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Research Article
Association Between Visceral Adipose Tissue and Estradiol with Bone Health among Obese Women with Metabolic Syndrome

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Abstract

Background and Objective: Visceral Adipose Tissue (VAT) which is associated with a higher risk of Metabolic Syndrome (MS) shows adverse effects on bone health. Moreover, MS is associated with high concentrations of serum estradiol (E2), which is essential for bone, as it inhibits bone resorption. This study aimed to investigate the impact of visceral fat and serum E_2 levels on bone health markers (vitamin D, C-terminal peptide, Ca and BMD) in obese women with and without MS. **Materials and Methods:** This cross-sectional study was conducted on 64 obese women, with and without MS. Waist Circumference (WC) was measured in cm. Bone Mineral Density (BMD) was assessed by energy X-ray absorptiometry (DEXA), VAT was evaluated using Body Composition Analyzer "Tanita". Serum E2, C-terminal peptide and vitamin D (Vit. D) were assessed using ELISA technique. Serum calcium (Ca), triglyceride (TG), total cholesterol (Tchol), High Density Lipoproteins (HDL), Low Density Lipoproteins (LDL) and Fasting Blood Sugar (FBS) were also assessed. **Results:** In women with MS, VAT showed significant positive correlations with Body Mass Index (BMI), WC and FBS. Whereas, in women without MS, VAT showed significant positive correlations with BMI, TG, age and significant negative correlation with E2. On the other hand, in women with MS, estradiol (E2) had significant negative correlation with age and significant positive correlations with BMD, BMI, FBS and body weight. While, in obese women without MS, it had significant negative correlations with Ca, VAT, age and systolic blood pressure. **Conclusion:** In obese women with MS, increased VAT, higher BMI, older age and low E_2 levels have clinical significance and hence, they should be considered when predicting bone health risk.

Key words: Visceral adipose tissue, estradiol, bone health, obese women, metabolic syndrome

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Literatures revealed that about 50% of adults will be classified as obese by 2030[1]. Recently, factors that typically affect older adults have dramatically increased, for example, the rates of disease spreading and unfavorable environmental conditions. The last three decades have witnessed an elevated prevalence of obesity among all age groups, in addition to doubling in the number of obese older adults[2,3]. Factors which contribute to obesity epidemic include: A disturbed balance between energy intake and expenditure, age-related hormonal changes, genetic, environmental and social factors. Although, obesity has many direct consequences of on individual's health, yet it also increases the risks of numerous chronic diseases which deteriorate the quality of life and may contribute to premature death[2,3].

Metabolic Syndrome (MS) is typically defined as a cluster of at least three out of five clinical risk factors which include visceral obesity, elevated blood pressure, higher TG, lower HDL and insulin resistance "IR"[4]. MS causes major problem to health services and deteriorates health economies as well. However, visceral obesity or ectopic fat accumulation around the viscera is directly related to the development of both insulin resistance "IR"[1] and enlarged and dysfunctional adipose cells 'sick fat'[5].

Vitamin D has many important functions. It is plays a major role to skeletal tissues, as it affects bone mineralization (BMD), bone turnover rate, occurrence of fractures, osteoporosis[6]. Moreover, accumulation of vitamin D in adipose tissue is important for its subsequent release when needed as for example during winter when the fat storage decreases[7]. It also plays a key role in bone metabolism as it increases the plasma levels of both Ca and phosphorus, which are essential for bone mineralization[6]. However, it's prolonged deficiency (reduced serum Vit. D) results in bone loss, osteopenia and finally osteoporosis[8].

The mechanism explaining the direct effect of menopause on vitamin D levels remains uncertain. However, low levels of E2 could be an important factor for vitamin D metabolism in post-menopausal women. This can be attributed to the fact that, E2 not only has a critical role in both reproductive and sexual functioning, but also affects bone metabolism[9].

During the process of bone formation, type I collagen which is the main protein of bone matrix, cleaves into 2 propeptides, namely N-terminal (P1NP) and C-terminal (P1CP). Serum procollagen type I N propeptides (P1NP) is responsible for bone formation, while, serum C-terminal propeptides of type I collagen (P1CP) is responsible bone resorption[10].

So, this study aimed to investigate the impact of visceral fat and serum E_2 levels on bone health markers (vitamin D, C-terminal peptide, Ca and BMD) in obese women with and without MS.

MATERIALS AND METHODS

This cross-sectional study involved 64 Egyptian obese women with age range 25-65 years and mean age 48.85 ± 9.88 years. Their BMI was $\geq$30 kg m^{-2} and their Waist Circumference (WC) $\geq$94 cm. They were all recruited and randomly chosen from employees and workers, from all categories at the "Medical Excellence Research Center (MERC)" which is part of the "National Research Centre". This research paper was derived from a cross-sectional survey of a project funded by National Research Centre (NRC) Egypt, 2016-2019 entitled "Bone mass among Overweight and Obese Women: Mechanism and Intervention." (11th Research Plan of the NRC), with an approval obtained from Ethics Committee of NRC (Registration Number is 11010110). A written informed consent was obtained from all participants after being informed about the purpose of the study.

For each participant women, the following parameters were taken: blood pressure, anthropometric measurements, visceral fat, DEXA and laboratory investigations.

Blood pressure measurement: Blood pressure was measured using the standardized mercury sphygmomanometer with a suitable cuff size. It was measured on the right arm, while the participant was sitting relaxed for 5 min. Two readings were obtained and the average was recorded. Systolic Blood Pressure (SBP) was determined by the onset of the "tapping" korotkoff sounds (K1), while the fifth korotkoff sound (K5) or the disappearance of korotkoff sounds as the definition of Diastolic Blood Pressure (DBP).

Anthropometric measurements: Anthropometric assessments included body weight, height and WC following the recommendations of the International Biological Program[11]. Body Weight (Wt) was determined to the nearest 0.01 kg by using a Seca Scale Balance, with the woman wearing minimal clothing and with no shoes. Body Height (Ht) was measured to the nearest 0.1 cm using a Holtain portable anthropometer. The WC was measured using non-stretchable tape and approximated to the nearest 0.1 cm. It was measured, at the umbilicus level with the participant in an upright standing position, relaxed shoulders, face directed forward and breathing normally. The BMI was calculated using this Eq:

$$BMI = \frac{Wt\ (kg)}{Ht^2\ (m)}$$

Visceral fat: Visceral fat (ratio) was assessed by using Tanita Body Composition Analyzer [bioelectrical impedance apparatus (BIA)]. Visceral fat was measured based on the woman's age, body weight and height approximated to the nearest units. Women with visceral fat values $\geq$13 are regarded as having visceral obesity, according to the machine instructions manual (Tanita Body Composition Analyzer-MC-780 MA III).

DEXA measurements: Both Bone Mineral Density (BMD) (g cm^{-2}) and BMD t-score at both the femoral neck and lumbar spines sites were measured using dual-energy DEXA (DEXA Norland XR-46 version 3.9.6/2.3.1, USA). Full body DEXA scan based on the subject's age, weight and height was performed with the participant keeping the precise distance between her arms and legs according to the machine instructions manual. A well-qualified operator executed and evaluated all analyses using the same protocol for all assessments.

Laboratory investigations: After overnight 8 h fasting, participant's venous blood samples were obtained by venipuncture in the morning to assessthe following parameters: Fasting Blood Sugar (FBS), serum calcium (Ca), serum Vit D, C-terminal peptide and E2. Another venous blood samples were obtained after 12-4 h fasting to measure lipid profile (TG, Tchol and HDL). The blood samples were left to clot were then centrifuged at 5000 rpm for 10 min to separate sera and were then stored at -80°C to be assayed later on.

Fasting Blood Sugar (FBS), serum Ca, Tchol, HDL-C and TG levels were measured by using the automated clinical chemistry analyzer Olympus AU 400 analyzer. LDL-C was calculated by using the formula developed by Friedewald *et al.*[12] as follows:

$$LDL\text{-}C = \frac{T\ chol\text{-}TG}{5+HDL\text{-}C}$$

Serum Vit D and C-terminal peptide were measured using ELISA kit, Cataloge number SL1831 HU., SL2109 HU., Sun long Biotech. Co. LTD and E2 Cataloge number ES180S. Dal Biotech, respectively. The assessment of these parameters were done in the laboratory of "Medical Excellence Research Center (MERC), which is part of "National Research Centre (NRC), Egypt.

Statistical analyses: Data were analyzed using the Statistical Package for Social Sciences (SPSS/Windows Version 16, SPSS Inc., Chicago, IL, USA). Normality of data were tested using the Kolmogorov-Smirnov test. The $p<0.05$ was regarded as statistically significant for all tests. Blood pressure, FBS, Vit.D, C-terminal peptides and E2 were normally distributed, on the contrary most of the variables such as; the data of DEXA, weight, BMI, VAT, lipid profile and Ca were not normally distributed.

Criteria for MS were defined according to the International Diabetes Federation[13] for example, central obesity (WC $\geq$94 cm and/or BMI $\geq$30 kg m^{-2}) plus any two of the following: Elevated TG ($\geq$1.7 mmol L^{-1}), reduced HDL ($\leq$1.03 mmol L^{-1}), elevated blood pressure (systolic $\geq$130 mm Hg^{-1} or diastolic $\geq$85 mm Hg^{-1}), elevated FBS ($\geq$5.6 mmol L^{-1}) or drug treatment for the individual features.

The study sample was classified into 2 groups as follows: A group with MS (n = 25) and another without MS (n = 39). The parametric data were expressed as mean$\pm$SD, whereas, the qualitative ones (frequency distribution) were expressed as number and percentage (%). Various variables of the 2 groups were analyzed and compared using Mann-Whitney test for independent groups.

Spearmen's correlation coefficients, associations between anthropometric parameters, body composition and bone data, were all used to examine the correlation between both VAT and E2 and between the other variables in the present study.

RESULTS

Characteristics of the current sample: Elevated level visceral fat ($\geq$13) among both women without MS (38.5%) and women with MS (40%) has revealed insignificant differences. All participant women in the current study were suffering from central obesity (WC $\geq$94 cm and/or BMI $\geq$30 kg m^{-2}). The other criteria for MS have shown highly significant differences between the two groups. Among women without MS, 51.3% had no criteria and 48.7% had only one criterion in addition to central obesity. Among women with MS in addition to central obesity, 68% had 2 criteria, 24% had 3 criteria and 8% had 4 criteria (Table 1). The most common criteria for MS among women of current study were decreased HDL (39.1%), increased SBP (34.4%), increased fasting blood glucose (26.6%), increased DBP (21.9%) and increased triglycerides (17.2%), respectively.

Table 1: Characteristics of the current sample

Variables		Without MS (N = 39)		With MS (N = 25)		
		Number	Percentage	Number	Percentage	P (Chi-square)
Increased visceral fat ratio	Yes	15	38.5	10	40	0.902
	No	24	61.5	15	60	
MS criteria (in addition to central obesity	No	20	51.3	0	0	0.000
(WC $\geq$94 cm and/or BMI >30 kg m^{-2})	1 criterion	19	48.7	0	0	
	2 criteria	0	0.0	17	68	
	3 criteria	0	0.0	6	24	
	4 criteria	0	0.0	2	8	

**p-value<0.01: Highly significant differences

Table 2: Comparison between the different criteria for women with and without Ms (Mann-Whitney test)

Variables	Without MS (N = 39)		With MS (N = 25)			
	Mean	±SD	Mean	±SD	Z	p
Age (years)	48.33	10.93	49.65	8.12	-0.213	0.831
Blood pressure (mm Hg)						
Systolic	114.85	10.62	133.40	19.93	-4.057	0.000**
Diastolic	72.35	6.99	83.60	11.86	-3.826	0.000**
Anthropometry						
Weight (kg)	91.01	18.49	89.07	12.53	-0.317	0.752
Height (cm)	156.67	6.31	154.92	8.32	-0.145	0.885
BMI (kg m^{-2})	37.08	6.86	37.30	6.56	-0.241	0.810
W C (cm)	103.63	16.37	106.64	12.28	-0.833	0.405
Visceral fat ratio	11.44	3.41	11.56	3.11	-0.235	0.814
DEXA						
Lumbar spines						
BMD	0.94	0.25	0.97	0.15	-0.626	0.531
T-score	-0.74949	1.05	-2.32760	8.16	-1.115	0.265
Femur neck						
BMD	0.86	0.15	0.81	0.12	-0.977	0.329
T-score	-1.1650	1.32	-1.5784	1.07	-0.850	0.395
Laboratory						
Fasting blood glucose (mg dL^{-1})	101.68	50.07	118.36	48.91	-1.103	0.270
Triglycerides (mg dL^{-1})	95.55	31.74	146.00	68.99	-2.951	0.003**
Cholesterol (mg dL^{-1})	201.08	38.67	209.56	37.23	-0.724	0.469
HDL (mg dL^{-1})	47.41	11.31	40.96	9.25	-2.442	0.015*
LDL (mg dL^{-1})	133.42	38.27	137.40	37.03	-0.239	0.811
Calcium	9.12	0.83	9.30	0.58	-0.842	0.400
Vitamin D	23.95	11.36	21.83	3.24	-0.367	0.713
C-terminal peptide	1612.43	1599.77	1703.84	1287.65	-0.014	0.989
Estradiol	52.39	42.15	66.95	90.46	-0.310	0.756

*p-value<0.05: Significant differences, Z: Difference between groups, **p-value<0.01: Highly significant differences, P: Significance (2-tailed)

Comparative results: Comparing women with and without MS (Table 2) revealed highly significant differences in blood pressure (both systolic and diastolic) and TG, where women with MS had the higher values. Women with MS had significantly lower value of HDL than those without MS. In contrast, insignificant differences were shown in age, anthropometric measurements (weight, height, BMI and WC), visceral fat, BMD and its T-score at lumbar spines and femoral neck and the other laboratory findings including FSB, Tchol, LDL, Ca, Vit. D, C-terminal peptide and E2.

Correlation results: Spearman's correlations revealed insignificant association between visceral fat and BMD and its T-score at lumbar spines and femoral neck and the related laboratory findings as Ca, Vit. D and C-terminal peptide, in both the total sample and the 2 groups.

Visceral fat showed significant positive correlations with: (a) Body weight and BMI (in the total sample and in the 2 groups), (b) WC (in the total sample and in the group with MS group only) and (c) Age and TG (in the total sample and for the group without MS group). On the contrary, visceral fat showed significant negative correlations with body height and E2 in the group without MS (Table 3).

Spearman's correlation between E2 and DEXA findings revealed highly significant positive correlations between E2 and BMD and its T-score at lumbar spines and femoral neck,

Table 3: Spearman's correlation between visceral fat ratio and the other variables

	Visceral fat ratio					
	Without MS (N = 39)		With MS (N = 25)		Total (N = 64)	
Variables	r	p	r	p	r	p
Age (years)	0.370*	0.021	0.168	0.421	0.327**	0.008
Blood pressure (mm Hg)						
Systolic	-0.033-	0.852	0.133	0.527	0.129	0.330
Diastolic	-0.091-	0.611	0.125	0.551	0.114	0.391
Anthropometry						
Weight (kg)	0.419**	0.008	0.493*	0.012	0.437**	0.000
Height (cm)	-0.413**	0.009	0.102	0.627	-0.225	0.074
BMI (kg m^{-2})	0.563**	0.000	0.622**	0.001	0.585**	0.000
Waist circ. (cm)	0.288	0.076	0.622**	0.001	0.408**	0.001
Visceral fat ratio						
DEXA						
Lumbar spines						
BMD	0.029	0.859	0.325	0.113	0.112	0.380
T-score	0.064	0.700	0.315	0.124	0.138	0.276
Femur neck						
BMD	-0.131	0.425	0.272	0.189	-0.011	0.929
T-score	-0.084	0.617	0.252	0.225	0.021	0.868
Laboratory						
Fasting blood glucose (mg dL^{-1})	-0.008	0.960	0.410*	0.042	0.161	0.208
Triglycerides (mg dL^{-1})	0.393*	0.015	0.144	0.493	0.324**	0.010
Cholesterol (mg dL^{-1})	-0.054	0.749	0.111	0.599	0.020	0.877
HDL (mg dL^{-1})	0.007	0.966	0.266	0.198	0.061	0.638
LDL (mg dL^{-1})	-0.047	0.777	0.054	0.796	-0.011	0.932
Calcium	0.098	0.564	0.193	0.356	0.158	0.219
Vitamin D	0.131	0.440	-0.121	0.583	0.060	0.646
C-terminal peptide	0.028	0.868	0.279	0.177	0.128	0.323
Estradiol (pg mL^{-1})	-0.388*	0.018	0.205	0.336	-0.134	0.302

*p-value<0.05: Significant differences, **p-value<0.01: Highly significant differences

for the total sample and for women with MS. In addition, there were significant positive correlations between E2 and body weight, BMI and FBS for women with MS. Among women without MS, significant negative correlations were found between E2 and systolic blood pressure, visceral fat and Ca. Among total sample, E2 had significant positive correlations with body weight and height, while it had significant negative correlation with HDL (Table 4).

DISCUSSION

The last decades witnessed a rapid increase in the prevalence of both obesity and osteoporosis[14]. The relation between bone and fat, commonly known as bone-fat relationship is a complex one, since the published findings are still unclear. The prevalence Metabolic Syndrome (MS), one of the major public health problems has increased dramatically during the recent decades. Moreover, obesity and MS are associated with low-grade inflammation[15]. Many researches has focused on the role of VAT on bone, since Visceral Adipose Tissue (VAT) produces inflammatory cytokines that are harmful to bone[16].

The current study aimed to investigate the association between visceral fat levels, E2 and MS, as well as its components, in obese women with and without MS. The study also aimed to investigate the impact of visceral fat and serum levels of E2 on bone markers (Vit. D, C-terminal peptide, Ca and BMD) in obese women with and without MS.

In the present study, the prevalence (percentage) of MS was 39.1% in obese subjects and 60.9% in the non-MS ones. Visceral fat, which is recently recognized as a common health problem is found to be related to several chronic diseases including osteoporosis, diabetes and CVD[1] and it is to be a cause for increasing the risk of vitamin D insufficiency and deficiency in Chinese adults[17].

The current results revealed that MS has no effect on the bone health and the other related laboratory investigations (Ca, Vit. D, C-terminal peptide and estradiol). However, visceral

Table 4: Spearman's correlation between estradiol and the other variables

	Estradiol					
	Without MS (N = 39)		With MS (N = 25)		Total (N = 64)	
Variables	r	p	r	p	r	p
Age (years)	-0.572**	0.000	-0.487*	0.016	-0.535**	0.000
Blood pressure (mm Hg)						
Systolic	-0.435*	0.013	-0.121	0.572	-0.290*	0.030
Diastolic	-0.140	0.445	-0.084	0.698	-0.145	0.285
Anthropometry						
Weight (kg)	0.030	0.860	0.527**	0.008	0.296*	0.021
Height (cm)	0.414*	0.011	0.188	0.379	0.342**	0.007
BMI (kg m^{-2})	-0.160	0.343	0.440*	0.031	0.095	0.468
Waist circ. (cm)	0.085	0.616	0.119	0.579	0.117	0.369
Visceral fat ratio	-0.388*	0.018	0.205	0.336		
DEXA						
Lumbar spines						
BMD	0.165	0.330	0.662**	0.000	0.349**	0.006
T-score	0.142	0.403	0.604**	0.002	0.357**	0.005
Femur neck						
BMD	0.312	0.060	0.698**	0.000	0.465**	0.000
T-score	0.287	0.089	0.704**	0.000	0.455**	0.000
Laboratory						
Fasting blood glucose (mg dL^{-1})	-0.195	0.247	0.505*	0.012	0.117	0.369
Triglycerides (mg dL^{-1})	-0.197	0.242	0.164	0.443	-0.058	0.655
Cholesterol (mg dL^{-1})	-0.183	0.278	-0.224	0.294	-0.223	0.084
HDL (mg dL^{-1})	-0.325	0.053	-0.276	0.192	-0.260*	0.045
LDL (mg dL^{-1})	-0.169	0.318	-0.315	0.134	-0.230	0.075
Calcium	-0.325*	0.049	-0.139	0.518	-0.247	0.055
Vitamin D (mg mL^{-1})	-0.018	0.918	-0.047	0.836	-0.035	0.793
C-terminal peptide (pg mL^{-1})	-0.024	0.889	-0.061	0.777	-0.056	0.668

*p-value<0.05: Significant differences, **p-value<0.01: Highly significant differences

fat showed insignificant correlations with BMD and its T-score at lumbar spines and femoral neck sites, as well as with the related laboratory investigations (Ca, Vit. D and C-terminal peptide). On the contrary, visceral fat showed significant positive correlations with BMI and WC among the total sample and women with MS group, while, it had weak significant negative correlations with estradiol among the women without MS.

Among women with MS, estradiol showed significant positive correlations with both bone health and BMI, while it has insignificant correlations with visceral fat. Moreover, estradiol showed significant negative correlations calcium, among women without MS.

Cohen[18] stated that large VAT depot is associated with the elevated levels of E2, which acts as a bone protective substance. In contrast, our results revealed that E2 level had significant negative correlation with visceral fat, while it showed significant positive correlation with BMD. Khosla *et al.*[19] in Rochester found no association between bone density and sex steroid levels. Choi *et al.*[20] in Korea, also found that VAT was negatively correlated with BMD.

In concordance with the present study, Maggio *et al.*[21] investigated adults with and without MS and found higher E2 levels in subjects with MS. Pedersen *et al.*[22] demonstrated that E2, only through the estrogen receptor α, inhibits adrenaline-stimulated lipolysis in human subcutaneous fat cells by increasing the amount of α2-adrenergic antilipolytic receptors. This may explain how E2 is related to typical female subcutaneous adipose tissue distribution, since this inhibition is not observed in visceral fat depots. In women, E2 may shift accumulation of fat from visceral into subcutaneous depots[4].

As, it was concluded that fat distribution is affected by E2 level, it was expected to find a positive association between E2 levels and fat volume, due to increased aromatase activity[18]. The study showed significant correlation between E2 and VAT in women without MS.

Current analysis revealed that VAT was insignificantly associated with BMD, although, it was associated with E2 level. In Denmark, it is concluded that[23,24] when including metabolic markers in an analysis, E2 is still the only marker to be significantly associated with BMD.

The findings indicated that visceral fat is significantly associated with BMI, WC and FBS, which represented the principal causative factors of the development of MS. Thus, the findings are in agreement with those of Damiri *et al*.[25] in Palestine. Park *et al*.[26] have concluded that, higher BMI is associated with lower levels of serum 25(OH)D. However, some studies could not reveal the association between Vit. D deficiency the occurrence of MS[27]. These are in agreement with observations of the current research, where insignificant negative correlations were found between Vit. D and both E2 and VAT.

The findings of the present research showed that the level of C-terminal peptide was insignificantly higher in obese women with MS than in those without MS. Several studies suggested that C-terminal peptide is a reliable factor for early declines in BMD and can be regarded as a risk factor for rapid bone loss in Iraq[28] and in China[29]. In spite of the insignificant low level of Vit. D in women with MS, observed in this research as well as in other studies, we recommend further investigations to confirm the effect of using Vit. D, as prophylaxis for improving bone health and to preventing occurrence of osteoporosis.

CONCLUSION

The prevalence of MS increases significantly with increased obesity and older age. More attention, through health care providers should be given to adult population who are at risk. The high VAT, BMI, age and low E_2 level have a magnitude implying clinical importance for predicting future fracture risk in obese women suffering from MS.

SIGNIFICANCE STATEMENT

This study discover the clinical significance of the interaction between old age, increased visceral adiposity and BMI and low estradiol level that can be beneficial for prediction of bone health risk among obese women suffering from MS. This study will help the researcher to uncover the critical areas of bone health among obese women that many researchers were not able to explore, for early protection from osteoporosis. Thus, a new theory on these interactions may be arrived at.

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