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Influence of bone mineral density in circulating adipokines among postmenopausal Arab women

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ABSTRACT

Osteoporosis and osteopenia has a significant link with substantial fracture risk. Epidemiological data revealed a protective role of adipose tissue on bone biology in postmenopausal osteoporosis. The current study assessed the associations between select adipokines and bone mineral density (BMD) in postmenopausal women. A total of 175 Saudi postmenopausal women were selected and categorized based on their BMD (normal & low-BMD). Circulating levels of select adipokines (adiponectin, resistin, leptin, and adipsin), insulin, 25(OH)D and RANKl were determined using commercially available assay kits. BMD was measured by dual-energy X-ray absorptiometry (DXA). Overall and among low-BMD subjects, adiponectin consistently showed a significant inverse association with BMD (overall −0.34, $p < 0.01$; low BMD group −0.34, $p < 0.01$). In multiple regression, adiponectin (−0.29 ± 0.06, $p < 0.00$) and resistin (−0.08 ± 0.04, $p < 0.05$) were inversely significant with BMD overall, but after stratification the significance was lost for resistin (−0.05 ± 0.04, $p < 0.224$) whereas adiponectin remained (−0.22 ± 0.07, $p < 0.02$) in low-BMD subjects. Adipsin, leptin and lipocalin-2 showed no significant associations. Findings of the present study revealed that only adiponectin showed a significantly strong inverse association with low BMD, suggesting that insulin sensitivity may influence bone health in Arab postmenopausal women.

1. Introduction

Osteoporosis is characterized as reduced bone mineral density (BMD) and microstructural deterioration of bone tissues with a consequent decrease in bone strength and increased risk of fragility. Chronic low bone mineral density can adversely impact the patient's mobility, function, and quality of life (Maria et al., 2014; Pasco et al., 2006). There are over 200 million subjects affected by these disorders (Cooper, 1999), making them a major global health issue in the elderly population (Hiligsmann et al., 2013).

Studies in the Saudi population (≥50 years) revealed that the mean prevalence of male osteoporosis and osteopenia is between 32.2% and 41.23% respectively (Ardawi et al., 2005; El-Desouki and Sulimani, 2007; Sadat-Ali and AlElq, 2006) and these were consistently higher in postmenopausal women (El-Desouki, 2003). This is possibly due to the decline in estrogen levels and increase in proinflammatory and pro-osteoclastic cytokines (Ershler et al., 1997; Pfeilschifter et al., 2002). Several studies have recently emphasized the endocrine regulatory function of adipose tissue in bone metabolism via adipokines (Kochetkova et al., 2017; Uzum et al., 2014). Hence excess fat can be involved in bone health by protecting against the onset of postmenopausal osteoporosis (Albala et al., 1996).

Adipose tissue has long been established as endocrine organ involved in multiple metabolic pathways by releasing a plethora of immune and inflammatory mediators (Gomez et al., 2011). Data from *in vitro* and *in vivo* studies observed that adipokines such as

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lipocalin-2, resistin, adipsin, and leptin play a direct or indirect protective role on bone resorption by inducing osteoblast survival, differentiation, and proliferation (Gimble et al., 1996; Gordeladze et al., 2002; Lim et al., 2015). On the other hand, several other preclinical models and *in vivo* studies reported contrary results on the positive interaction between obesity, adipokines and bone biology (Cao, 2011; Ducy et al., 2000; Zhao et al., 2008). Findings of our previous study suggested the contributing role of pro-inflammatory markers towards cytokine-mediated inflammation in osteoporotic postmenopausal women (Al-Daghri et al., 2017). The present study aimed to shed a light on the associations of various circulatory adipokines with BMD in Saudi postmenopausal women.

2. Materials and methods

2.1. Subject recruitment

We recruited 200 postmenopausal women (all women had menopause for over a year) from the outpatient clinic of King Salman Hospital, King Fahad Medical City (KFMC) and from the osteoporosis clinic at KKUH, Riyadh, KSA. All participants were requested to fill a pre-structured questionnaire, including past/current medical history. Participant inclusion occurred after physical examination and undertaking a written informed consent. All the sampling methods and assessments were done according to the guidelines and regulation of the Helsinki declaration. Institutional Review Board (IRB) and the ethics committee of the College of Medicine, King Saud University in Riyadh, Saudi Arabia, has endorsed this study.

2.2. Exclusion criteria

Exclusion criteria included participants on antioxidant supplements or steroids; those with other conditions such as cancer, diabetes, malabsorption, cardiovascular diseases; metabolic disease (Paget's disease or osteomalacia), under pharmacological treatment including thyroid hormones, on diuretics as well as women undergoing hormone therapy.

In total, 175 postmenopausal women were eligible/enrolled in this study. These participants were further categorized into two groups (N = 55 Normal; N = 120 low BMD) based on their BMD T-score.

2.3. Anthropometry and bone mineral density (BMD) measurements

Anthropometrics (height, weight, waist and hip circumference (cm), systolic/diastolic blood pressure) and body mass index (kg/m^2) were recorded by trained personnel. Fasting blood samples were extracted and serum isolated for the serological assessments.

BMD (g/cm^2) was assessed for all the selected participants using Prodigy-(GE Healthcare, USA), a dual-energy X-ray absorptiometry. T-Scores were recorded in accordance with World Health Organization guidelines. Based on these criteria, women with T-Scores value higher than −1.0 were considered normal and below −1.0 were considered low BMD group.

2.4. Biochemical analysis

The set of selected adipokines (adiponectin: inter-assay <10% CV intra-assay <15% CV, Adipsin: inter-assay <10% CV intra-assay <10% CV, iipocalin-2: Inter-assay <10% CV intra-assay <15% CV, resistin: inter-assay <10% CV intra-assay <20% CV) was measured using commercially available (Catalogue# HADK1MAG-61 K, MILLIPLEX MAP Human Adipokine Magnetic Bead Panel 1) multiplex assay kit by using Luminex xMAP technology, which enables the simultaneous analysis of five biomarkers in human serum.

Serum insulin was measured using commercially available (Catalogue# HBNMAG-51 K, MILLIPLEX MAP Human Bone Magnetic Bead Panel) multiplex assay kits by using Luminex MAP Technology platform (Luminexcorp, Texas). Inter- and intra- assay variations were <15 and <10 respectively. RANKL was done by the MILLIPLEX MAP Human RANKL Magnetic Bead-Single Plex (HRNKLMAG-51 K-01). The intra- and inter-assay CVs are <10% and <15% respectively. Circulatory serum 25(OH) D levels was measured using DEQAS-accredited electrochemiluminescence (ECL) immunoassay on Roche Elecsys Cobas e411 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) at CBCD, KSU. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin (IU) × fasting glucose (mmol/L)/22.5. HOMA-β secretion (%) was calculated as 20 × fasting insulin (IU)/(fasting glucose − 3.5).

2.5. Statistical analysis

The total required sample size at 95% CI, with the power of 0.80, and the effect size of 0.044 using linear multiple regression analysis, is 142. SPSS version 24.0, IBM (USA) was used to analyze the data. Variables were expressed as mean ± standard deviation (SD) for normal variables and median (1st quartile – 3rd quartile) for non-normal variables. Kolmogorov-Smirnov test and histogram used to test data normality, whereas group differences for normal and non-normal variables were determined by ANOVA and Kruskal–Wallis H test respectively. Spearman correlation coefficient applied to determine the association among the selected variables. To identify the effect of adipokines on bone mineral density multiple linear regression was used while the stepwise method was also used to identify the most important predictors. A p-value <0.05 was considered statistically significant.

3. Results

Table 1 presents descriptive statistics according to normal and low BMD. Median adiponectin concentration was found to be lower but insignificant in controls [332.1 ug/ml (302.6–371.7)] as compared to low BMD group [346.0 ug/ml (308.6–381.5)]. Although no significance, median resistin concentration was also found to be lower in controls [713.8 ng/ml (236.0–1313.7)] than the low BMD group [969.3 ng/ml (313.6–1392.2)] after adjusting for age and BMI. No significant differences in median concentrations of lipocalin-2, adipsin, leptin, HOMA-IR, RANKL were found between controls and low BMD group. Median 25(OH)D levels were found to be significantly higher in low BMD participants as compared to their counterparts. However, it the significance was lost after adjusting for age and BMI.

Table 2 illustrates the results of linear regression of BMD with adipokines. Results showed that adiponectin was inversely associated with BMD (-0.27 ± 0.002, P < 0.01). Other adipokines including 25(OH)D showed no significant associations with BMD.

Table 3 shows the results of linear regression of femoral neck BMD with adipokines after stratification. Results revealed that only adiponectin was inversely associated with femoral neck BMD (-0.39 ± 0.16, $p < 0.01$) after controlling for other adipokines, RANKL and 25(OH)D in the low BMD group. No relationship was observed in the control group.

Fig. 1 shows the significant inverse correlation between adiponectin and BMD at the femoral neck ($r = -0.34$, $p < 0.001$) in all participants. Stratification according to normal and low BMD revealed a significant inverse association ($r = -0.33$, $p < 0.01$) only

Table 1
Participant's characteristics according to groups.

Biochemical Parameters	Control	Low BMD	P-value	P-value*
N	55 (31.4)	120 (68.6)		
Age (years)	52.4 ± 7.9	56.2 ± 8.3	<0.001	–
BMI (kg/m^2)	33.5 ± 5.7	31.8 ± 5.8	0.001	–
Age of menarche	13.0 ± 1.5	13.4 ± 1.6	0.001	0.004
Years of menopause	9.4 ± 11.7	11.7 ± 11.1	0.05	0.28
Age during first pregnancy	19.8 ± 3.9	19.3 ± 3.9	0.17	0.18
Amenorrhea (years)	6.8 ± 5.4	9.6 ± 7.0	<0.001	0.06
Waist-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.88	0.80
Systolic blood pressure (mmHg)	124.5 ± 17.1	123.2 ± 16.3	0.39	0.33
Diastolic blood pressure (mmHg)	75.7 ± 10.1	75.1 ± 9.8	0.45	0.40
BMD Spine	1.2 ± 0.1	0.9 ± 0.1	<0.001	<0.001
BMD Femoral Neck	1.02 ± 0.11	0.85 ± 0.12	<0.001	<0.001
Adiponectin (ug/ml) #	332.1 (302–372)	346.0 (308–382)	0.12	0.28
Resistin (ng/ml) #	713.8 (236–1314)	969.3 (313–1392)	0.10	0.25
Lipocalin-2 (ng/ml) #	658.4 (426–1045)	661.3 (491–976)	0.52	0.26
Adipsin (ug/ml) #	64.3 (44.5–80.2)	57.5 (42.1–78.9)	0.36	0.47
Leptin (ng/ml) #	19.0 (7.4–35.4)	22.3 (9.2–38.2)	0.31	0.21
Insulin (pg/ml)#	558.3 (339–868)	508.8 (316–733)	0.38	0.65
HOMAIR #	3.2 (2.0 – 5.9)	2.93 (1.83–4.96)	0.55	0.75
RANKL (pg/ml)#	39.0 (21.5 – 67.0)	30.9 (21.4 – 53.2)	0.34	0.21
25(OH) D (nmol/l)	50.7 (33.1 – 74.5)	69.8 (44.2 – 96.1)	<0.0011	0.33

Note: Data presented as Mean ± SD for normal variables while Median (1st Quartile – 3rd Quartile) are presented for non-normal variables; ANOVA and Kruskal-Wallis are used for normal and non-normal respectively; # indicates non-normal variables; * indicates P-value adjusted for age and BMI

Table 2
The relationship between BMD and Adipokines (regression).

Parameters	BMD Femoral Neck	
	B ± SE	P-value
Adiponectin (ug/ml) #	−0.27 ± 0.08	0.002
Resistin (ng/ml) #	−0.05 ± 0.07	0.52
Lipocalin-2 (ng/ml) #	0.17 ± 0.09	0.06
Adipsin (ug/ml) #	0.01 ± 0.05	0.86
Leptin (ng/ml) #	0.02 ± 0.02	0.45
Insulin (pg/ml) #	−0.08 ± 0.06	0.14
RankL (pg/ml) #	0.04 ± 0.08	0.61
25(OH) D (nmol/l)	0.15 ± 0.08	0.07

Note: Data presented as Beta coefficient and standard error; Multiple regression analysis with BMD as dependent and Adiponectin, Resistin, Lipocalin-2 (ng/ml) , Adipsin (ug/ml) , /Leptin (ng/ml), Insulin (pg/ml) as independent variables were used; p-value < 0.05 considered significant. All non-normal variables were log transformed; # indicates non-normal variables.

in the low BMD group (Fig. 2). No other significant associations were observed.

4. Discussion

To our best knowledge, this is the first study in Arab ethnicity particularly in Saudi postmenopausal women focusing on the association of adipokines with low BMD. The current study explored the correlation among the set of selected adipokines and BMD in the Saudi cohort of non-diabetic postmenopausal women. The main outcomes included a consistent association between adiponectin and BMD at the femoral neck and that post multiple regression, the significant association was found in resistin, which was later lost after stratifying data into normal and low-BMD groups. Adiponectin plays a potent role in diagnostics related with atherogenic protection, insulin resistance, obesity, as a marker for metabolic syndrome (Cnop et al., 2003; Sandhya et al., 2010) and biomarker for bone turnover (Agbaht et al., 2009; Rosen et al., 2009; Shinoda et al., 2006). We found a significant inverse association between adiponectin and low BMD, which confirms prior studies (Cervellati et al., 2016; Tanna et al., 2017). Some other studies reported that adiponectin has no significant correlation with BMD in non-diabetic women in general and postmenopausal non-diabetic cohort in particular (Sodi et al., 2009). Increased adiponectin levels has a direct association with osteocalcin, suggesting a significant role in osteoclastogenesis (Richards et al., 2007). Expression of adiponectin receptors in osteoclast has also been reported therefore, it can be involved in the activation of bone resorption (Kanazawa, 2012). Furthermore, Shinoda et al. (2006) reported three different adiponectin activities for osteogenesis—positive action of locally produced adiponectin via the autocrine/paracrine pathway, an adverse effect by circulating

Table 3
The relationship between Femoral Neck BMD and Adipokines (regression in low BMD).

Parameters	Control		Low BMD	
	B ± SE	P-value	B ± SE	P-value
Adiponectin (ug/ml) #	−0.03 ± 0.17	0.002	−0.39 ± 0.16	0.026
Resistin (ng/ml) #	−0.13 ± 0.11	0.52	−0.01 ± 0.11	0.91
Lipocalin-2 (ng/ml) #	0.22 ± 0.15	0.21	0.18 ± 0.11	0.12
Adipsin (ug/ml) #	−0.02 ± 0.20	0.93	0.00 ± 0.07	0.99
Leptin (ng/ml) #	−0.02 ± 0.03	0.58	0.01 ± 0.04	0.85
Insulin (pg/ml) #	0.00 ± 0.06	0.98	−0.16 ± 0.09	0.08
RankL (pg/ml) #	−0.07 ± 0.09	0.51	0.09 ± 0.13	0.50
25(OH) D (nmol/l)	−0.09 ± 0.15	0.58	0.27 ± 0.10	0.02

Note: Data presented as Beta coefficient and standard error; Multiple regression analysis with BMD as dependent and Adiponectin, Resistin, Lipocalin-2 (ng/ml), Adipsin (ug/ml), /Leptin (ng/ml), Insulin (pg/ml) as independent variables were used; p-value < 0.05 considered significant. All non-normal variables were log transformed; # indicates non-normal variables.

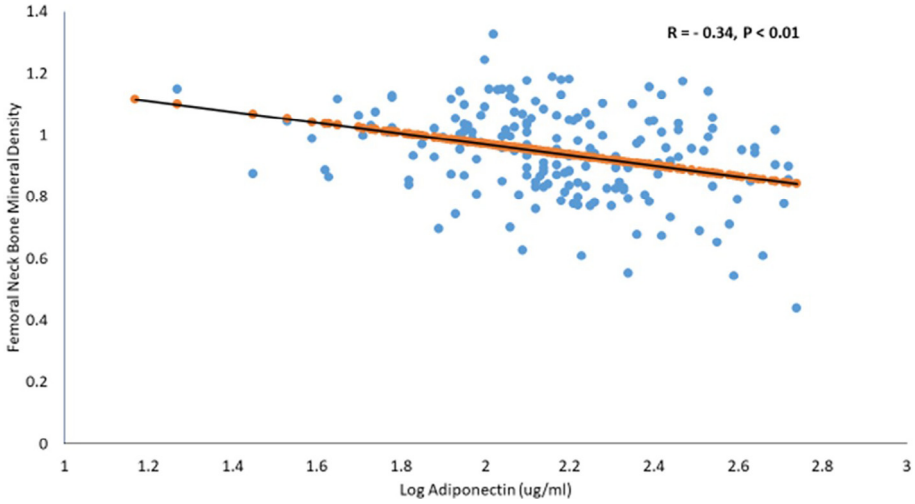

Fig. 1. Correlation between Log Adiponectin and BMD Femoral Neck in all patients.

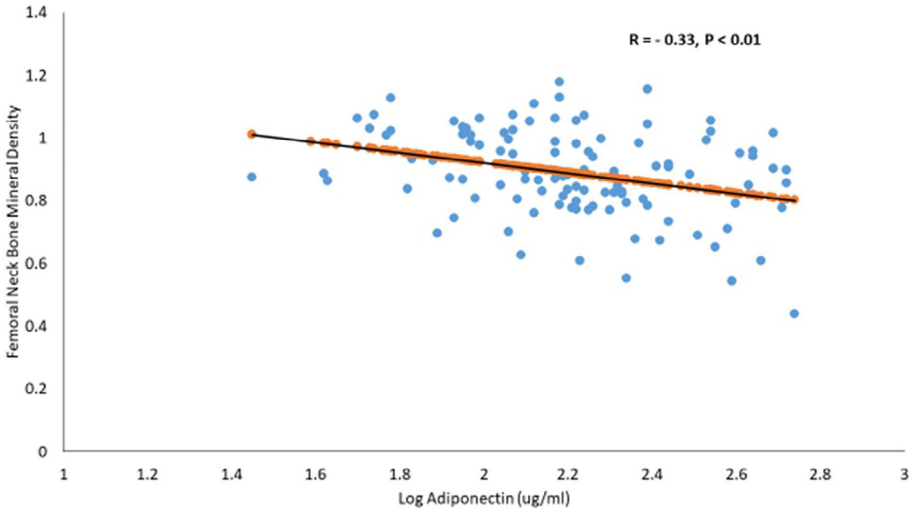

Fig. 2. Correlation between Log Adiponectin and BMD Femoral Neck in Low BMD patients.

adiponectin through the direct pathway and decisive action through the indirect pathway via enhancement of insulin signalling.

Some of the mesenchymal stem cells act as the common origin for the marrow adipocytes and osteoblasts (Wiren et al., 2011). Furthermore, data from previous studies reflect the impact of human adipose tissue on bone metabolism via adipokines and the role it played in osteoporosis pathophysiology (Cnop et al., 2003; Sandhya et al., 2010).

RANKL measured in the study showed insignificant inverse association which is in line with the findings of Nabipour et al. (Nabipour et al., 2009). Nevertheless, previous research suggested that adiponectin effects on bone metabolism maybe due to RANKL pathway promotion, which stimulates osteoblast formation introducing recombinant adiponectin into human osteoblasts (Luo et al., 2005; Richards et al., 2007). RANKL also triggers osteoclast activation, maintaining their resorption activity.

The current study also showed the lack of significant correlations between resistin, leptin, lipocalin-2 and adipsin. However, after regression analysis, resistin showed a borderline significant inverse correlation with BMD, in line with the results reported by Mohiti-Ardekani et al. (2014), whereas this significance lost post-stratification. The insignificant correlation of resistin and leptin with BMD demonstrated in the present study are consistent with a recent study on postmenopausal women (Tanna et al., 2017). Moreover, results from some other studies showed positive association at all sites with leptin and BMD (Cervellati et al., 2016; Di Carlo et al., 2007).

Lipocalin-2 acts as an independent predictor of future non-traumatic fractures (Lim et al., 2015). In addition, it also plays other roles in different cell types (Costa et al., 2013; Yan et al., 2007) under different pathological states (D'Anna et al., 2009; Makris et al., 2012; Sun et al., 2011; Wu et al., 2014). However, the insignificant correlation of lipocalin-2 with BMD in the current study are parallel to the results reported by Lim et al. (2015) and Cervelatti et al. (2016), in the large cohort of postmenopausal women.

Adipsin plays a role in regulating systemic energy balance (Choy, Rosen, & Spiegelman, 1992) with natural protection against infectious agents and red cell lysis by triggering the alternative pathway of complement. It has the similar function of human complement factor D (White et al., 1992). The non-significant correlation of adipsin with BMD is in agreement with the study of Cervelatti et al. (2016) in postmenopausal women cohort.

The authors acknowledge the limitation of small sample size which may have hidden associations with other markers that may have been significant. Further investigations using a larger

number of participants and inclusion of known T2DM genetic markers (Al-Daghri et al., 2014) with other adiposity indices linked to cardiometabolic disorders (Al-Daghri et al., 2015) in the Saudi population may provide a more clear and interesting insight on the overall cross-talk between adiposity and bone health in Arab post-menopausal women.

5. Conclusion

In conclusion, only adiponectin was inversely correlated with BMD among all adipokines measured. This association persisted even after adjusting for confounders. As adiponectin is a measure of insulin sensitivity, alterations in insulin resistance may affect BMD in Saudi postmenopausal women.

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Declaration of Competing Interest

The authors declared no potential conflicts of interest.

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