



CORRELATION BETWEEN SERUM ADIPONECTIN AND RESISTEN WITH MEASURES OF INSULIN RESISTANCE IN NON-DIABETIC OBESE

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ABSTRACT

Obesity is a well known contributor for the development of insulin resistance, although the exact mechanism remains unclear. In obesity adipose tissues secretes adiponectin and resistin, which can antagonize insulin action. The objectives of the present study were to evaluate the role of adipokines (adiponectin & resistin) in obesity and its relation to insulin resistance. The study included 30 obese non-diabetic subjects (BMI ≥ 30), 15 male with mean age of $31.16 \pm \text{SEM } 1.72$ years and 15 female with mean age of 32.18 ± 2.27 years. In addition to, 18 non-obese (BMI < 30), non-diabetic subjects (12 female with mean age of $25.23 \pm \text{SEM } 1.81$ years and 6 male with mean age of $30.83 \pm \text{SEM } 5.28$ years) as a control group. Fasting serum was used to measure insulin, glucose, resistin & adiponectin. There was a slight increase in FSG values of obese non-diabetic patients when compared with the control values ($P=0.142$), but there was a significant increase in fasting serum insulin of obese when compared with that of the control ($P = 0.023$). However, there was no significant variation in lipid profile components between obese and controls ($p > 0.05$). However, there was a significant increase in serum resistin of the obese patients compared with the control ($P = 0.039$), but there was no significant alteration in serum total adiponectin of the obese patients when compared with the control ($P = 0.135$). Considering correlations studies neither serum total adiponectin, nor resistin exhibited significant correlation with HOMA-IR ($r=0.144, r = -0.01$, respectively) for obese, meanwhile, the non-obese showed similar relationships ($r=0.10, r=0.19$, respectively). In conclusion, this study revealed that although obesity is a state of low grade of inflammation, none of the measured adipokines to be significantly related to insulin resistance determined as, Homeostasis Model Assessment –for Insulin Resistance (HOMA-IR) in non-diabetic obese subjects, although serum total adiponectin seems to be associated with FSG in the obese group.

KEYWORDS: Obesity, Adiponectin, Resistin, Insulin resistance, HOMA-IR.

INTRODUCTION

Obesity is defined as an excessive amount of body fat in relation to lean mass of sufficient magnitude to produce adverse health consequence⁽¹⁾. Obesity can be divided into two principal types: 1) central or visceral, characterized by fat depots surrounding organs deep in the abdominal area. 2) Subcutaneous, superficial fat depots under the skin which can occur anywhere including the abdomen. Visceral obesity is more dangerous from a health standpoint⁽²⁾. Meanwhile, obesity is considered as a risk factor for different chronic diseases, to a variable degree in different ethnicities⁽³⁾, such as diabetes mellitus, hypertension, hyperlipidaemia, and atherosclerotic diseases such as coronary artery disease⁽⁴⁾. Adipose tissue is now considered an endocrine tissue^(5,6) that secretes various substances (adipokines) including tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), leptin, resistin, visfatin, omentin, and adiponectin⁽⁷⁾. Modulating haemostasis, blood pressure, lipid and glucose metabolism, predispose to inflammation and atherosclerosis⁽¹⁾. The adipocyte-derived hormones: leptin and adiponectin, are likely candidates for elucidating the biological mechanisms underlying pathogenesis of these risks^(4,5). It has been reported previously, that low serum adiponectin is an independent predictor of incident type 2 diabetes⁽⁶⁾ and cardiovascular disease⁽⁷⁾. Adiponectin has both anti-atherogenic and anti-inflammatory activities; it has an effect on energy

homeostasis and body weight⁽⁸⁾. It also plays a crucial role in insulin resistance in type 2 diabetes, in obese people⁽⁹⁾. Several findings suggested that adiponectin is a predictive index for insulin resistance in type 2 diabetes⁽¹⁰⁾. Adiponectin binds to a number of receptors. So far, two receptors have been identified, with homology to G protein-coupled receptors and one receptor similar to the cadherin family – ADIPOR1, – ADIPOR2⁽¹¹⁾. Adiponectin circulates in plasma as a low-molecular weight trimer, a middle-molecular weight hexamer, and high-molecular weight (HMW) 12- to 18-mer, and these forms were postulated to differ in biologic activity⁽¹²⁾. HMW adiponectin was proposed to be the biologically active form of the hormone⁽¹³⁾, and was shown to be superior to total adiponectin in predicting insulin resistance and the metabolic syndrome trait cluster⁽¹⁴⁾. Resistin is a newly described 12.5-kDa adipokine that is a member of a cysteine-rich secretory protein family 116. Considering the crosstalk between inflammatory pathways and the insulin signaling cascade, resistin may represent a link between inflammation and metabolic signals⁽¹⁵⁾. The objectives of the present study were to evaluate the role of adipokines (adiponectin & resistin) in obesity and its relation to insulin resistance. The objectives of the present study were to evaluate the role of adipokines (adiponectin & resistin) in obesity and its relation to insulin resistance (measured as HOMA-IR).

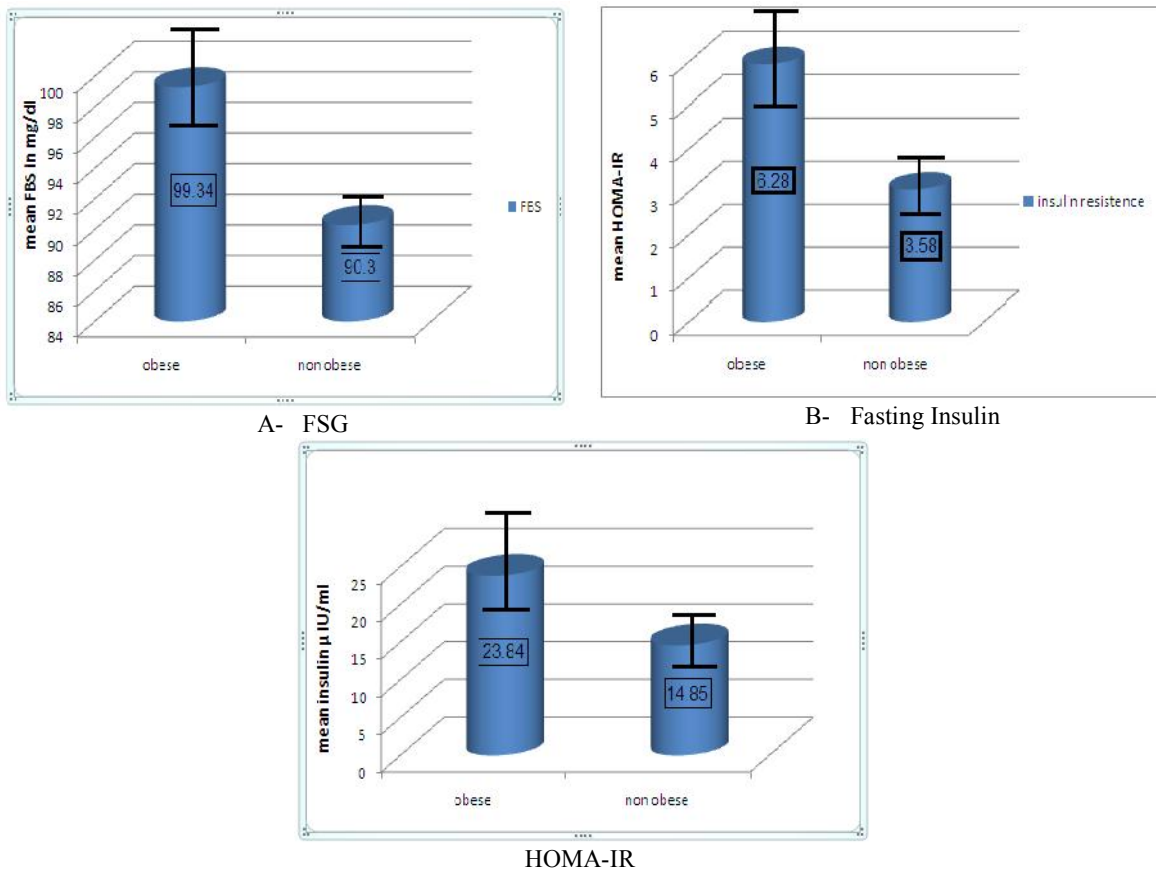
SUBJECTS AND METHOD

The study included 30 non-diabetic obese subjects (BMI ≥ 30)⁽¹⁶⁾, the consisted of 15 male with mean age of 31.16 \pm SEM of 1.72 years and 15 female with mean age of 32.18 \pm 2.27 years, for the period from November/2011 to April/2012. In addition to 18 non-diabetic, non-obese (BMI <30) subjects(12 female with mean age of 25.23 \pm SEM 1.81 years and 6 male with mean age of 30.83 \pm SEM 5.28 years) as a control group. All of the participants were estimated for clinical examination and medical history at the outpatient clinics in Alsaddr city/at Al-Najef /Iraq, under the supervision of a specialist physician according to: BMI, Fasting serum glucose. Patients suffering from cardiovascular diseases, rheumatoid arthritis, on steroid, NSAID therapy, suffer from kidney disease, pregnancy or cancer were excluded from the study. Fasting venous blood specimen (5 ml) were used to obtain serum & divided into aliquots to be stored frozen for determination of serum adiponectin⁽¹⁷⁾, serum resistin⁽¹⁸⁾, serum insulin⁽¹⁹⁾ [all measured by ELISA(Demeditic. Gerneny)] and lipid profile [triglyceride⁽²⁰⁾, total cholesterol⁽²¹⁾, high density lipoprotein⁽²²⁾, low density lipoprotein, very low density lipoprotein (Biolabo. France)]. Homeostasis Model

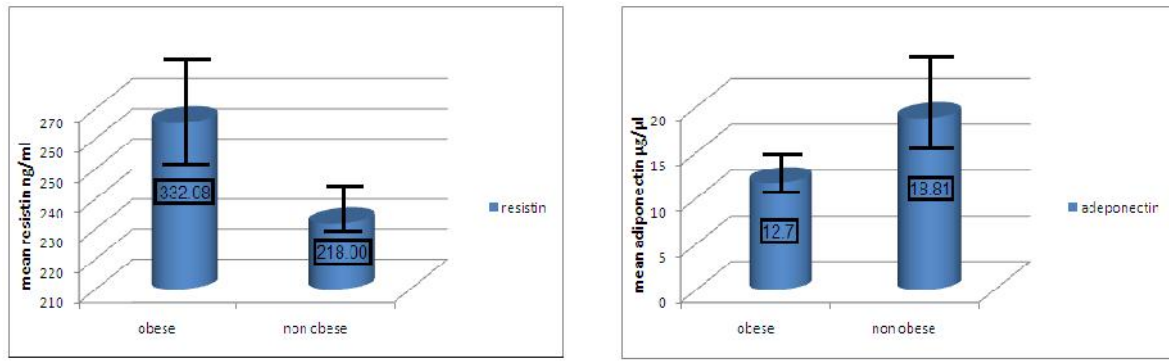
Assessment for Insulin Resistance (HOMA-IR) were estimated according to Matthews *et al.*, 1985⁽²³⁾. The results were expressed as mean \pm standard error of mean (SEM) or percent changes. Student t-test and analysis of variance (ANOVA) were used to examine the degree of significance. P-values less than 0.05 were considered significant. Pearson's correlation coefficient (**r**) was used to test for statistical association, using SPSS, version 17.

RESULTS

There is no significant increase in FSG values of the obese non-diabetic subjects when compared with the non-obese control (P=0.142), but there is a significant increase in fasting serum insulin levels (by ~ 64 %) for obese patients, when compared with that of the controls (P = 0.023), as illustrated in Figure -1. Whereas, lipid profile results showed no obvious variations between obese and control groups (p > 0.05), Table-1. However, there is a significant increase in serum resistin levels of obese subjects (by ~ 52 %) when compared with controls (P = 0.039), but no significant alterations in serum total adiponectin concentrations of the obese subjects from that of controls (P=0.135), as shown in Figure-2.



FSG=fasting serum glucose, HOMA-IR= Homeostasis Model Assessment for Insulin Resistance
FIGURE1: Fasting Serum Levels of Glucose, Insulin & HOMA-IR in Obese and Non- Obese Subjects

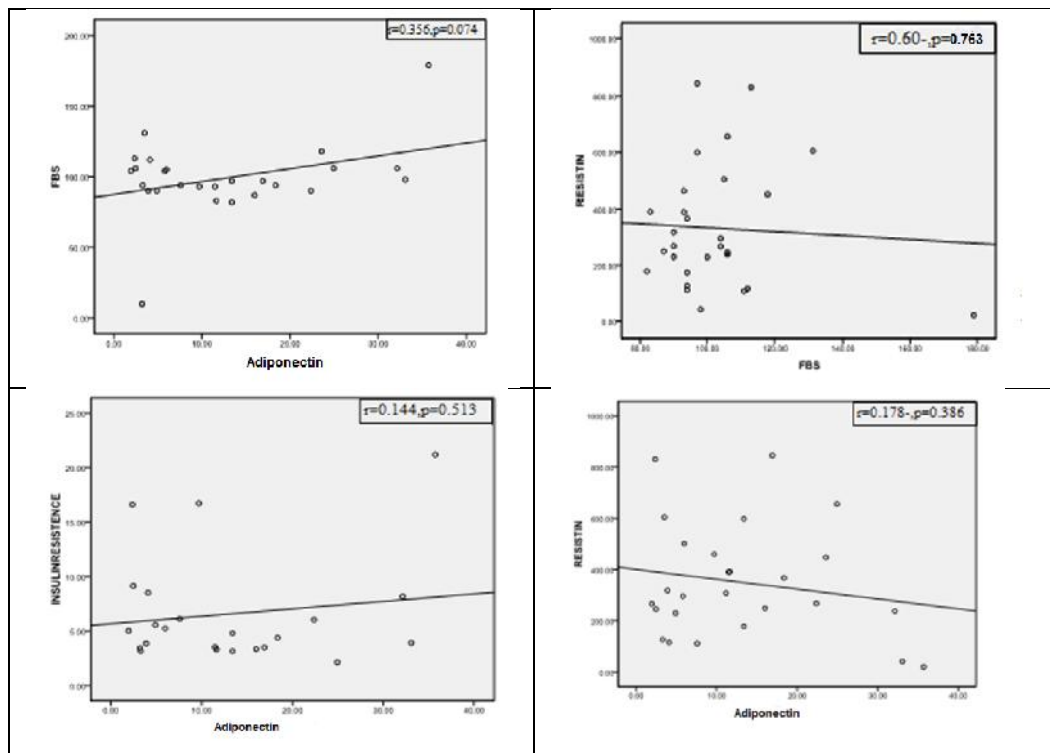


a .Resistin b-Adiponectin
FIGURE 2: Serum Resistin and Adiponectin Levels in Obese and non-Obese Groups.

TABLE 1: Lipid Profile and Atherogenic index of The Studied Groups

Parameter	Obese Subjects (N=30)	Controls (Non-Obese) (N=18)	P value
Total Cholesterol (mg/dL)	156.66±9.33	139.83±9.90	0.229
Triglyceride (mg/dl)	172.75±18.43	147.91±16.79	0.330
VLDL-Cholesterol (mg/dl)	33.21±3.11	29.58±3.35	0.436
HDL-Cholesterol (mg/dL)	42.75±2.17	43.58±3.67	0.847
LDL-Cholesterol (mg/dL)	80.70±5.94	65.83±4.49	0.058
TC/HDL	3.70±0.20	3.29±0.19	0.159

Data are presented as mean ± SEM ,VLDL=Very low density lipoprotein ,HDL=High density lipoprotein ,LDL=Low density lipoprotein, TC/HDL = Atherogenic index .



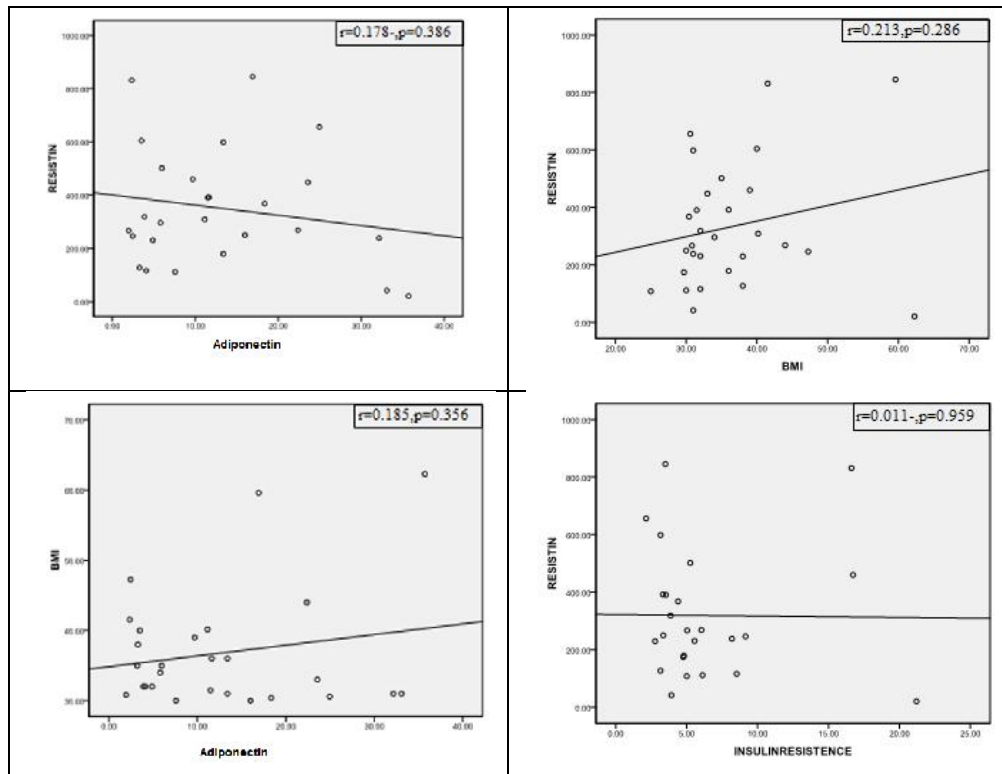


FIGURE 3: Pearson's Correlations of Serum Adiponectin , Resistin with Some Studied Parameters in Obese Group

DISCUSSION

The prevalence of obesity has been increased dramatically as a result of the modern lifestyle and is one of the most important targets of public health programs. Accumulating evidence derived from both clinical and experimental studies highlighted the association of obesity with a number of chronic diseases⁽²⁴⁾. Insulin is one of the pivotal physiological factors in regulating different adipocyte functions, including secretion of various adipokines, which in turn modify insulin action⁽²⁵⁾. Although fasting serum insulin levels were elevated in obese subjects as compared to the controls (figure-1). Which might be attributed to that obesity is known to be an important risk factor for the development of insulin resistance, although the mechanism remains unclear⁽¹⁸⁾. As reported previously by Hotamisligil et al (1993) , whom first showed that the proinflammatory cytokine tumor necrotic factor α , was able to induce insulin resistance . this was a revolutionary idea, that a substance produced by fat had both local & potential systemic effects on metabolism⁽²⁶⁾. These bioactive substances quickly extend to include : leptin , interleukin-6 ,adiponectin ,resistin ,monocyte chemoattractant protein -1 (MCP-1) ,plasminogen activator inhibitor -1, visfatin , serum amyloid A (SAA)⁽²⁷⁾. These cytokines and chemokines activate of intracellular pathways that promote development of insulin resistance. One potential mechanism is through activation NADPH -oxidase by lipid accumulation in adipocytes , which increases ROS production⁽²⁸⁾ consistently , the antioxidant N-acetyl cysteine can reduce ROS and improve insulin resistance in hyperglycemia-induced model . Also lipid excess increases the activities of various protein kinases C enzymes isoforms⁽²⁹⁾.

Adiponectin level is partially determined by inflammatory marker levels, most factors with significant impact on adiponectin regulation have inhibitory effects. Decreased serum levels of adiponectin may serve as a marker of increased metabolic & inflammatory risk. The potential role of adiponectin in obesity and related pathologies is directed for protection against atherogenesis and insulin resistance⁽³⁰⁾. As adiponectin has been reported to exert anti-inflammatory & anti-atherogenic properties within arteries thereby may negatively modulate atherogenesis. Adiponectin increases insulin sensitivity in various models of insulin resistance and *in vitro* increases the ability of sub -physiological levels of insulin to suppress glucose production in isolated hepatocytes . Unlike most other adipokines, plasma adiponectin levels were reduced in animal models of insulin resistance It increase glucose uptake and fat oxidation in muscle, reduced hepatic glucose production⁽⁴⁰⁾, and improved whole-body insulin sensitivity. It must be highlighted that several physiological factors affect the circulating levels of adiponectin. First, aging, gender and puberty have effects on circulating adiponectin levels⁽³¹⁾, as an age-associated elevation of plasma adiponectin levels has been reported⁽³²⁾. In our study serum adiponectin levels were significantly higher in female subjects ,indicating of a sex hormone affect on circulating adiponectin levels⁽³³⁾. It is expected, therefore, that circulating levels of adipokines may be useful as biomarkers to evaluate the risk of other disease states associated with obesity .Thus, the HMW form is more strongly associated with insulin sensitivity than is total adiponectin⁽³⁴⁾. The increased fasting serum insulin levels (figure-1) ,whereas ,fasting serum glucose level in obese patients were not significantly elevated as

compared to control subjects. This may be caused by the low serum adiponectin levels (figure-2), which is negatively correlated with BMI, fasting serum glucose, insulin, HOMA-IR (figure -3). The correlations between serum adiponectin level and insulin, HOMA-IR. In a study of Pima Indians, Weyer et al. reported that the plasma adiponectin level was positively correlated with insulin sensitivity⁽³⁵⁾. However, they did not check the relationship between adiponectin and Lipids.

Others studies have shown recently that administration of thiazolidinediones increases plasma adiponectin levels in diabetic subjects⁽³⁶⁾. In present study serum levels of triglyceride, total-,LDL-, and VLDL-Cholesterol, were elevated, but HDL was decreased in obese patients as compared to controls table -1. These results are in agreement with previous studies⁽³³⁾. These results may be due to lowered serum adiponectin level in obese patients, adiponectin positively correlated with BMI, FSG and negatively correlated with HDL-cholesterol, insulin and resistin (figure-3), although these correlations were not significant. Whereas the correlations between serum adiponectin level and insulin, HOMA-IR, triacylglycerols, HDL-cholesterol, LDL-cholesterol and uric acid were significant even after adjustment for age, sex and BMI⁽³⁷⁾. In humans, data regarding a possible association of adiponectin receptor expression in adipose tissue or skeletal muscle and obesity or insulin resistance were highly divergent and dependent on the population studied. Furthermore, although polymorphisms in adiponectin receptor genes have been found to be associated with insulin resistance and type 2 diabetes, these associations have not been replicated widely across populations. Thus, the number of studies available to date is still too small to draw firm conclusions on the role of variability in AdipoR1 and/or AdipoR2 expression in predicting insulin resistance and related disorders. Upregulation of adiponectin/adiponectin receptors or enhancing adiponectin receptor function may represent an interesting therapeutic strategy for obesity-linked insulin resistance⁽¹⁾. In our study the serum levels of Adiponectin, was decreased in obese patients as compared to controls. These results are in agreement with previous studies. Adiponectin was found to be decreased in obesity.⁽³⁸⁾ This down regulation has not been fully explained. The gene was localised to chromosome 3q27, a region highlighted as affecting genetic susceptibility to type 2 diabetes and obesity⁽³⁹⁾. Moreover, adiponectin may possess anti-atherogenic properties by inhibiting the expression of adhesion molecules and smooth muscle cell proliferation, as well as suppressing the conversion of macrophages to foam cells⁽⁴⁰⁾. Secretion of adiponectin from epididymal rat adipocytes is susceptible to the short-term regulation by insulin, epinephrine, adenosine and energy deprivation. It was found that insulin potentiated adiponectin secretion⁽⁴¹⁾. However, reports recorded adiponectin levels to be tend to decrease throughout puberty, which parallels the development of IR⁽⁴²⁾. Furthermore, the glomerular filtration rate has been recognized as a strong inverse predictor of serum adiponectin. The clearance of adiponectin by the kidney may have a strong influence on its concentration⁽⁴³⁾. Hence, high adiponectin levels may reflect impaired renal

function. Last but not least, an increased adiponectin level has been suggested to act as a compensatory mechanism to dampen inflammation. Indeed, elevated plasma adiponectin concentrations are observed in several diseases associated with inflammation: arthritis⁽⁴⁴⁾, preeclampsia⁽⁴⁵⁾, and end-stage renal disease⁽⁴⁶⁾. All of these factors must be considered when evaluating the clinical significance of circulating adiponectin levels in metabolic syndrome or vascular diseases related to obesity⁽⁴⁷⁾. Resistin was originally described as an adipocyte-derived polypeptide that provided the link between obesity and insulin resistance⁽⁴⁸⁾. Resistin is expressed at very low levels, if at all, in resting endothelial cells, and in placenta⁽⁴⁹⁾. However, no difference in resistin expression in adipocytes and myocytes was found between nondiabetic vs type 2 diabetic subjects, although the circulating levels of resistin in these groups were different. It has been shown in subjects with type 2 diabetes that increased C-reactive protein levels are related to higher circulating levels of resistin but also other cytokines are elevated⁽⁴⁸⁾. Human resistin gene polymorphisms have showed that resistin single nucleotide polymorphisms were associated with an insulin sensitivity index or risk of type 2 diabetes in non diabetic obese people, suggesting that resistin may be related to insulin resistance⁽⁵⁰⁾. In this study the serum levels of resistin, was elevated in obese patients as compared to controls (figure -2) These results are in agreement with previous studies, that reported that resistin is predominantly secreted by adipose tissue macrophages. Resistin has a controversial history regarding its role in the pathogenesis of obesity-mediated insulin resistance and type 2 diabetes⁽⁵¹⁾. Although a clear function for resistin in glucose metabolism in humans is still lacking; data indicate that resistin has a role in inflammatory⁽⁵²⁾. Resistin is secreted by mature adipocytes in proportion to the level of obesity and acts on insulin-sensitive cells to antagonize insulin-mediated glucose uptake and utilization in mice. Treatment of wild-type mice with recombinant resistin resulted in IR, whereas administration of an anti-resistin antibody increased insulin sensitivity in obese and insulin-resistant animals⁽⁵³⁾. The circulating resistin level is also reported to be an inflammatory marker of atherosclerosis⁽⁵⁴⁾. However, the resistin levels in humans are thought to correlate more closely with inflammation than with insulin resistance⁽⁵⁵⁾. Our results indicated that adiponectin resistance, induced by a high-fat diet, causes dysregulation of lipid metabolism in skeletal muscles and contributes to the development of insulin resistance⁽⁵⁶⁾. An inverse correlation between adiposity and blood adiponectin is well documented⁽⁵⁷⁾. Importantly, weight reduction can significantly increase blood adiponectin levels in both diabetic and non-diabetic subjects⁽⁵⁸⁾. In addition to its insulin-sensitizing effects, adiponectin may alter glucose metabolism through stimulation of pancreatic insulin secretion⁽⁵⁹⁾, a part from peripheral action, adiponectin was shown to modulate food intake and energy expenditure during fasting (increased food intake and reduced energy expenditure) and re-feeding (produces opposite effects) through its action in the central nervous system⁽⁶⁰⁾. In conclusion obesity is a chronic state of inflammation associated with pre-diabetic state because of increased production of inflammatory mediators,

indicating existence of insulin resistance state among obese non-diabetic patients presented by altered serum adiponectin and resistin levels

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