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CONTRIBUTION OF SERUM ADIPONECTIN IN DEVELOPMENT OF INSULIN RESISTANCE IN POSTMENOPAUSAL WOMEN IN RELATION TO BMI, HS-C-REACTIVEPROTEIN & ESTROGEN

[1]Zainab.A.Hasan, [1]Shatha H. Ali & [2]Khalid A. AL Liheebi
[1]Department of Clinical Laboratory Science .Baghdad University ,Collage of Pharmacy, Iraq.
[2]AL- Kindy Specialist Center for Endocrinology and Diabetes Baghdad, Iraq.

ABSTRACT
The aim of current study was designed to evaluate the role of adiponectin in glucose disposal in postmenopausal women in relation to their BMI , compared to corresponding postmenopausal diabetic women. The study comprised of 135 postmenopausal women (PMW) with age ranged from 45 to 65 yrs. Sixty five of them were of type 2 diabetes patients had been grouped as: Group D1 of 30 diabetic PMW (BMI<23) and group D2 of 35 diabetics PMW, overweight (BMI > 25), in comparison to 70 apparently healthy PMW divided into : Group C1 of 33 normal weight PMW (BMI<23) and group C2 of 37 women overweight PMW (BMI > 25). Blood specimens were analyzed for measuring the fasting serum glucose (FSG), fasting serum insulin (FSI), serum adiponectin, serum high sensitive C-reactive protein (hs-CRP) and serum estrogen levels. The Body mass index showed significantly effect on FSG levels among both non-diabetic and diabetic PMW. Meanwhile, BMI showed a significant effect on FSI levels among non-diabetic PMW. Whilst, BMI showed a significant effect on serum estrogen levels among both over weight diabetic and non-diabetic PMW. BMI showed a significant effect on adiponectin levels among diabetic and non-diabetic PMW. The Serum CRP levels in diabetic and non-diabetic PMW were significantly affected by BMI .While, hs-CRP values were significantly correlated with serum estrogen, adiponectin and QUICKI values, irrespective of being diabetic or not. Iraqi PMW groups showed that body weight may exert important effects on parameters measured in this study and serum adiponectin may be an independent predictor for the development of diabetes in women, and even though estrogen levels declined in healthy postmenopausal women but it was increased in overweight diabetic women .Thus Over weight and diabetic state could be considered as important factors that can lead to further lowering effects on serum adiponectin levels in these women ($p<0.05$).

KEY WORDS: BMI, Insulin resistance, Diabetes mellitus, adiponectin, estrogen,hs-CRP.

INTRODUCTION

Insulin resistance can be defined as a smaller than expected biological response to a given dose of insulin and is thought to be present within all obese subjects, although there is a large degree of variation in its severity. Importantly, insulin resistance is mostly related to central obesity and forms a part of metabolic syndrome [(1)] .The accumulation of central abdominal fat in women at menopause is associated with a decline in the production of a protein called adiponectin. It's, a protein secreted from adipocytes , has been reported to have anti-inflammatory, antidiabetic, and antiatherogenic properties that are probably partly mediated through down regulation of circulating high sensitive C-reactive protein(hs- CRP) and the inflammatory response [(2)] .The recent identification of adiponectin receptors in skeletal muscle and liver, have indicated that adiponectin may play an integral role in the pathogenesis of insulin resistance associated with obesity, it makes cells in the body, particularly muscle and liver cells, more sensitive to the actions of insulin [(3)] .

Adiponectin in addition to the intra-abdominal weight gain at menopause is believed to play important role in the development of insulin resistance after menopause[(4,5)]. Adiposity is inversely, associated with circulating adiponectin levels [(6,7)] and hypoadiponectinemia has been reported to predict the development of type 2diabetes in healthy subjects [(8)]. Type 2 diabetes could be considered as an inflammatory disease that is largely based on reports stating that increased levels of inflammatory markers , including CRP, white blood cell count, fibrinogen and sialic acid and can predict its development [(9,10)] .Whilst many studies strongly related basal CRP levels to adiposity, CRP is also associated with insulin sensitivity[(11,12)] .

The present study was designed to evaluate the correlation of body weight with some biomarkers such as serum (adiponectin, hs-CRP, estrogen) with the degree of insulin sensitivity in diabetic postmenopausal women in comparison with healthy postmenopausal women.

MATERIAL AND METHODS

This study was carried out at the Al -Kindy Specialist Center for Endocrinology and Diabetes in Baghdad (Iraq) .The study comprised of 135 postmenopausal women (PMW)

with age ranged from 45 – 65 years (table -1). Sixty five of them were type 2 diabetic patients were grouped as: Group D1 of 30 diabetic PMW (BMI<23) and group D2 of 35 diabetic PMW, overweight, with BMI > 25, in comparison to 70 apparently healthy PMW(control) divided into : Group C1 of 33 PMW (BMI<23) and group C2 of 37 overweight PMW(BMI > 25) . Patients were selected not have other prominent chronic disease like liver or kidney diseases , nor hypertension or other cardiovascular complication.

Blood serum specimens were used to measure the levels of : fasting serum glucose (FSG) [13] , fasting serum insulin(FSI) [14], serum adiponectin[15], serum high sensitive C-reactive protein (hs-CRP) [16]. serum estrogen [VIDAS Estradiol II (E211)] levels [17].

Insulin sensitivity was determined using the quantitative insulin sensitivity check index (QUICKI) which is calculated using the following formula [18] .

$$QUICKI = \frac{1}{[\log (FPI \text{ in } \mu U/ml) + \log (FPG \text{ in mg/dL})]}$$

Where (FPG) = Fasting plasma glucose , (FPI)=Fasting plasma insulin

The results were expressed as mean ± standard deviation (mean ±SD).One way analysis of variance (ANOVA) test was utilized to evaluate significant differences between means of different groups . In all cases, probability (P-value) $p < 0.05$ was considered statically significant, statistical analysis was performed by using SPSS 17.

TABLE- 1. Baseline Characteristics of Subjects

Variables	Types 2 Diabetic PMW (BMI<23) (D1)	Control Non-diabetic PMW (BMI<23) (C1)	Type2 Diabetic PMW (BMI >25) (D2)	Control Non-diabetic PMW (BMI >25) (C2)
Number	30	33	35	37
Age (yrs.)	55 ± 5.74	50 ± 4.62	60 ± 7.17	47 ± 4.20
BMI (kg/m^2)	21.840±1.448*	22.140±1.933	37.89±2.470*	35.860±3.560
Duration of diabetes (yrs.)	6.08±4.91	-	9.83±3.49	-
Duration of menopause (yrs.)	5.0 ±3.05	4.0 ±7.31	7.0 ±3.89	5.0±3.86
Fasting serum Glucose(mmol/L)	7.090±0.709*	5.350±0.970	9.495±0.69*	6.320±0.865

The data are expressed as mean ± SD.
BMI = Body Mass Index, yrs = years
* = Significantly different from their control

RESULTS

I -Fasting Serum Glucose:

Data presented in table(2) indicates that fasting serum glucose levels in type2 diabetic PMW with BMI > 25 were significantly higher than those in type2 diabetic PMW with BMI < 23. Also FSG levels in non-diabetic PMW with BMI > 25 were significantly higher than the corresponding PMW with BMI < 23.

II- Fasting Serum Insulin

Table(2) showed that fasting serum insulin levels in non-diabetic PMW with BMI < 23 were significantly lower ($p< 0.05$) than those with BMI > 25. While , type2 diabetic PMW with BMI > 25 expressed higher levels(11.398±1.466mIU/ml)than those with BMI < 23 (9.79±1.199 mIU/ml),and expressed higher levels than healthy PMW with BMI > 25(10.554±2.05 mIU/ml).

III- Quantitative Insulin Sensitivity Check Index – QUICkI

Estimation of insulin sensitivity check index for diabetics PMW and their control groups indicant that they were no significant difference among studied groups, but the result expressed lower values of insulin sensitivity in diabetic PMW when compared to their controls , and QUICKI values expressed lower values in those with BMI > 25 compared with those of BMI < 23(both diabetic and healthy PMW) as shown in table(2).

TABLE-2. Glycemic Indices

Parameter	Types 2 Diabetic PMW (BMI<23) (D1) (N=30)	Control non-diabetic PMW(BMI<23) (C1) (N=33)	Type- 2 Diabetic PMW (BMI>25)(D2) (N=35)	Control non-diabetic PMW (BMI >25) (C2) (N=37)
Fasting Serum Glucose (mmol/L)	5.350±0.970	6.320±0.865	7.090±0.709*	9.495±0.691
Fasting Serum Insulin (mIU/ml)	7.284± 0.851	10.554±2.054	9.790±1.199*	11.398±1.466
Insulin Sensitivity Check Index (QUICKI)	0.62±0.050	0.54±0.031	0.54±0.053	0.49±0.047

- All data are presented as mean +SD, $p <0.05$. N=No. of subjects . * = Significantly different from their control.

IV. Serum Adiponectin Levels

Data in table(3) showed that serum adiponectin levels in type2 diabetics PMW(both BMI > 25;BMI < 23) were significantly different ($p < 0.05$) from their corresponding controls . Furthermore, serum adiponectin levels in type2 diabetic PMW with BMI < 23 were significantly higher than type2 diabetic PMW with BMI > 25.Meanwhile , serum adiponectin levels in non-diabetic PMW with BMI < 23 were significantly higher than their corresponding PMW with BMI >25.

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V. Serum highly sensitive C-Reactive Protein Levels

As presented in table(3) , serum hs-CRP levels in type 2 diabetic PMW with BMI > 25 were significantly higher than other groups . Furthermore; hs-CRP levels in type2-diabetic PMW with both BMI < 23 and BMI > 25 were significantly higher than their corresponding control groups. Also hs- CRP levels significantly higher in non-diabetic with BMI > 25 than their corresponding PMW with BMI < 23

TABLE -3. Serum Adiponectin and hs-CRP Levels

Parameters	PMW type2DM BMI<23 (D1)(N=30)	Control PMW BMI<23 (C1)(N=33)	PMW type2 DM BMI>25 (D2) (N=35)	Control PMW BMI>25 (C2) (N=37)
Adiponectin µg/ml	7.362±0.496*^	11.314±0.783	3.304±0.350*^	4.568±0.400
hs-CRP mg/L	2.3970±0.5894*	1.4510±0.4045	3.2420±0.6447*^	2.2300±1.0080

- All data are presented as mean+SD N=No. of subjects. *=Significantly different from their control. PMW=Postmenopausal women. ^=Significantly different from the corresponding group with different BMI.

IV. Serum Estrogen Levels

As shown in table(5) serum estrogen levels in diabetic PMW with BMI > 25 were significantly higher than their corresponding control group, but estrogen levels in type 2 diabetic PMW with BMI < 23 showed no difference with their corresponding controls. Furthermore; serum estrogen levels in non-diabetic PMW with BMI > 25 were significantly higher than those with BMI < 23 .

TABLE -4. Serum Estrogen Levels

Parameters	PMW type2 DM BMI<23 (D1) (N=30)	PMW control BMI<23 (C1) (N=33)	PMW type2 DM BMI>25 (D2) (N=35)	PMW control BMI>25 (C2) (N=37)
Estrogen ng/ml	1.3680±0.1428	1.3940±0.3271	2.0490±0.2436*	1.7570±0.7014

-All data are presented as mean +SD , p less than 0.05 . PMW=Postmenopausal women.
*= Significantly different from their control. N=No. of subjects.

CORRELATION STUDIES

1. Effect of BMI (Body Mass Index) on Glycemic Indices and Some Biomarkers in Diabetic and Non-Diabetic Postmenopausal women

A strong negative correlation between BMI and insulin sensitivity Check index (QUICKI) in diabetic PMW ($r = -0.831$,$p=0.002$), while in non-diabetic PMW ($r = -0.918$, $p=0.002$),but a positive correlation was detected with both glucose and insulin in both diabetics and non-diabetics ($r = 0.949$, $p = 0.001$, $r = 0.740$, $p = 0.003$ for glucose , and $r = 0.720$, $p = 0.003$, $r = 0.925$, $p = 0.002$ for insulin, respectively).Furthermore ,BMI values were significantly correlated with serum estrogen levels in diabetic PMW ($r=0.958$, $p=0.0001$) more strong than those in non-diabetic PMW ($r=0.672$,$p=0.004$), as summarized in table (5).

Furthermore, BMI values were significantly correlated with serum hs-CRP , serum adiponectin values ($r = 0.743$, $p=0.003$ for hs-CRP and $r = -0.993$, $p=0.001$ for adiponectin) for diabetics while in non-diabetic ($r = 0.780$, $p = 0.003$ for hs-CRP, $r = -0.965$, $P = 0.001$ for adiponectin ,table 5) .

2. Correlations Between Serum Estrogen Levels and Some Biomarkers in Diabetic and Non-Diabetic PMW

A strong negative correlation had been detected between serum estrogen values and serum adiponectin values in diabetic PMW ($r = -0.933$,$p=0.001$) and even a stronger association than in non-diabetic PMW ($r= -0.474$,$p=0.006$) ,as summarized in table(6). Serum estrogen values in PMW were strongly correlated with QUICKI values, irrespectively of being diabetic or non-diabetic where $r= -0.932$,$p=0.001$for QUICKI in diabetic vs. ($r= -0.890$,$p=0.002$) in non-diabetic PMW.

TABLE 5. Pearson's Correlation Between BMI and Some Biomarkers in Diabetic and Non-Diabetic PMW

Biomarkers	Type 2 Diabetic PMW		Non-Diabetic PMW	
	r	P	r	P
QUICKI	-0.831	0.002	0.918-	0.002
Glucose	0.949	0.001	0.740	0.003
Insulin	0.720	0.003	0.925	0.002
Estrogen	0.958	0.001	0.672	0.004
hs-CRP	0.743	0.003	0.780	0.003
Adiponectin	0.993-	0.001	0.965-	0.001

TABLE -6. Pearson's Correlation Between Serum Estrogen and Some Biomarkers in Diabetic and Non-diabetic PMW

Biomarkers	Type 2 Diabetic PMW		Non-Diabetic PMW	
	r	P	r	P
Adiponectin	- 0.933	0.001	- 0.474	0.006
QUICKI	- 0.932	0.001	- 0.890	0.002

TABLE -7. Pearson's Correlation Between Serum hs-C Reactive Protein (hs-CRP) and Some Biomarkers in Diabetic and Non-diabetic PMW

	Type 2 Diabetic PMW		Non-Diabetic PMW	
Biomarkers	r	P	r	P
Estrogen	0.883	0.002	0.969	0.001
Adiponectin	- 0.730	0.003	- 0.601	0.004
QUICKI	- 0.939	0.001	- 0.882	0.002

3. Correlations Between Serum hs-CRP Values and Some Biomarkers in Diabetic and Non-Diabetic PMW

Pearson's correlation coefficient showed that serum hs-CRP values were significantly correlated with serum estrogesn, adiponectin and QUICKI , irrespective of being diabetic or non-diabetic as summarized in table (7).

4. Correlations Between Serum Adiponectin Values And Some Biomarkers in Diabetic and Non-diabetic PMW:

Pearson's correlation coefficient show that the effect of serum adiponectin on **QUICKI** values were more obvious in diabetic PMW than those in non-diabetic PMW ,where (r=0.824, r=0.002) for QUICKI in diabetic PMW vs. (r=0.591 ,p=0.005) in non-diabetic PMW ,as shown in table (8).

TABLE-8 Pearson's Correlation Between Serum Adiponectin and Insulin Sensitivity index in Diabetic and Non-diabetic PMW

Biomarkers	Type 2 Diabetic PMW		Non-Diabetic PMW	
	r	P	r	P
QUICKI	0.824	0.002	0.591	0.005

DISCUSSION

As insulin resistance could be related to obesity and physical inactivity, several mechanisms had been proposed to mediate such relation. A number of circulating hormones, cytokines, and metabolic fuels, such as free fatty acids (FFA) originated in the adipocytes could modulate insulin action [4]. An increased mass of stored triglyceride, especially visceral or deep subcutaneous adipose depot, leads to large adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis; this result in increased release of circulating FFA and glycerol, both of which may aggravate insulin resistance in skeletal muscle and liver[19]. These FFA can influence insulin signaling pathway by activating of several serine/thrionine kinases, reducing the tyrosine phosphorylation on IRS and impairing IRS/phospho-inositide-3-kinase pathway [20,21] . Recently, several studies provided strong evidence to support the concept of adipose tissue as an endocrine organ producing cytokines which modulate glucose homeostasis [22].

If insulin resistance exists, more insulin needs to be secreted by the pancreas[23] . If this compensatory increase does not occur, blood glucose concentrations increase and type 2 diabetes occurs [24,25] . This study agrees with previous study that state the BMI was significantly associated with increased parameters of insulin resistance[26]. Our results indicated that BMI could exhibit important role in determining insulin response in postmenopausal women. BMI showed a significant effect on FSG&FSI level in non-diabetic and in diabetic PMW(table-5).Obesity has long been recognized as an important risk factor for diabetes and impaired glucose tolerance, an association that was confirmed in many prospective studies [27].Endocrine

alterations in menopause are known to increase the abdominal visceral fat content as well as blood concentrations of cholesterol, triacylglycerol, glucose, and insulin [28]. Changes in visceral fat content were found to be associated with subsequent impaired glucose-insulin homeostasis [29].Sex hormones may act as a protective factor against type 2 diabetes and high glucose concentrations. In this context it is interesting to note that women with type 2 diabetes completely lose their sex-related protection from cardiovascular disease [30]. BMI showed significant effect on estrogen level among both diabetic and non-diabetic over weight PMW (table -5). Furthermore ,in this study a strong inverse correlation had been detected between serum estrogen values and serum adiponectin values in diabetic PMW and even stronger association than in non-diabetic PMW as shown in table(6) . Estrogen biosynthesis is catalyzed by the enzyme aromatase (aromatase cytochrome P450), a product of the *CYP19* gene. Aromatase catalyzes the aromatization of the A ring of C19 androgens to the phenolic A ring of C18 estrogens[31]. In obese-post menopausal women, adipose tissue of the breast, abdomen, thighs, and buttocks are the main sites of estrogen biosynthesis, with levels of aromatase increasing with age and BMI [32].

The average age of menopause is 51 years (45 to 55 yrs) [33] . During the transition from the reproductive years through menopause and beyond, women experience many changes, one of them changes in adipose tissue metabolism that may contribute to body fat distribution [34,35]. Weight gain, especially in the abdominal region, causes insulin resistance and subsequent increases in plasma insulin and insulin growth factor (IGF-1), which leads to increasing levels of estrogens and bioavailable androgens, testosterone and androstenedione. This excess weight results in increased estrogen concentrations from conversion of androgens, mainly androstenedione, to estrogens, mainly estrone. After menopause, when ovarian production of estrogens stops, this conversion becomes the primary source of estradiol [36]. The menopausal transition increases serum adiponectin concentration. Two large studies have shown a significant inverse correlation of adiponectin with estradiol levels that was observed in healthy postmenopausal women, even after adjustment for age and body mass index (BMI) [37,38] . Visceral fat accumulation results in reduced levels of adiponectin that has been shown to exert anti-inflammatory and antiatherogenic properties within the arteries and thus may negatively modulate the process of atherogenesis [39,40]. BMI show significant effect on CRP level in diabetis and non-diabetis PMW (table-5), Pearson's correlation coeffient showed that serum hs-CRP values were significantly correlated with the following biomarkers (serum estrogesn, ,adiponectin and QUICKI) independent of being diabetic or non-diabetic (table -7). Recently, "inflammation" and "inflammatory" cytokines have been postulated to be important additional pathogenetic factors in the development of insulin resistance and type 2 diabetes [41] . C-reactive protein (CRP), a nonspecific marker of the inflammatory response [42] , is most consistently associated with the development of type 2 diabetes [43] .

Traditionally, inflammatory disease involves elevation (i.e., above the normal range) of at least some of these markers, most consistently CRP, although their biological diversity suggests that not all, if any, would be directly involved in the inflammatory process. Although the primary source of CRP is the liver, CRP mRNA has recently been identified in human subcutaneous adipose tissue [2]. Furthermore, 25% of circulating interleukin-6 (IL-6), the principal stimulus of hepatic CRP production, is derived from adipocytes [44] or, as has been recently suggested, from macrophages within adipose tissue [45]. While many studies strongly relate basal CRP levels to adiposity, CRP is also associated with insulin sensitivity [46].

Insulin suppresses the levels of inflammatory markers. So that some reports suggested that insulin has anti-inflammatory properties, a proposal supported by evidence that it attenuates cytokine stimulation of acute-phase protein gene expression [47]. It was found that plasma adiponectin levels and hs-CRP correlate inversely which may suggest that decreased production of adiponectin contributes to the systemic and vascular inflammation commonly found in obesity. So, adiponectin may play an important role in the pathogenesis of diabetes, and may be an independent predictor of the development of diabetes in women, and even though estrogen levels decline in healthy postmenopausal women but it increased in overweight diabetic women. Hence, over weight and diabetes could act cumulatively leading to further decreased adiponectin levels in these women [48]. And because the results stated that higher BMI to be associated with higher CRP concentrations , suggesting a state of low-grade systemic inflammation in overweight and obese persons that could adversely affect adiponectin levels in PMW with BMI >25.

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