonstrate reduced adipogenesis. In addition, mice treated with AdipoRon showed faster bone regeneration and suppressed adipogenesis.

Shinoda *et al.* pointed out that APN participates in bone metabolism mainly in three pathways: positive effect realized via autocrine/paracrine pathway; nega-



tive effect via the direct pathway in the form of circulating APN; and positive effect via the indirect pathway of enhancing insulin signaling [24]. This, to a certain extent, explains the conflicting results in different population-based studies as well as experimental studies *in vitro* and *in vivo*.

We compared relevant data collected from the above clinical studies [9] [14] [15] [27] and found that the middle-aged and ageing Zhuang women included in our study had lower BMI and body fat percentage, and higher APN levels, which is in line with our knowledge that APN is negatively correlated with fat mass [28] [29]. However, the coexistence of low body fat mass and high APN levels may be related to different dietary habits and lifestyles, including a low-carbohydrate diet [30], a low-calorie diet [31], and more exercise or labor, among others. In the questionnaire survey, it was found that middle-aged and ageing Zhuang women often ingest coarse grains, such as corn and sweet potatoes. Under the influence of geographical and climatic conditions, their diets are relatively light, with vegetables as the main part and meat as supplements. Therefore, further studies with an expanded sample size are required to examine whether this dietary habit, together with more exercise or labor in these women due to the mountainous terrain in the locality, would sustain the effect of APN or factors related to it on OP. Our results suggest that APN levels can be measured to predict the risk of OP in postmenopausal women in Zhuang.

There are also some limitations to our study. Firstly, this study only focused on the Zhuang population in the Guangxi Zhuang Autonomous Region, so our findings are limited and may not apply to other populations. Secondly, no further follow-up was carried out in our study, so changes in APN and bone mineral density caused by ageing have not been assessed more accurately.

## 5. Conclusion

Our study detected the BMD of postmenopausal women in the Guangxi Zhuang Autonomous Region using QUS technology and investigated the correlation of APN with bone mineral density and OP. The results showed that APN was negatively correlated with bone mineral density and elevated APN was an independent risk factor for OP. Moreover, further research is required to explore the relevant mechanism of APN in OP occurrence and its application in postmenopausal Zhuang women.

## Fund

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## Ethical Statement

This study had been approved after the medical ethics review by the Medi-

cal Ethics Committee of Youjiang Medical University for Nationalities (No. 2015030101), and all participants had given their informed consent.

### Data Availability

The research article data used to support the findings of this study are available from the corresponding author upon request.

### Contributorship

YL, PS, LH, RL and JW researched the literature and conceived the study. YL, PS, SM, JL, XM and ZF were involved in protocol development, gaining ethical approval, patient recruitment and data analysis. YL and PS wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

### Policy Impact Statement

This study has found that adiponectin was inversely associated with bone density, and elevated adiponectin was an independent risk factor for osteoporosis, but the relevant mechanisms were unclear. This suggests that further studies can be conducted on how adiponectin regulates the development of osteoporosis in postmenopausal Zhuang women and the application of APN in other aspects.

### Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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