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Pro-inflammatory Cytokine does not affect indicator markers of type II Diabetes directly

Seyyed Rafi Shafabakhsh Kolor, Mona Hafezi and Mehdi Ebrahim Baysalami
Department of Physical Education and Sport Sciences,
Islamshahr Branch, Islamic Azad University, Islamshahr, IRAN

(Corresponding author: Seyyed Rafi Shafabakhsh Kolor)
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ABSTRACT: Pro-inflammatory cytokines have emerged over the last decade as key adipokine linking obesity, insulin resistance and type 2 diabetes, although the physiopathological mechanisms underlying these associations are largely unknown. In present study, we aimed to determine the relation of serum Tumor necrosis factor-alpha (TNF-α) as proinflammatory cytokine with some indicators of type II diabetes. To achieve this outcome, fasting blood glucose (FBG), insulin and serum TNF-α were measured in thirty adult men with type II diabetes. Insulin sensitivity and beta cell function were calculated by fasting glucose and insulin. Statistical analysis was performed with the SPSS software version 15.0 using a Pearson's correlation coefficient. A P-value of < 0.05 was considered to be statistically significant. Data showed that serum TNF-α is not correlated with mentioned variables. Based on these data, we can say serum TNF-α does not affects indicator markers of type II diabetes. In seems that this pro-inflammatory cytokine affect glucose and insulin action by indirectly.

Keywords: Pro-inflammatory cytokine, diabetes, Insulin action

INTRODUCTION

Today, diabetes especially type II has become the locus of many health and hygiene researchers. Such that, at least in the past two decades, the number of studies on the causes of diabetes prevalence, as well as the methods used for treating and reducing its severity have been reporter far larger than other diseases. Type 2 diabetes is the most common endocrine disease caused by glucose resistance due to the imbalance between insulin supply and demand.

Although the pathophysiologic mechanisms of insulin resistance and impaired insulin secretion, as the major determinants of diabetes 2, have not been yet fully understood, clinical studies have repeatedly indicated the axial role of markers or pre-inflammatory cytokines increase in the pathogenesis of type 2 diabetes and insulin resistance. Over the past two decades, the role of peptides released from the fat tissues, as well as the inflammatory cytokines secreted from the fat and other body tissues, especially in obese people and those with high levels of fat, have been found with central importance in the development of such chronic diseases as type II diabetes, cardiovascular diseases, and metabolic syndrome. Their important role is specifically highlighted in corporation with a low active life style of obese people in the severity of this and other obesity related diseases.

As the majority of peptides, particularly inflammatory cytokines, are released from the fat tissue, higher levels of obesity are associated with increased secretion of them; therefore, several studies have been conducted on the effect of these cytokines, especially on the prevalence and/or severity of type II diabetes. Since inflammatory cytokines secretion increase occurs also in non-diabetic obese people, this question has been recently arisen that whether inflammatory markers impairment can directly determine type II diabetes or the obesity of diabetic patients charges the levels of these variables. Among the inflammatory cytokines, it has been determined that Tumor necrosis factor-alpha (TNF-α) is with an important role in the development of metabolic abnormalities such as obesity and insulin resistance. In addition, obesity is associated with increased level of TNF-α. Thus, its increase is expected in the obesity caused diseases (e.g. cardiovascular or type II diabetes). Yet, the relationship between its levels and the determinants of such chronic diseases, as type 2 diabetes, has less been investigated. In the present study, the serum levels of TNF-α will be recognized with type II diabetes determinant indices such as glucose, insulin sensitivity, and B-cells performance.

MATERIAL AND METHODS

A. Human subjects, Inclusion and exclusion criteria

Subjects were thirty six sedentary adult men with type II diabetes that participated in study by accessible sample.

A medical history to retrieve information about health status, current medications and a physical examination including height, weight, waist circumference and blood pressure were monitored of all patients. Inclusion criteria were Type 2 diabetes diagnosis, Overweight or obese stable body weight for 6 months. Subjects had not participated in regular exercise for the preceding 6 months, nor did all subjects have stable body weight. All subjects were non-smokers. The exclusion criteria were infections, renal diseases, hepatic disorders, use of alcohol and a history of other chronic diseases. After introduction and awareness of the subjects of the objectives of the study and once they had completed consent forms.

B. Anthropometric measurements

Obesity was measured by body mass index (BMI). Body mass index was measured for each individual by division of body weight (kg) by height (m^2). After signing the consent, subjects were weighed without shoes on a calibrated digital scale (Omrun, B590, Finland)) to the nearest 0.1 kg. Height measurements were obtained barefooted at midexpiration and recorded to the nearest 0.5 cm using a stadiometer. Blood pressure was measured using the left arm after the subject had been sitting comfortably for 5 min, using an oscillometric device (Alpikado, japens). The waist girth was measured at the level of the umbilicus horizontally without clothing, while the hip girth was measured at the level of the greatest protrusion of the gluteal muscles with underwear. Waist-hip ratio (WHR) was calculated. All of these measurements were conducted by the same researcher. Each of these measurements was conducted two times and the average was reported.

C. Blood analysis

Blood was drawn after 12 h of fasting and 48 hours without physical activity. Those patients unable to avoid taking hypoglycemic drugs or other therapeutic drugs within 12 hours before blood sampling were barred from participating in the study. Blood samples were obtained were taken between 8:00 and 9:00 a.m, and then centrifuged for separate serum. Serum used to measuring insulin and TNF-α by ELISA method. Glucose was determined by the oxidase method (Pars Azmoon kit, Tehran). The homoeostasis model assessment (HOMA) for estimating insulin sensitivity and Beta cell function was calculated using by fasting insulin and glucose concentration.

D. Data analysis

After calculation of the mean and the standard deviation, the statistical analysis was conducted using the SPSS software version 15.0. Kolmogorov-Smirnov test was used to determine of normal status of the data. The bivariate associations between serum and beta cell function, insulin sensitivity or others were examined with the Pearson rank correlation analysis. A p-value of less than 0.05 was considered statistically significant and all reported p-values were 2 two-tailed.

RESULTS

This study aimed to determine the relation of serum TNF-α with beta cell function, insulin sensitivity and glucose concentration as indicator markers of diabetes. As mentioned above, at first, we measured anthropometrical and metabolic markers. Anthropometric and metabolic characteristics of the study participants are shown in Table 1.

ble 1: Descriptive Statistics of anthropometric and metabolic characteristics of studied patients

	Minimum	Maximum	Mean	Std. Deviation
Age (year)	36	49	41.89	3.808
Height (cm)	165	180	173.42	3.065
Weight (kg)	78	103	92.31	6.422
Systole (mmHg)	11	17	13.11	1.508
Diastole (mmHg)	7	11	8.72	.914
Abdominal (cm)	94	117	104.64	6.081
Hip (cm)	95	113	102.42	4.544
WHO	.98	1.08	1.0222	.02269
BMI (kg/m2)	25.76	34.72	30.7006	2.09012
Body fat (%)	21.3	33.9	29.292	2.9948
Visceral Fat	9	16	12.78	1.476
TNF-a (pg/ml)	20	77	35.95	9.168
Insulin (µIU/ml)	4.5	12.2	8.336	1.7155
Insulin Sensitivity (HOMA-IS)	.47	.65	.5139	.03782
Insulin resistance (HOMA-IR)	1.53	5.92	4.1642	1.01794
Beta cell function (HOMA-BF)	10.7	47.7	23.533	9.3465
Glucose (mg/dl)	138	296	204.11	45.473

We also stipulate previous that the relation of serum TNF-α and beta cell function is main objective of our study. Based on Pearson correlation method, serum TNF-α was not correlated with beta cell function (p = 0.62, r = 0.09, Fig. 1) in studied subjects. No significant correlation were found between this pro-inflammatory cytokine with insulin sensitivity (p = 0.64, r = 0.08, Fig. 2) and glucose concentration (p = 0.56, r = 0.10) and serum insulin (p = 0.43, r = 0.14) in studied patients.

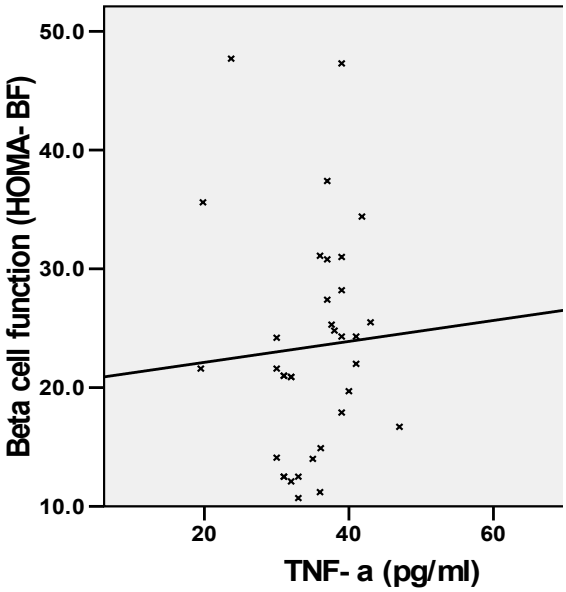

Fig. 1. This Fig shows the serum TNF-α is not related with Beta cell function in diabetic patients.

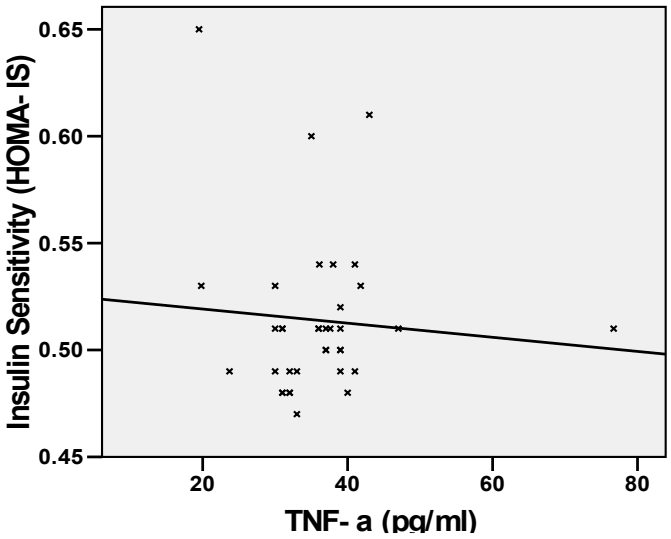

Fig. 2. This Fig shows the serum TNF-α is not related with insulin sensitivity in diabetic patients.

DISCUSSION

Although the majority of recent studies have noted the increased cytokines levels in obesity related chronic diseases as type II diabetes, findings of this study show that TNF-α level in such patients is not related to the blood glucose and other influential factors. In other words, based on the findings of this study, TNF-α serum levels in type II diabetic patients are not significantly associated with insulin sensitivity, B-cells performance, blood glucose levels, and insulin. Although, these findings are debatable, they pave the way for further investigations in the field. It has been determined that many obesity related abnormalities like hypoglycemia, hypertension, atherosclerosis, insulin resistance, dyslipidemia and inflammation in the etiology of coronary artery disease are the consequences of type II diabetes. Insulin resistance syndrome plays an important role in thepathogenesis of type II diabetes and cardiovascular diseases, in which multiple mechanisms involve. Although the main involved mechanisms in a relationship between increased adipocytes and insulin resistance has not been fully understood, increased fat tissue has a central role in this phenomenon. On the other hand, the role of inflammatory mediums should be taken into consideration. TNF-α is mainly synthesized and released from the fat tissue, in which macrophages are also involved. Recent studies have noted the significant correlation between the TNF-α systematic levels and the risk of cardiovascular factors such as the blood triglyceride levels. Its multiple functions such as hypertrophy, cardioset, and impaired contractile function have previously been reported. Based on some clinical studies, it has been determined that their level in obese people is 7.5 times higher than people with healthy weights. Moreover, researchers have referred to the increased production of vLDL through TNF-α to explain the relationship pf cytokines to TG. Furthermore, researchers have noted that the synthesis of muscular proteins is inhibited via higher levels of inflammatory cytokines. Increase in its systematic levels is known as an inflammatory marker in obese people; in addition, weight loss has been introduced as a key intervention to decrease its plasma concentration. TNF-α is indeed one of the most important cytokines secreted from fat tissue, and increases the presence of other inflammatory cytokines such as IL-6 and IL-1 in the blood. On the other hand, it has been found that TNF-α, as an inflammatory marker, is correlated with hyperglycemia, insulin resistance, and type II diabetes. Additionally, its major role has been discovered in the inflammatory processes, such that its increased concentration accelerates the synthesis of some inflammatory interleukin. Its plasma concentration is positively correlated with TG, which has a major role in such metabolic abnormalities as obesity, type 2 diabetes, insulin resistance, and cardiovascular diseases. Yet, the findings of this study support the lack of relationship between it and other factors that affect type II diabetes.

Based on these evidence, it may be concluded that TNF-α, as a pre-inflammatory cytokines, does not directly affect the factors that have influence on type II diabetes. On the other hand, some studies have noted that there is not any significant difference in the plasma levels of pre-inflammatory cytokines, as well as other adipocytokines between non-obese diabetics patients and healthy people. In fact, according to the research findings, level changes of the mentioned variables can be attributed to obesity, and not to type II diabetes. In supporting the findings of this research, some recent studies have also reported the lack of significant correlation between insulin resistance with pre-inflammatory cytokines (i.e. TNF-α, CRP, and IL-6). In this regard, Gomez *et al.* (2009) have also shown that TNF-α is not a determinant of vascular inflammation in diabetic rats.

Yet, although some previous studies have reported findings consistent with the present research, the lack of significant correlation between INF-α and the effective factors in type 2 diabetes can be attributed to the small sample size, as a limitation of this study. Therefore, conduction of similar studies with more samples is recommended.

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