Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231-6345 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jls.htm
2014 Vol. 4 (1) January - March, pp.438-443/Sabegh and Vasmehsara
Research Article

SERUM TNF-A CAN BE AFFECT FASTING GLUCOSE INDEPENDENT OF INSULIN RESISTANCE IN OBESE OR OVERWEIGHT FEMALES

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ABSTRACT

Tumour necrosis factor-alpha (TNF-α) as a pro-inflammatory cytokines are produced by human adipose tissue dependent on the degree of obesity. The objective of this study was to estimate the association in serum TNF-α with insulin resistance and glucose in obese or overweight women. For this purpose, thirty middle-aged women aged 38 ± 5 year and body weight 82 ± 7 kg were participated in this study. Venous blood samples were collected after an overnight fat between 7:00 and 8:00 a.m. and serum separate immediately in order to measuring insulin and TNF-α. The insulin resistance index was assessed by homoeostasis model assessment (HOMA-IR). Statistical analysis was performed with the SPSS software version 15.0 using a Pearson's correlation tests. The level of significance was taken as $p<0.05$). A positive correlation was found between serum and TNF-α ($p = 0.006$, $r = 0.49$). There were no correlations between serum TNF-α concentrations and insulin resistance and insulin in studied subjects ($p\geq0.05$). Based on these finding, it is concluded that TNF-α as an inflammatory cytokine can be affect glucose independent of insulin resistance. However, the mechanisms underlying the effect of inflammatory cytokines on insulin resistance would require further studies.

Keywords: *Insulin Resistance, Obesity, Inflammation*

INTRODUCTION

Undoubtedly, several studies compared baseline levels of inflammatory or anti-inflammatory cytokine or other adipocytokine between different populations, such as obese or normal, diabetic and non-diabetic, athletes and non-athletes or healthy populations and patients. Contradictory findings were obtained in these studies. In addition to social and psychological problems, obesity, especially abdominal obesity, is responsible for prevalence of many chronic diseases and perhaps such irreversible diseases as heart-cardiovascular diseases, diabetes, liver and respiratory diseases and some cancers (Campfield *et al.*, 1995; Vanltallie, 2001; Alexandraki *et al.,* 2006). The hormonal is considerably important in imbalance in incidence of obesity and related diseases Scientific resources suggested the potential impact of impaired secretion of such peptide hormones as leptin, ghrelin, resistin and other anti-inflammatory and proinflammatory cytokines in incidence of obesity and relevant abnormalities. The baseline levels of these inflammatory mediators in overweight and obese individuals differ from healthy individuals with normal weight (McMurray *et al.,* 2005). It was also found out that in addition to genetics and lack of exercise, obesity is the most important environmental factors underlying the prevalence of insulin resistance syndrome, which consequently make a balance between losing weight or reducing body fat levels as well as insulin levels and reducing insulin resistance (Bjornholt *et al.,* 2000; Bennett *et al.,* 2004).

Cytokines are such inflammatory mediators produced by blood mononuclear cells, adipocytes and hepatocytes and skeletal muscles (Charles *et al.,* 2008). Tumor necrosis factor-alpha (TNF-α) is the most important inflammatory cytokine in incidence of metabolic abnormalities such as obesity and insulin resistance (Ye, 2008). It is reported that TNF-α levels are increased in the presence of obesity (Warne,

2003). Several scientific resources showed that TNF-α levels increased 7.5 times in obese populations compared with lean subjects (Kern *et al.*, 1995). However, scientific resources have consistently supported increased insulin resistance in obese individuals (Galica *et al.*, 2003; Shimizu *et al.*, 2007). In addition to the effects on various organs, TNF-α also plays an important role in pathogenesis of obesity and insulin resistance (Skolnik *et al.*, 1995). Although both TNF-α levels and insulin resistance in obese individuals increases, the molecular mechanisms between these two variables are not yet entirely clear. It is not clear whether the change in each of them is associated with a change in another or they are independently affected by obesity. The present study aimed to examine the relationship between TNF-α as an inflammatory cytokine with insulin resistance and fasting serum glucose and insulin levels.

MATERIALS AND METHODS

***Subjects*:** Subject was twenty nine middle-aged apparently healthy obese overweight women were recruited for this study through local advertising. Subjects aged 38 ± 5 year years old with a body mass index (BMI) of 31.1 ± 2.4 kg/m2. The study aimed to determine relationship between serum TNF-α with insulin resistance in glucose in mentioned subjects. After the nature of the study was explained in detail, informed consent was obtained from all participants. The weight and height of the participants were measured by the same person when the participant had thin clothes on and was wearing no shoes. BMI was calculated as weight (kg)/height (m2). Abdominal-to-hip ratio was calculated as abdominal circumference divided by hip circumference as measured to the nearest 0.5 cm with a standard measuring tape. Visceral fat and body fat percentage was determined using body composition monitor (OMRON, Finland).

***Inclusion and Exclusion Criteria*:** Subjects were non-smoker and non-pregnancy. Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. None of the subjects used drugs or therapies for obesity. Furthermore patients with overt diabetic were also excluded from the study. Those with known history of acute or chronic respiratory infections, neuromuscular disease and cardiopulmonary disease were excluded. Exclusion criteria also included medications that alter carbohydrate metabolism.

***Blood Samples and Biochemistry*:** Blood samples were taken between 7:00 and 8:00 a.m. after 10 to 12 hours overnight fast to measure fasting glucose, insulin and serum TNF-α. All participants refrained from any severe physical activity 48 h before measurements. Serum glucose was determined by enzymatic (GOD-PAP, glucose oxidase-amino antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran). Blood samples were dispensed into EDTA-coated tubes and centrifuged for 10 minutes in order to separate serum. Serum TNF-α and insulin were measured by Eliza method. Insulin resistance was derived using the HOMA method using the following formulae: Insulin resistance (HOMA-IR) = [fasting insulin (μ/ml) × fasting glucose (mmol/l)] / 22.5 (Marita *et al.*, 2005)

***Statistical Analysis*:** Statistical analysis was performed with the SPSS software version 15.0 using a Pearson correlation method to determine the relationship between serum TNF-α with glucose, insulin and insulin resistance. A p-value of less than 0.05 was considered statistically significant and all reported p-values were 2 two-tailed.

RESULTS

Means and standard deviations were calculated for all variables. Anthropometric and clinical characteristics of the study participants are shown in Table 1. Table 2 also shows the relationship between serum TNF-α with insulin resistance, glucose and insulin. Based on these data, serum TNF-α positively correlated with fasting glucose concentration ($p = 0.006$, $r = 0.49$, Fig 1). No significant correlation was observed in serum TNF-α and insulin resistance ($p = 0.64$, $r = 0.09$, Fig 2). Serum TNF-α was not also correlated with serum insulin ($p = 0.29$, $r = 0.20$).

Table 1: The descriptive anthropometric and biochemical features of the studied subjects

	N	Minimum	Maximum	Mean	Std. Deviation
Age (year)	29	28	46	37.76	4.533
Height (cm)	29	152	172	160.93	5.787
Weight (kg)	29	67	96	81.76	6.956
Abdominal (cm)	29	96	124	108.91	7.448
Hip (cm)	29	100	123	112.78	5.703
WHO	29	.79	1.08	.9662	.06167
BMI (kg/m2)	29	28	39	31.58	2.366
Body fat (%)	29	4	54	43.92	8.183
TNF-a (pg/ml)	29	18	50	36.41	10.030
Glucose (mg/dl)	29	74	114	89.41	10.259
Insulin (µIU/ml)	29	2.00	18.80	7.1731	4.35896
Insulin Resistance (HOMA-IR)	29	.42	4.50	1.5562	.93653

Table 2: the correlation between serum TNF-α and other clinical variables in studied subjects. Data by Pearson correlation method

		TNF-a (pg/ml)	Glucose (mg/dl)	Insulin (µIU/ml)	Insulin Resistance (HOMA-IR)
TNF-a (pg/ml)	Pearson Correlation	1	.494**	.090	.202
	Sig. (2-tailed)		.006	.641	.294
	N	29	29	29	29
Glucose (mg/dl)	Pearson Correlation	.494**	1	-.250	-.088
	Sig. (2-tailed)	.006		.190	.648
	N	29	29	29	29
Insulin (µIU/ml)	Pearson Correlation	.090	-.250	1	.981**
	Sig. (2-tailed)	.641	.190		.000
	N	29	29	29	29
Insulin Resistance (HOMA-IR)	Pearson Correlation	.202	-.088	.981**	1
	Sig. (2-tailed)	.294	.648	.000	
	N	29	29	29	29

***Correlation is significant at the 0.01 level (2-tailed)*

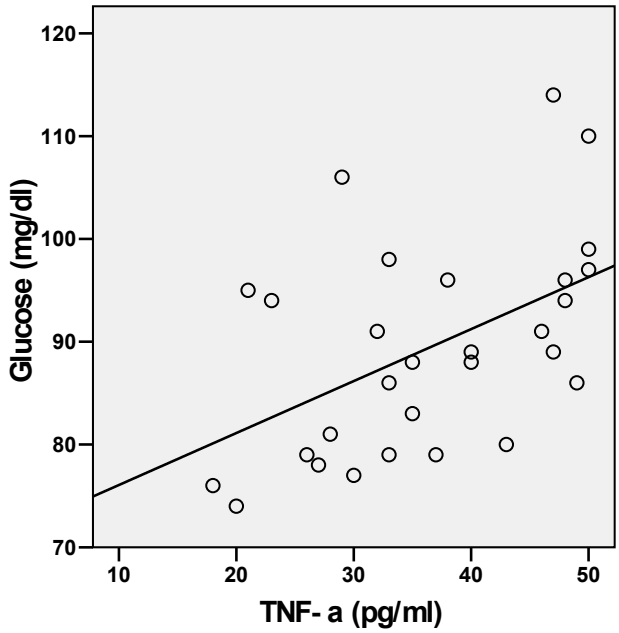

Figure 1: Positive significant correlation between serum TNF-α and fasting glucose in studied subject

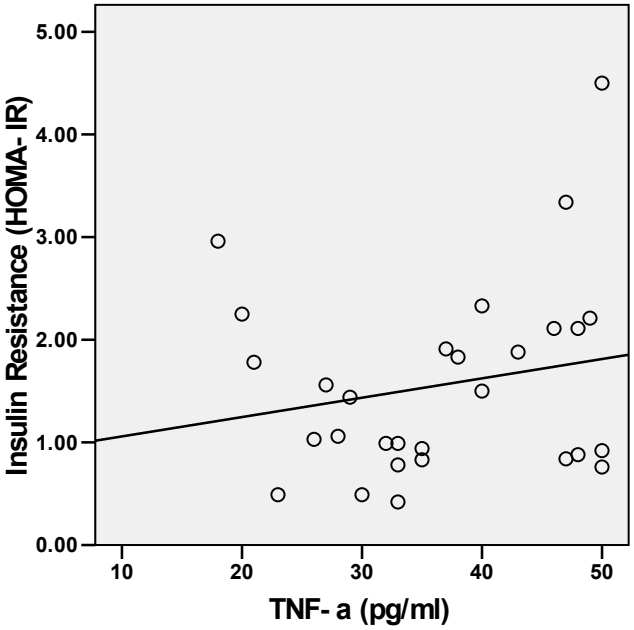

Figure 2: No correlation between serum TNF-α and insulin resistance in studied subject

DISCUSSION

It was reported by many previous studies or researchers that overweight are the most important predictor of chronic diseases or many metabolic disorders. The studies conducted over the past two decades aimed to determine the effective molecular obesity mechanisms in chronic diseases associated with insulin resistance. Although various findings were obtained dependent on the type of population studied or obesity levels or severity of relevant diseases, a consensus on this issue is not achieved yet. Most

scientific studies supported increased TNF-α and insulin resistance or blood glucose in obese subjects (Uysal *et al.*, 1997).

Based on this evidence, it seems that increased levels of TNF-α as an inflammatory cytokine leads to increased blood glucose levels and insulin resistance in obese individuals or patients. However, the findings obtained in this study showed that there is no relationship between this inflammatory cytokine with insulin resistance in obese females. Based on these findings, it seems that TNF-α levels and insulin resistance in obese individuals are completely independent of each other. However, based on the findings obtained from previous studies, the results of the present study is somewhat controversial. Academic sources showed multiple function of this inflammatory cytokine such as cardiomyocyte hypertrophy and impaired contractile function (Murray *et al.*, 2003). Although adipose tissue is a major source of secretion of this inflammatory mediator, macrophages and other cells are involved in its plasma levels. This mediator is effective inflammatory processes, which was reported frequently. Higher levels of this mediator are associated with increased synthesis and secretion of other inflammatory cytokines such as IL-8 (Gerszten *et al.*, 1999). It was also found out that higher level of TNF-α is associated with increased production of vLDL, which suggest the relationship between this cytokine and plasma triglycerides (Qin *et al.*, 2008). Literature often suggests higher levels in obese individuals. Weight loss is also introduced as an effective factor in improvement or reduction in plasma or serum levels of TNF-α in obese healthy subjects or patients (Puglisi *et al.*, 2008).

Literature has always emphasized that TNF-α is effective in incidence of metabolic abnormalities such as obesity and insulin resistance (Ye, 2008). The role of this inflammatory cytokine in pathogenesis of obesity and insulin resistance was reported earlier (Liang *et al.*, 2008). TNF-α leads to insulin resistance due to disruption in mediated signals of insulin receptors (Shimizu *et al.*, 2007). Academic sources also reported that TNF-α negatively regulate genes that are required for normal function of insulin and accelerate the increase in free fatty acids through lipolysis (Moller, 2000). It is also found out that weight loss in obese patients is associated with reduced both insulin resistance and TNF-α (Dandona *et al.*, 1998).

Previous studies on obese humans and animal species showed that increased secretion of TNF-α by adipose tissue is associated with decreased insulin sensitivity (Hotamisligil *et al.*, 1993; Hofmann *et al.*, 1994) and changes in TNF-α expression in adipose tissue is directly related to the degree of obesity and hyper insulin levels (Hotamisligil *et al.*, 1993; Hotamisligil *et al.*, 1995). Despite diverse findings on importance of TNF-α as an inflammatory cytokine in obesity and insulin function, these findings showed that there is no relationship between these variables. Based on these findings, it can be concluded that TNF-α levels and insulin resistance are both independently affected by obesity. In addition, TNF-α may indirectly affect blood glucose levels independent of insulin function. However, lack of relationship between these variables may be due to small sample size, which is considered as one limitation of the present study.

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