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EFFECTS OF ADIPONECTIN ON CARDIOVASCULAR RISK MARKERS & BONE METABOLISM IN OBESE POSTMENOPAUSAL WOMEN

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ABSTRACT
In this study 71 apparently healthy postmenopausal women (PMW) were enrolled into 2 groups : Group -1 included thirty-five PMW with age (mean ±SEM) of (55.76±7.34 years), BMI (24.30±2.56), and Group -2 included thirty-six obese (BMI >30) PMW, with mean age of 52.35±9.87 years and BMI of 34.58±3.00. Fasting venous blood specimens were obtained to determine: Hb_{A1C}, serum glucose, serum total alkaline phosphatase (ALP), serum calcium (Ca) and serum phosphates (P). Besides ELISA measurement of serum insulin, total adiponectin, highly sensitive C - reactive protein (hs-CRP) and interleukin-8. Data analysis indicate a significant decrease in serum adiponectin levels in group 2 (obese PMW) compared to group 1 (4.71 ±0.11 and 8.89±0.52 µg/ml, respectively). Furthermore, serum levels of hs-CRP and IL-8 were higher in obese PMW (group 2) 31.45±1.02ug/ml p<0.0001and 110.53±2.58 ng/ml p<0.0001, respectively, compared to non-obese PMW (group 1) 3.90±0.11ug/ml and 65.61±1.70ng/ml, respectively. While, serum ALP activity and serum P levels were elevated in obese PMW (by >6% for ALP, 30 % for P) compared to non-obese PMW .Whilst, serum Ca levels were not altered by variation in BMI of the two groups. Significant correlations in group 1 included: a negative correlation of adiponectin with Hb_{A1C} (r=-0.361,p=0.03) .While serum ALP activity shows a positive correlation with fasting serum insulin (r=+0.381, p=0.022) and serum IL8 was positively correlated with serum P (r= +0.506 ,p=0.002) . In group 2 (obese PMW) serum adiponectin levels were negatively correlated with fasting serum insulin (r=-0.328, p=0.044), as well as with hs-CRP (r= -0.322, p=0.049) .Whereas, serum P levels were positively correlated with BMI (r=+ 0.338,p=0.047). Data analysis indicated that total adiponectin levels are significantly lowered in obese compared to non-obese PMW at the same stage of postmenopause, because of weight gain and obesity. Centrally located fat was the main determinant of variability in adiponectin concentration in healthy postmenopausal women, as indicated by variation in waist to hip ratio between the two studied groups.

KEYWORDS: Postmenopausal Women, Obesity, Osteoporosis, Adiponectin, hs-CRP, IL-8.

INTRODUCTION

At menopause the loss of ovarian function is associated with an increased risk for cardiovascular disease (CVD) that may be related to a decrease in glucose tolerance and insulin sensitivity and increased plasma insulin levels, as a result of increased total body and abdominal adiposity that begins to occur at menopause [1,2] . Part of the increased rate of CVD for a postmenopausal woman seems to be due to the loss of the protection offered by endogenous estrogen. This point is supported by the dramatic increase in cardiovascular (CV) events seen in women who have undergone surgically induced menopause[3].Which could be due to the fact that postmenopausal women are more insulin-resistant with women of comparable total and abdominal adiposity[4].Meanwhile, the prevalence of obesity has raised dramatically in recent years .Increased adiposity, particularly, visceral fat accumulation, is closely associated with premature atherosclerosis and many metabolic alterations including insulin resistance, dyslipidemia and hypertension[5,6]. However, obesity is one of the most common disorders in climacteric women and occurs in approximately 65% of them [7]. Recent data suggested that menopause status is associated with differences in adipose tissue metabolism in both, the abdominal and gluteal region [8]. In obese women higher morbidity and mortality from cardiovascular disease was observed with the progress of climacterium, with a primary cause for this situation seems to be a menopausal metabolic syndrome observed in 40% of climacteric women [9].The more atherogenic lipid profile and increased level of the prothrombotic plasminogen activator inhibitor-1 is observed in women after menopause [10].

Adipose tissues, especially the visceral adipose tissues have been widely recognized as endocrine and paracrine organs that secrete many bioactive molecules (adipokines)which influence metabolic processes such as insulin resistance. Most of adipokines are overproduced during obesity including: leptin, TNF-α, IL6 and resistin , whereas expression and plasma levels of adiponectin are down regulated during obesity. IL6 production by human adipose tissues increases during obesity. It may induce hepatic CRP synthesis and promote the onset of CV complications [11].Interestingly; weight loss is associated with an improvement in the inflammatory profile of gene expression [12]. Hence, obesity corresponds to a sub-clinical inflammatory condition that promotes the production of pro-inflammatory factors that are associated with premature atherosclerosis [13], that is closely associated with the menopause transition, as well as with the early postmenopausal period[14]. Among the different possible mechanisms, some had suggested a link between sex hormones and adiponectin metabolism[15] . Decreased

expression and plasma levels of adiponectin may serve as a marker of increased metabolic and inflammatory risk[16].Adiponectin is in contrast to other adipokines , have anti-inflammatory anti-thrombic and anti-atherogenic properties .It is abundant in plasma of normal subjects , but decreased in obesity and type 2 DM. In healthy subjects lowered plasma adiponectin levels have been associated with increased risk of CV events [17].Low adiponectin level most likely mediates the effect of obesity on insulin resistance in liver and muscles. Most probably, the adipose tissue-specific insulin sensitivity rather than general adiposity itself determines the adiponectin expression in the adipose tissues [18]. Besides that hypoadiponectinemia was shown to be associated with coronary artery disease. Several authors point out that high level of circulating adiponectin reduce risk of coronary heart disease among type 2 diabetes patients and is associated with reduced risk of myocardial infarction in apparently healthy men . In the last several years, this adipokine has attracted much attention because of its multiple beneficial effects on a cluster of obesity-related metabolic and cardiovascular dysfunctions [19] .In addition, adiponectin counteracts the pro-inflammatory effects of TNF-α on the arterial wall and probably protects against the development of arteriosclerosis [12]. Furthermore, adiponectin accumulates in injured vascular walls, bound to collagens I, III and V present in the sub -endothelial intima, indicating that it may be involved in the repair process of damaged vasculature[20].Insulin resistance is also often associated with a hypercoagulable state (impaired fibrinolysis) and increased inflammatory cytokine levels [21] . In a cohort of male patients (325) undergoing coronary angiography a single baseline determination of plasma adiponectin is independently predictive of the subsequent risk of death or MI [17]. Thus in addition to its role as an insulin sensitizer, adiponectin can protectagainst almost all of the major obesity-related pathologies, including hypertension ,atherosclerosis , heart failure, airway inflammation and several types of cancer[22,23].

Since 1990 evidence accumulated to establish that inflammatory processes are important contributors to atherogenesis and most extensively studied marker in CVDs is CRP. Hence CRP is considered as a predictive marker for development of CVD [24]. Jung –Min *et al*., 2005 had suggested that subclinical systemic inflammation may be associated with bone turnover rate and bone mass in postmenopausal women [25]. In this study we try to understand the mechanisms by which total and regional body fat distribution (serum total adiponectin) would widen our knowledge about path physiology of obesity by its impact on CVD risk markers (hs-CRP & IL-8) ,as well as, on bone metabolic state(serum ALP, Ca & P),that might provide important therapeutic and preventive implications for women at menopause.

SUBJECTS & METHODS

In this study 71 apparently healthy postmenopausal women (PMW) were selected from the staff of the specialized center for Endocrinology & Diabetes at Al-Kindy Teaching Hospital/ Baghdad and from the staff of the College of Pharmacy –Baghdad University , for the period from October 2010 to April 2011.Subjects were enrolled into two groups : Group -1 included thirty-five PMW with age (mean ±SEM) of (55.76±7.34 years),BMI (24.30±2.56) ,and Group -2 included thirty-six obese (BMI >30) [26]PMW , their age 52.35±9.87 years and BMI of 34.58±3.00.These women were selected not to have : diabetes mellitus ,CVD ,hypertension ,liver disorders ,renal diseases , nor rheumatoid arthritis.(Table -1 summarizes subjects characteristics). The study was approved by The Local Research Ethics Committee and all subjects were provided with awritten informed consent to participate in this study.

After an overnight fasting venous blood specimens were obtained to measure : $Hb_{A1C}$was estimated by the variant®(Bio-Rad USA[27], fasting serum glucose (FSG)[28],serum total alkaline phosphatase (ALP)[29] serum calcium (Ca)[30] and serum phosphates (P)[31] . In addition to determination of serum insulin[32] ,serum total adiponectin[33], serum hs-CRP[34] and serum interleukin-8 [35] by specific ELISA kits . Statistical analysis was performed using SPSS version 17 to express data as mean± SEM, and applying paired t-test with a degree of significance at $P \leq 0.05$ and Pearson's correlation for each of the studied parameters within each of the studied groups.

RESULTS

As presented in table-2, serum total alkaline phosphatase (ALP) activity of the obese –PMW, were significantly elevated compared to non-obese PMW (146.66±2.31 Vs 137.26±1.89 U/L, respectively).Whereas, serum Calcium (Ca) levels were not altered by variation in BMI of the two groups. But serum Phosphate (P) levels were elevated in obese PMW (by about 30 %).Figure-1, shows significant decrease in serum adiponectin levels in group 2 (obese PMW) compared to group 1 (4.71 ±0.11 Vs. 8.89±0.52ug /ml, respectively). Furthermore ,serum highly-sensitive C-Reactive protein (hs-CRP)and interleukin -8 (IL-8) were higher in obese PMW (group 2)31.45±1.02ug/ml $p<0.0001$ and 110.53±2.58 ng/ml $p<0.0001$, respectively, compared to values of non-obese PMW(group 1) 3.90±0.11ug/ml and 65.61±1.70ng/ mlp<0.0001, respectively . Considering correlation studies , significant correlations in group 1 included: serum total adiponectin values exerts a negative correlation with Hb_{A1C} (r=-0.361,p=0.03) .While , ALP shows a positive correlation with fasting serum insulin (r=+0.381,p=0.022) and serum IL -8 was positively correlated with serum P (r= +0.506 ,p=0.002) . In group 2 (obese PMW) serum total adiponectin levels were negatively correlated with fasting serum insulin (r=-0.328, p=0.044) and it also negatively correlated with hs-CRP (r= -0.322, p=0.049) and serum P levels were positively correlated with BMI (r=+ 0.338,p=0.047).

TABLE -1 Characteristics of Subjects Involved in the Study.

Parameter	Group 1	Group 2	P-value
Number	35	36	>0.05
Age (years)	55.76±7.34	52.35±9.87	>0.05
BMI (Kg/m^2)	24.30±0.46	34.58±0.50	<0.001
WHR	0.84±0.007	0.92±0.008	<0.001
Duration of menopause (years)	2.37±0.06	2.11±0.03	>0.05
Insulin (µIU/ ml)	14.3±0.07	19.4±0.07	<0.001
FSG (mg/dl)	92.97±1.86	109.25±1.78	<0.001
HbA1C (%Hb)	6.12±0.15	7.56±0.10	<0.001

Group 1=Non-Obese Postmenopausal Women, Group 2= Obese Postmenopausal Women, BMI=Body Mass Index, WHR=Waist/Hip Ratio, µIU=Micro International Unite, Values are presented as Mean ±SEM, P—values ≤ 0.05 are significantly different.

TABLE -2 Serum Levels of Total Alkaline Phosphatase , Total Calcium and Inorganic Phosphates.

Parameters	Group 1	Group 2	P-value
ALP(U/L)	137.26±1.89	146.66±2.31	<0.01
Ca (mg/dl)	10.55±0.16	10.76±0.40	>0.05
P (mg/dl)	1.60±0.07	2.07±0.08	<0.0001

Group 1=Non-Obese Postmenopausal Women, Group 2= Obese Postmenopausal Women, U=Micro International Unite , Values are presented as Mean ±SEM , P—values ≤ 0.05 are significantly different .

TABLE -3 Significant Pearson's Correlations Among the non –Obese Postmenopausal Women(Group1)

Parameter 1	Parameter 2	r-value	p-value
Adiponectin	Hb_{A1C}	-0.361	0.030
ALP	Insulin	+0.381	0.022
Ca	p	-0.335	0.046
IL8	P	+0.506	0.002

Correlation is significant at the 0.05 level (2-tailed)

TABLE 4. Significant Pearson's Correlations Among the Obese Postmenopausal Women(Group2)

Parameter 1	Parameter 2	r-value	P-value
Adiponectin	Insulin	-0.328	0.044
Adiponectin	hs-CRP	0.322-	0.049
P	BMI	+0.338	0.047

Correlation is significant at the 0.05 level (2-tailed)

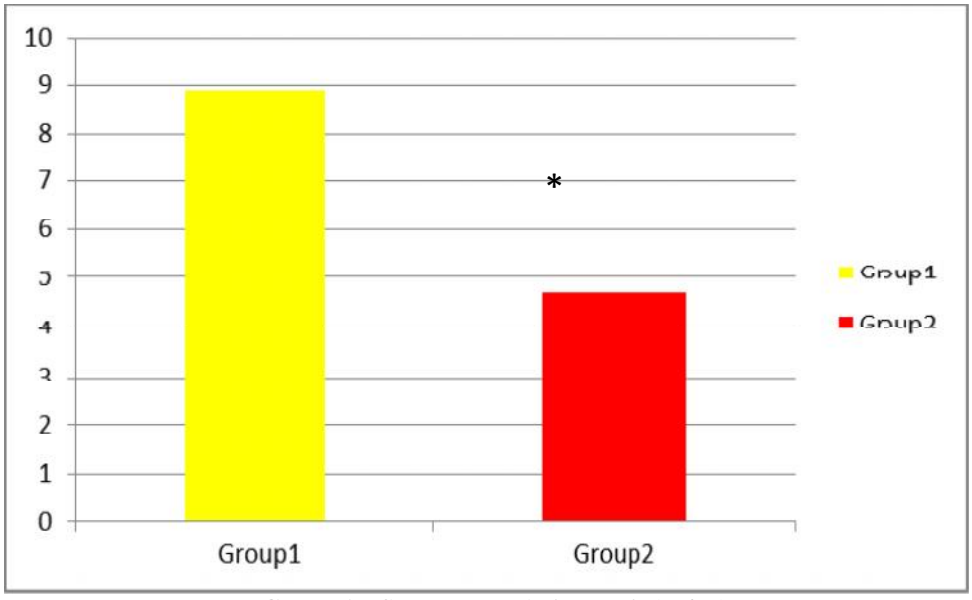

FIGURE-1 Serum Total Adiponectin(µg/ml)
*=significant difference p<0.05

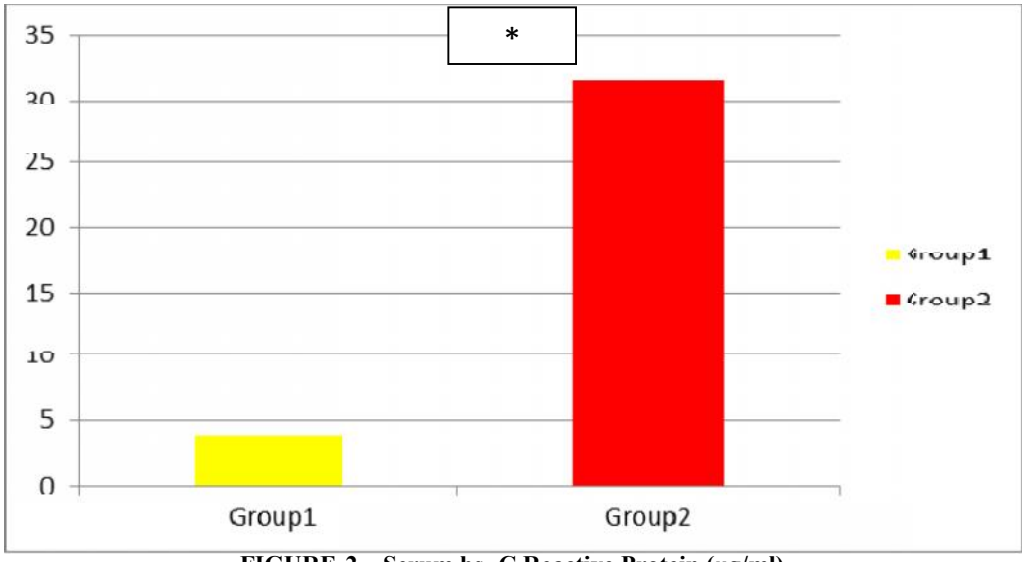

FIGURE-2 Serum hs- C Reactive Protein (µg/ml)
*=significant difference p<0.05

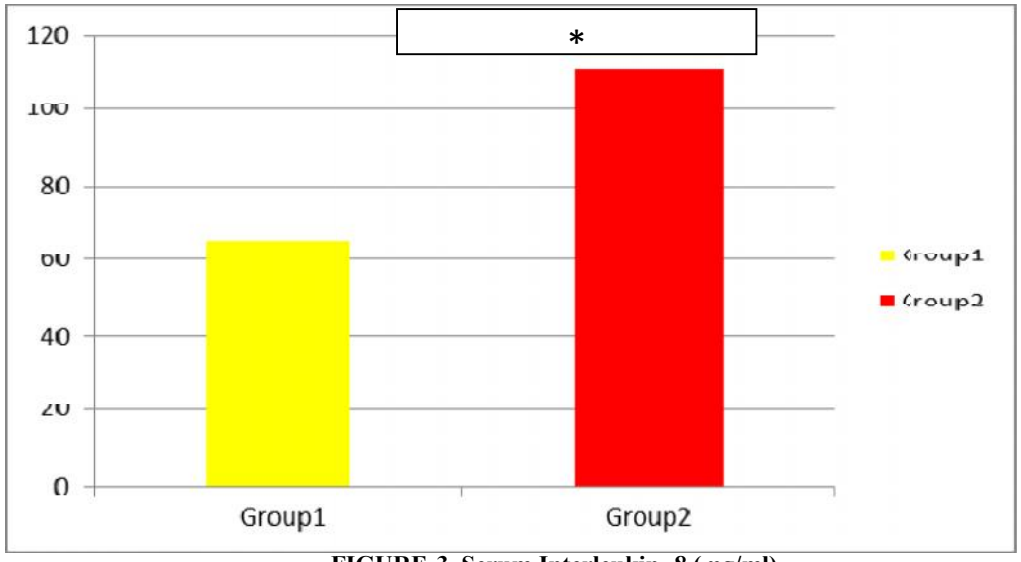

FIGURE-3 Serum Interleukin -8 (ηg/ml)
*=significant difference p<0.05

DISCUSSION

The potential diagnostic usage of adiponectin in obesity and related pathologies was a subject of increasing interest in recent years .In addition to adiponectin potential role in protection against atherogenesis and insulin resistance some studies suggest that adiponectin could be a marker of risk for developing menopausal metabolic syndrome [(36)]. The menopausal transition increases serum adiponectin concentration, however, the data related to its levels and association with body fat and regulatory factors arecontradictory. FSH in postmenopausal women is undoubtedly significantly and positively associated with higher adiponectin. However, two big studies have shown a significant inverse correlation of adiponectin with estradiol that was observed in healthy postmenopausal women, even after adjustment for age and body mass index (BMI)[(9)]. Laughlin et al assessed the determinants of serum adiponectin in postmenopausal women and men aged 50-92 years and found positive association of adiponectin with testosterone, and negative with bioavailable estradiol in both sexes.This was not explained by differences in age and adiposity[(37)]. As plasma adiponectin concentration in females did not change significantly with age. In contrast to females, elderly males over 70 years of age are characterized by significantly higher levels of adiponectin than younger ones[(38)]. Recently, it has been reported that dehydroepiandrosterone sulfate (DHEA-S), a precursor of androgens and estrogens, may upregulateadiponectin gene expression in a depot-dependent manner .The effect of DHEA-S was observed only in visceral adipocytes from fat depots of morbidly obese humans[(39)]. Meanwhile, increased levels of free testosteroneand low sex hormone binding globulin (SHBG) in postmenopausal women were shown to be associated with decreased production of adiponectin[(40)].

Present data indicated that total adiponectin levels are significantly lowered in obese compared to non-obese women at the same stage of postmenopausal (figure-1) , similar results were reported by Lobo (2008) whom

reported that weight gain and obesity lead to theincreased prevalence of metabolic syndrome in postmenopausal women and use oftransdermal hormonal therapy has beneficial overall for reducing many of the parametersof metabolic syndrome[41].Visceral fat accumulation results in reduced levels of adiponectin, as centrally located fat was the main determinant of variability inadiponectin concentration in healthy postmenopausal women [42] , as indicated by increased waist to hip ratio between the two studied groups (table-1) .The associations between adipokines and traditional risk factors for cardiovascular disease were assessed in women at postmenopausal stage. The larger decreases in adiponectin over the menopause transition were associated with greater increase in systolic blood pressure, insulin and insulin resistance and with greater decreases in high density lipoprotein (HDL-cholesterol)[43]. As previous reports confirmed positive association of adiponectin with HDL – cholesterol and negative relation with low-density lipoprotein (LDL-cholesterol) and triglycerides (TG) but not with high total cholesterol (TC), thusadiponectin should be regarded as a most important among adipokines[21] . Recently it was shownthat low adiponectin concentration in postmenopausal women was associated with adverse changes in carotid intima-media thickness and stiffness that was not dependent on other cardiovascular risk factors[44].

Despite the lack of diagnostic specificity for the measurement of serum levels of acute phase proteins ,it is useful because it may reflect the presence and intensity of an inflammatory process .Studies demonstrated a significant decrease in plasma adiponectin in low grade chronic inflammation and suggest that an important linkage between inflammation /adipose tissue / atherosclerosis [45] . As illustrated in Table-4, plasma adiponectin and hs-CRP correlates inversely what may suggest a decrease in production of adiponectin contributes to the systemic and vascular inflammation that commonly associated with obesity (increased hs-CRP & IL-8, Figures- 2,-3, respectively)[46]. However, the change in CRP was not, however, related to the decrease in glucose disposal in post menopausal women with HRT due to obesity –induced insulin resistance [47]. In elderly elevated levels of CRP predict failure to thrive and even increased mortality [48] .Where, CRP was found to be significantly correlated with TC, TG, glucose & uric acid in patients with metabolic syndrome, suggesting the association of a systemic inflammatory response[49].

Moreover, elevated blood levels of other pro inflammatory cytokines IL-6, IL-8 and monocyte chemoattractant protein -1 (MCP-1) increase insulin resistance and the risk for CVD [50]. Considering the determination of IL-8, which was elevated in obese PMW (Figure -3), it has been reported that patients with type 2 DM had higher fasting IL -8 & IL- 18 levels with lowered adiponectin concentrations when compared to non diabetics [51].

As IL-8 has been shown to be produced and released from human adipose tissue suggesting it's involvement in some obesity – related complications and suggesting that IL-8 is the main adipokine contribute to insulin resistance via inhibiting insulin- induced AKT phosphorylation in adipocytes .However ,no significant correlations were detected in this study between any of insulin resistance related parameters with IL-8. The attenuation of IL-8 action might be a target for the prevention of impaired insulin activity & related complications. However, CRP is no further considered as only abiomarkers , but also as a proatherosclerotic molecule ,which mediate it's effects upon the endothelium through the production of interleukin -8 [52] . Moreover, IL-8 induces migration & proliferation of endothelial cells & smooth muscles cells , also it is a potent angiogenic factor[53]. Where IL-8 is retained on cell surface by interaction with heparansulphate proteoglycan to establish a local chemokine concentration gradient for recruitment of neutrophils[54]. AsIL -8 is predominantly produced by endothelial cells serving as apoptosis inducing factor ([55], it also enhances the metabolism of reactive oxygen species, increases chemotaxis and enhance expression of adhesion molecule [56].

In an experimental CRP infusion in mice , a marked elevation in IL -6, LI -8 as well as coagulation factors (prothrombin , plasminogen activator inhibitor-1) and increased infarct size of MI in ischemic tissues of mice[57] . However, our data did not found a significant correlation for CRP with IL -8, but the former was negatively correlated with total adiponectin levels in obese PMW (Table-4). On the other side, factors involved in inflammation are linked with those critical for bone remodeling. As presented in Table -2 both ALP &P were elevated in obese group, but not serum Ca. However, non –obese PMW ALP levels were correlated insulin level ($r=0.381$,$p<0.022$) and P levels were related to level of IL8 (but not in obese PMW) , indicating that in non obese women inflammatory process play more important role in bone metabolism independent on adiponectin (Table-3).While , obese PMW serum P levels seems to be correlated positively to BMI with $r= 0.338$,$p<0.047$ (Table -4) , although , no significant correlation was detected between adiponetin with any of the studied bone markers .However , recent evidence for a link between systemic inflammation and osteoporosis at menopause due to the possible association between serum hsCRP levels and bone mineral density (BMD) in postmenopausal women . It was found that both premenopausal and postmenopausal women had serum levels of total ALP levels to be higher in the subjects with higher hsCRP quintiles than those with the lowest quintile. These findings suggest that subclinical systemic inflammation may be associated with bone turnover rate and bone mass in healthy women [25].Thus the elevation in serum CRP levels (Fiure-2) in obese group could contribute to the variation in bone related measures (Table -2) , and it is for the first time to report an association of elevated IL-8 levels with that of phosphate in serum of non-obese postmenopausal women (Table-3), which might reflect the possible benefit of anti-inflammatory treatment to reduce the undesirable alteration in bone metabolism due to hormonal and cytokines modification during menopause. Hence, modulation of inflammatory processes in the setting of menopause is of great interest. Also it is possible that in coming years , the new therapeutic strategies would be based on anti- inflammatory properties of adiponectin with beneficial effects on complications related to its deficiencies , which can be translated into real clinical treatment

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