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Serum resistin levels as predictor of low bone mineral density in postmenopausal women

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ABSTRACT

Resistin, a novel adipokine may play an important role in bone metabolism. The study is designed to discover the association of bone mineral density (BMD) with serum resistin levels, anthropometric measures and to elucidate serum resistin as a predictor of BMD in postmenopausal women. Postmenopausal women ($n = 160$) were recruited and divided into two groups, non-osteoporotic ($n = 70$) and osteoporotic ($n = 90$). BMD was evaluated by DXA scan. High serum resistin levels and low weight are independent contributors to low BMD and can influence BMD at lumbar spine, right femoral neck, right hip, left femoral neck, and left hip in postmenopausal women.

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Osteoporosis is a skeletal disease characterized by low bone strength. Bone strength is regarded as the integration of bone density and quality. Osteoporosis is known to be a multifactorial disorder. The adipokines, released by the adipose tissue has a dynamic role in various metabolic processes of the body including the bone metabolism. Resistin, a novel adipokine may play an important role in bone metabolism, could be a predictor and new therapeutic target for osteoporosis, and can be used to reduce the risk of highly prevalent disease osteoporosis.

Osteoporosis is becoming a major health concern in developing countries (Gheita & Hammam, 2018). Osteoporosis, a disease causing the bones to become more porous and fragile due to decrease in density and quality of bone and make them more prone to fractures (Benzinger et al., 2016; International Osteoporosis Foundation, 2018). The worldwide prevalence of osteoporosis is over 200 million, with females affected more as compared to males (International Osteoporosis Foundation, 2018). The pathogenesis of osteoporosis is attributed to complex etiological factors. Recent data has

suggested a strong association of adipose tissue with bone tissue as they are derived from same cell lineage (Liu et al., 2013). It has been seen that high body mass index (BMI) or body weight is associated with low bone mineral density (BMD) and is protective against osteoporosis (Cervellati et al., 2016; Tariq et al., 2017). The protective effect of obesity or high weight on BMD is called the obesity paradox or reverse epidemiology, suggesting that it could be healthier to be overweight and is associated with better survival in individuals especially the elderly population (Fassio et al., 2018). The adipose tissue releases special chemical messengers, adipokines, also called adipocytokines that plays important role in different metabolic processes of the body especially bone metabolism. These adipokines are believed to regulate bone mineral density in osteoporotic subjects (He et al., 2015). Several adipokines like leptin, adiponin, lipocalin-2 might exert protective effects on the bone by enhancing osteoblastic activity (Gordeladze et al., 2002; W. H. Lim et al., 2015), while other adipokines may exert a negative effect on the bone metabolism by increasing osteoclastogenesis or osteoclastic activity (Cervellati et al., 2016). Resistin, a cysteine rich peptide hormone, also known as adipose tissue specific secretory factor (ADSF), is a relatively novel adipokine that may regulate BMD (Zhang et al., 2010). In humans, the major expression of resistin is in the monocyte and macrophages while less in the adipose tissue (Yang et al., 2003). The clinical relevance of body weight and other anthropometric measures and the adipokine, resistin remains unclear as a marker of bone health in postmenopausal osteoporotic women. Keeping all these factors in mind the present research was designed to see the association of bone mineral density with serum resistin levels and anthropometric measures like waist girth, hip girth, waist to hip ratio (W/H), weight, height and BMI, and to elucidate serum resistin as a predictor of bone mineral density in postmenopausal women.

Method

In this correlational analytical study, the participants were recruited using convenient sampling technique. First, a bone density screening camp was organized in outpatient department of Madina Teaching Hospital, Faisalabad. Postmenopausal females were invited for screening using quantitative ultrasound scan. BMD was assessed from the calcaneus for the purpose of screening. Written informed consent was obtained from all the participants in local language and they were informed about the study and given an opportunity to ask any question. Eighteen hundred postmenopausal females were screened and interviewed by the doctor. General information including age, education, marital status, number of children, menstrual history, past medical, surgical and drug history was obtained.

Postmenopausal women with at least 2 years of amenorrhea and age between 50 to 70 years were included while women with chronic renal or liver disease, malignancies, autoimmune diseases, having iatrogenic or premature menopause and having medications affecting bone mineralization were excluded from the study. General demographic information was collected from the study participants and anthropometric measures including waist girth, hip girth, waist to hip ratio, weight, height and BMI were assessed using standardized procedures. The selected normal and osteoporotic females ($n = 375$) as seen on QUS was sent for DXA analysis. BMD was evaluated at the lumbar spine (L2-L4), right femoral neck, right hip, left femoral neck and left hip by hologic-explorer (QDR-series) dual energy X-ray absorptiometry (DXA). The results of DXA were used for final analysis and presented as standard deviation units, which is T-scores. Postmenopausal non-osteoporotic women ($n = 70$) having T-score ≥ -1.0 and postmenopausal osteoporotic women ($n = 90$) with T-score ≤ -2.5 were finally included in the study for analysis.

Blood samples were obtained after overnight fasting and serum was extracted after centrifugation at 3000 revolutions per minute or 1000xg for 10 min. Serum resistin levels were quantified by human resistin enzyme-linked immunosorbent assay (ELISA) formulated by Elabscience Biotechnology Inc. with a sensitivity of 18.75 pg/mL, coefficient of variation $< 10\%$ and almost nil cross reactivity. The intra-assay and inter-assay coefficient of variation for low, middle and high levels of serum resistin was 6.79%, 5.61%, 4.6% and 6.88%, 5.61%, 3.7% respectively. The biochemical analysis was performed using microplate data collection and analysis software Gen5TM and Gen5 Secure, manufactured by BioTek® Instruments, Inc.

Institutional review board of University of Health Sciences, Lahore gave permission to conduct the study according to Helsinki declaration.

Statistical analysis

Statistical package for social sciences (SPSS) version 20 was used for data analysis. Kolmogorov–Smirnov test was applied to check the normality of the data. Mean \pm SD and Median with IQR were given for normally and non-normally distributed quantitative variables. For comparison between the groups, Mann-Whitney U test was applied. Correlations between serum resistin levels, BMD and anthropometric measures were calculated using spearman's rho correlation coefficient. Partial correlations were observed between serum resistin levels and BMD values after adjusting for age, waist girth, hip girth, waist to hip ratio, weight, height and BMI. To predict the value of BMD at various sites, stepwise multiple regression analysis was performed, keeping T-scores as dependent variable and waist girth, hip girth, waist to hip ratio, weight, height, BMI and serum resistin levels as the covariates.

Results

The general characteristics and anthropometric measures of females are given in Table 1. Serum resistin levels, BMD at lumbar spine, right femoral neck, right hip, left femoral neck and left hip were significantly different between the two groups (Table 1).

Correlation of BMD was observed with serum resistin levels and anthropometric measures (Table 2). Significant negative correlation of serum resistin levels was seen with BMD at lumbar spine ($r = -0.359$, $p < 0.001$), right femoral neck ($r = -0.400$, $p < 0.001$), right hip ($r = -0.342$, $p < 0.001$), left femoral neck ($r = -0.407$, $p < 0.001$) and left hip ($r = -0.368$, $p < 0.001$). This correlation remained significant after adjusting for age, height, weight, BMI, waist girth, hip girth and W/H ratio.

Serum Resistin levels, waist girth, hip girth, waist to hip ratio, weight, height and BMI were used in a multivariate linear stepwise regression analysis to predict T-scores at lumbar spine, right femoral neck, right hip, left femoral neck and left hip (Table 3).

Table 1. General Characteristics of the study population and comparison of bone mineral density and serum resistin levels between the groups using Mann-Whitney U test.

	Normal ($n = 70$)	Osteoporotic ($n = 90$)
Age (years)	54 (50–57)	62 (55 to 67)
Height (cm)	154.94 (152.40 to 157.48)	153.67 (149.86 to 157.48)
Weight (kg)	75.96 ± 14.94	61.44 ± 13.56
BMI (kg/m ²)	31.33 (27.21 to 34.69)	25.96 (22.78 to 29.51)
Waist girth (cm)	105.74 ± 9.67	98.87 ± 12.61
Hip girth (cm)	107.75 ± 9.70	99.83 ± 10.46
W/H ratio	0.98 ± 0.07	0.99 ± 0.07
Lumbar spine*	0.10 (–0.50 to 1.00)	–2.80 (–3.30 to –2.60)
Right femoral neck*	0.10 (–0.32 to 0.90)	–2.35 (–2.70 to –1.67)
Right hip*	0.35 (–0.30 to 1.2)	–2.10 (–2.50 to –1.30)
Left femoral neck*	0.10 (–0.60 to 0.80)	–2.20 (–2.70 to –1.50)
Left hip*	0.50 (–0.10 to 1.02)	–1.75 (–2.30 to –1.10)
Resistin (pg/mL)*	1963.37 (640.05–3937.54)	6929.76 (2697.50 to 14124.99)

* p -value <0.001, highly significant.

Values are given as Mean ± SD for normally distributed and Median (IQR) for non-normally distributed variables.

Table 2. Correlation of BMD with anthropometric measures and serum resistin levels in postmenopausal women using spearman's rho correlation coefficient.

	Lumbar spine r (p -value)	Right femoral neck r (p -value)	Right hip r (p -value)	Left femoral neck r (p -value)	Left hip r (p -value)
Resistin	–0.359 (<0.001)	–0.400 (<0.001)	–0.342 (<0.001)	–0.407 (<0.001)	–0.368 (<0.001)
Resistin*	–0.261 (0.001)	–0.261 (0.001)	–0.217 (0.007)	–0.282 (<0.001)	–0.283 (<0.001)
Height	0.115 (0.147)	0.106 (0.182)	0.111 (0.162)	0.133 (0.093)	0.142 (0.073)
Weight	0.458 (<0.001)	0.393 (<0.001)	0.417 (<0.001)	0.408 (<0.001)	0.411 (<0.001)
BMI	0.442 (<0.001)	0.372 (<0.001)	0.400 (<0.001)	0.388 (<0.001)	0.385 (<0.001)
Waist girth	0.260 (<0.001)	0.211 (<0.001)	0.238 (<0.001)	0.244 (0.002)	0.252 (0.001)
Hip girth	0.354 (<0.001)	0.306 (<0.001)	0.310 (<0.001)	0.319 (<0.001)	0.298 (<0.001)
W/H ratio	–0.071 (0.372)	–0.093 (0.241)	–0.061 (0.443)	–0.065 (0.415)	–0.020 (0.805)

*Partial correlation between BMD and serum resistin levels were seen after adjusting for age, hip girth, waist girth, waist to hip (W/H) ratio, weight, height, and BMI.

Table 3. Stepwise multiple regression analysis showing independent predictors of BMD.

Dependent variable	Models	Predictors	β coefficient	R ²	sr ²	p-value
Lumbar spine	1	Weight	0.047	0.198	0.160	<0.001
	2	Resistin	-0.000075	0.267	0.069	<0.001
Right femoral neck	1	Weight	0.034	0.150	0.116	<0.001
	2	Resistin	-0.000070	0.232	0.081	<0.001
Right hip	1	Weight	0.034	0.163	0.132	<0.001
	2	Resistin	-0.000054	0.219	0.056	<0.001
Left femoral neck	1	Weight	0.036	0.175	0.136	<0.001
	2	Resistin	-0.000069	0.261	0.085	<0.001
Left hip	1	Weight	0.035	0.174	0.137	<0.001
	2	Resistin	-0.000064	0.252	0.078	<0.001

Dependent variable is BMD at different sites.

Independent variables (predictors/covariates) used in the model were height, weight, BMI, waist girth, hip girth, W/H ratio and serum resistin levels.

p-value ≤ 0.05 is considered statistically significant.

sr² is the squared semipartial correlation.

At lumbar spine, the model accounted for approximately 20% of the variance of BMD. The independent predictors were weight and serum resistin levels that uniquely accounted for 16% and 7% of the variance of T-scores at lumbar spine as seen by the squared semipartial correlations.

At right femoral neck, the model accounted for approximately 23% of the variance of BMD. The independent predictors were weight and serum resistin levels that uniquely accounted for 11% and 8% of the variance of T-scores.

At right hip, the model accounted for approximately 22% of the variance of BMD. The independent predictors were weight and serum resistin levels that uniquely accounted for 13% and 5% of the variance of T-scores.

At left femoral neck, the model accounted for approximately 26% of the variance of BMD. The independent predictors were weight and serum resistin levels that uniquely accounted for 13% and 8% of the variance of T-scores.

At left hip, the model accounted for approximately 25% of the variance of BMD. The independent predictors were weight and serum resistin levels that uniquely accounted for 14% and 8% of the variance of T-scores.

Discussion

Adipose tissue and the adipocytokines may have role in the pathogenesis of osteoporosis by regulating the bone metabolism. Several researchers suggested a possible relationship between fat tissue and BMD (S. Lim et al., 2004; Mohiti-Ardekani et al., 2014). In this research, we investigated the association of BMD with serum resistin levels and anthropometric measures in postmenopausal females. Serum resistin and body weight were found to be most important factors that affect the BMD. Serum resistin, which is an important adipokine has negative impact on the strength of the bones while body weight has a positive impact.

Serum resistin levels were significantly more in osteoporotic as compared to non-osteoporotic postmenopausal women. A significant negative correlation of serum resistin levels with BMD at lumbar spine, right femoral neck, right hip, left femoral neck and left hip shows that higher resistin levels may be a contributing factor toward development of osteoporosis by effecting the BMD. This negative relation between serum resistin levels and BMD remained significant even after adjustment for age, height, weight, BMI, waist girth, hip girth and W/H ratio. The strength of this negative association became prominent with the regression analysis, where weight was the strongest predictor of BMD followed by serum resistin levels at lumbar spine, right femoral neck, right hip, left femoral neck and left hip. This negative correlation of serum resistin with BMD was also found at femur only in osteoporosis group but not at other sites in another research conducted on diabetic patients (Mohiti-Ardekani et al., 2014). Resistin was inversely related with bone mineral density at lumbar spine and in patients with hip and radio fractures (Oh et al., 2005; A. Fisher et al., 2011; A. Fisher et al., 2012). A negative correlation was found between serum resistin levels and BMD in both men and postmenopausal women (Zhang et al., 2010). However, some contradictory findings do exist. In postmenopausal women, resistin was associated with BMD in unadjusted model, but this association diminished after adjusting for age (Bilha et al., 2018). Previous research also showed no association of serum resistin levels with BMD (Biver et al., 2011; Peng et al., 2008).

Experiments on both murine and human preosteoblasts and preosteoclasts have shown that serum resistin may play an important role in bone metabolism and bone remodeling by weakly stimulating the proliferation and recruitment of osteoblast but strongly stimulating the osteoclastogenesis. This increase in osteoclastogenesis is mediated by the nuclear factor-kappa B (NF κ B) signaling pathway (Thommesen et al., 2006). In this way serum resistin may have a negative effect on bone mineral density thus supporting our findings.

This research delineated the role of serum resistin in bone strength, suggesting that altering the levels of this adipokine in body may be used to improve the overall density and strength of bones thus improving the quality of life and reducing the financial and social burden caused by the highly prevalent disease osteoporosis. However, randomized trials are required before any formal recommendations can be made.

In this research, weight, BMI, waist girth and hip girth were more in postmenopausal non-osteoporotic females as compared to postmenopausal osteoporotic females. Interestingly weight appeared to be the strongest independent predictor of BMD at lumbar spine, right femoral neck, right hip, left femoral neck and left hip in postmenopausal females. These findings represent a complicated relationship between obesity and BMD, the obesity paradox. The prevalence of osteopenia and osteoporosis was found

to be less in postmenopausal obese women as compared to their normal and overweight counterpart (Mazocco & Chagas, 2017). BMD at hip and lumbar spine was found to be high in obese and overweight subjects as compared to normal, irrespective of the menopausal status (Salamat et al., 2016). Chain et al. concluded in his research that fat mass and BMD are not inversely related while direct association between fat mass and bone mass was observed after adjusting for lean mass showing that slight obesity in postmenopausal women may add to bone density advantage (Chain et al., 2017). Similarly, femoral neck BMD loss was found to be less in overweight and obese women in another research (Leslie et al., 2018). In a research, waist girth, fat mass and lean mass but not body weight was found to be independent predictors of BMD in postmenopausal women.(Cherif et al., 2019). In another research, waist girth was the sole independent negative predictor of BMD, while trunk fat and lean mass were positively associated with BMD (Cherif et al., 2018).

This obesity paradox may be attributed to lack of ability of BMI to distinguish between fat mass and lean mass (Salamat et al., 2016). Higher osteoporosis in the low BMI category may be attributable to the sarcopenic obesity that is characterized by low muscle mass (Stenholm et al., 2008). The positive effects of fat on bone are said to be due to various mechanisms like the conversion of adrenal androstenedione to estrogen in adipocytes by aromatase enzyme (Strugnell et al., 2014), increase in serum leptin (Baig et al., 2015) or insulin like growth factor (Reid, 2010) due to adiposity led increase bone mass. The positive association of BMD with weight and BMI found in this research may be attributed to the positive mechanical loading effects on the bone and may not be due to the direct positive effects of fat mass on bones. Greater weight has been shown to be protective against osteoporosis but does not decrease fracture risk, as the bone density may not be high enough in obese people to resist the effect of various biomechanical stressors during fall (Fassio et al., 2018). Thus, obesity may be protective against osteoporosis due to the mechanical loading effects but it may bring with it several complications like diabetes, cardiovascular diseases that ultimately take a toll on the quality of life.

The limitations of this research included a cross sectional design and limited sample size.

Conclusion

High serum resistin levels and low weight are independent contributors to low BMD and can influence BMD at lumbar spine, right femoral neck, right hip, left femoral neck, and left hip in postmenopausal women.

Author Contribution

Sundus Tariq: Conception and design, acquisition, analysis, interpretation of data, drafted the manuscript.

Saba Tariq: Acquisition, analysis of data, carried out the literature search, helped in drafting the manuscript.

Saba Khaliq: Designed and supervised the research, analysis and interpretation of data, revised the manuscript critically for important intellectual content

Khalid Parvez Lone: Designed and supervised the research, revised the manuscript critically for important intellectual content

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