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Interleukin-1 beta is increased in presence of type 2 diabetes in addition to adiposity level

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Abstract

A large body of evidence suggests an inflammatory process; characterized by adipokines production regulates islet dysfunction and insulin resistance in type 2 diabetes. The present study is an attempt to find if serum IL-lb in diabetic subjects is increased with obesity, or diabetes disorder independent of body weight and fat level affects serum levels of this cytokines. For this purpose, fasting serum IL-1b and markers indicative of type 2 diabetic such as glucose, insulin resistance and Beta-cell function were measured in middle-aged obese men with type 2 diabetic (n=16) and those without diabetic (n=16) matched for age (38 ± 5, aged) in order to compare them between two group. Anthropometrical measurements were also performed of two groups. Diabetic patients have higher fasting glucose, insulin resistance and lower beta cell function than none-diabetic subjects. Serum IL-1b in diabetic patients was also significantly higher than none-diabetic subjects. Although participants of both diabetic and non diabetic groups were classified as obese, serum IL-1b in diabetic patients was higher than another group. Based on these data, we can say the presence of diabetes affect serum IL-1b independent of body fat levels or adiposity.

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Introduction

Chronic disease has been strongly associated with inflammation resulting from the body's release of inflammatory cytokines as a result of injury or infection (Puglisi *et al.,* 2008). Accumulating evidence indicates that White adipose tissue (WAT) metabolism and WAT-derived factors (fatty acids and adipokines) play an important role in the development of these metabolic disturbances (Moreno-Aliaga *et al.,* 2010).

It is reported that Pro-inflammatory cytokines such as interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNFalpha) are produced by human adipose tissue dependent on the degree of obesity (Moschen et al., 2010). Obesity in known to be associated with several chronic morbidities including type 2 diabetes, dyslipidaemia, atherosclerosis and hypertension, which are major components of the metabolic syndrome (Moschen *et al.,* 2010). Obesity particularly marked visceral obesity is associated with early-onset type 2 diabetes (Burns *et al.,* 2007). Sedentary, Inactive lifestyle, overweight, and obese individuals are generally insulin resistant but often are able to maintain normal glucose tolerance through compensatory increases in pancreatic insulin secretion (Cris *et al.,* 2009).

Type 2 diabetes, heart disease and metabolic syndrome have in common the increased concentration of circulatory cytokines as a result of inflammation (Ross, 1999). The inflammatory cytokines are secreted into circulation where they regulate different tissues through their local, central, or peripheral actions (Bruun *et al.,* 2003). There is considerable evidence that Type 2 diabetes mellitus (T2D) is predicted by central obesity and circulating adipokines regulating inflammation (Samaras *et al.,* 2010).

Recently there have been many research studies that repetitively report higher levels of inflammation cytokines such as IL-lb in obese people as compared to the people with normal weight individuals (Moreno-Aliaga *et al.,* 2010; Moschen *et al.,* 2010; Biasucci *et al.,* 2010) as well as the diabetic people compared with the non-diabetics (Samaras *et al.,* 2010). On the other hands, obesity is recognized as one of the factors contributing to the prevalence of type 2 diabetes (Burns *et al.,* 2007). Few studies have so far investigated whether inflammation cytokines in diabetics are increased in response to obesity, or diabetes affects serum levels of these cytokines independent of body weight and fat level. Therefore, this study compares levels of inflammation cytokine IL-lb of diabetic and non-diabetic obese subjects.

Material and methods

This study compared serum IL-1b and markers indicative of type 2 diabetic between none-trained adult obese males with and without type 2 diabetic. The study was conducted with the approval of the Ethics Committee of Islamic Azad University, Iran.

Subjects

Subjects were sixteen middle-aged none-trained obese men with type II diabetes and sixteen none-diabetic healthy subjects matched for age (38 ± 5 years of old) and BMI (30 ≤ BMI ≤ 36) that participated in this study by accidentally samples. After the nature of the study was explained in detail, informed consent was obtained from all participants.

Inclusion or exclusion criteria

Participants were included if they had not been involved in regular physical activity in the previous 6 months. None of the participants had ongoing cardiovascular disease, infections, renal diseases, hepatic disorders, use of alcohol, and use of nonselective β blockers and presence of malignancy. Participants were non-athletes, non-smokers and non-alcoholics. Inclusion criteria for study group were determined as existing type 2 diabetic for at least three years. Those that were unable to avoid taking hypoglycemic drugs or insulin sensitivity-altering drugs for 12 hours before blood sampling were also barred from participating in the study. Subjects were asked to avoid doing any heavy

physical activity for 48 hours before blood sampling.

Anthropometric measurements

Anthropometric measurements (body height and weight, abdominal and hip circumference) were performed with the subjects wearing light underwear and without shoes in the morning following a 10-h fast. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Hip circumference was measured at the level of the greater trochanter. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m). Waist and hip circumferences were measured and a waist-to-hip ratio (WHR) was calculated. Percentage body fat was measured using body composition monitor (OMRON, Finland).

Biochemical analysis

After anthropometric measurements, blood samples were taken between 8:00 and 9:00 a.m. after 10 to 12 hours overnight fast to measure fasting glucose, insulin and serum IL-1b. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated by the formula fasting blood glucose (mg/dl) x insulin (uIU/ml)/405 (Matthews *et al.,* 1985). Using fasting glucose and insulin concentration, beta cells function was measured. Beta cell function (HOMA-BF) = [(20 × fasting insulin (μ/ml] / [Fasting glucose (mmol/l) – 3.5] (Greenman *et al.,* 2004).Glucose was determined by the oxidase method (Pars Azmoon kit, Tehran). Serum IL-1β was determined by ELISA method (Enzyme-linked Immunosorbent Assay for quantitative detection of human IL-1β), using a Biovendor- Laboratorial kit made by Biovendor Company, Czech. The Intra- assay coefficient of variation and sensitivity of the method were 5.1% and 0.3 pg/mL, respectively. Insulin was determined by ELISA method (Demeditec, Germany) and the intra- assay and inter-assay coefficient of variation of the method were 2.6% and 2.88 respectively.

Statistical analysis

Statistical analysis was performed with the SPSS software version 15.0. The Kolmogorov-Smirnov test was applied to determine the variables with normal distribution. An Independent sample T-test was used to compare anthropometrical and biochemical variables between diabetic and none-diabetic subjects. The bivariate associations between IL-1b concentration with glucose, insulin and beta-cell function were examined with the Spearman rank correlation analysis. A p-value less than 0.05 were considered statistically significant.

Results

Anthropometric and metabolic characteristics of the study participants in the diabetic and none-diabetic groups are shown in Table 1. Data were expressed as individual values or the mean ± SD. Significant differences were not found in body weight, BMI, body fat percentage and other anthropometrical markers between diabetic patients with those without Type 2 diabetes ($p \geq 0.005$). These finding points out those body fat levels were similar in diabetic and non-diabetic subjects in this study. However, no significant differences were observed in body fat percentage or adiposity between groups, but Serum IL-1b level in diabetic patients was significantly higher than those healthy obese subjects ($p = 0.028$, Fig. 1). Diabetic participants had higher fasting glucose (Fig. 2) and insulin resistance than healthy subjects ($p = 0.011$). Beta cell function in diabetic was significantly lower in diabetic patients ($p = 0.023$, Fig 3). A significant positive association was observed between serum IL-1b with fasting glucose and insulin resistance in bout diabetic ($p = 0.021$, $r = 0.55$) and none-diabetic ($p = 0.19$, $r = 0.59$) subjects. IL-1b were also negatively correlated with Beta-cell function in bout groups (diabetes: $p = 0.012$, $r = 0.61$, Fig 4; none-diabetes: $p = 0.026$, $r = 0.60$). Significant negative correlations was found between serum insulin and IL-1b in diabetic patients ($p = 0.019$, $r = 0.63$). The association between serum IL-1b and insulin resistance was borderline significant ($p = 0.065$).

Table 1. Mean and standard deviation of anthropometric and metabolic characteristics of studied subject.s

Variables	Diabetic group	None-diabetic group
Age (year)	38 ± 5.3	39 ± 6.1
Weight (kg)	93 ± 7.6	95 ± 8.5
Height (cm)	176 ± 7.6	177 ± 5.6
Body Fat (%)	29.6 ± 4.11	30.2 ± 4.23
Body mass index (kg/m²)	30.01 ± 3.14	30.32 ± 2.65
Abdominal circumference (cm)	105 ± 7.21	107 ± 9.2
Glucose (mg/dL)	244 ± 52	101 ± 19
Insulin resistance	5.01 ± 1.68	1.97 ± 0.65
Beta-cell function	25 ± 6.42	75 ± 17.6
IL-1b (pg/ml)	2.56 ± 1.2	3.25 ± 1.14

** represent significant differences in variables between two groups.*

Discussion

The current study demonstrated higher insulin resistance, fasting glucose concentration and serum IL-1b in diabetic patients than none-diabetic subjects. In contrast, Beta cell function in diabetic patients was significantly lower than healthy subjects. Accumulating evidence indicates that this inflammation cytokine plays an important role in lipid metabolism by regulating insulin levels and lipase activity under physiological conditions (Matsuki *et al.,* 2003). Recent epidemiologic studies have demonstrated strong relationship between inflammatory markers and metabolic disturbances, obesity, whereas inflammation has been considered as a "common soil" between these clinical entities and type 2 diabetes (Alexandraki *et al.,* 2006). Diabetes is known to high insulin concentration and is a metabolic disease that occurs when pancreatic islets fail to produce sufficient insulin and/or the sensitivity of glucose-metabolizing tissues to insulin decreases (Greenman *et al.,* 2004).

Data from a recent observational study indicate that IL-1 and IL-6 are both involved in the regulation of body fat in a redundant manner in young mice (Manica-Cattani *et al.,* 2010). Recent epidemiologic studies have demonstrated that expression of IL-1b is increased in adipose tissue of both obese rodents and humans (Juge-Aubry *et al.,* 2004). IL-1b is a proinflammatory cytokine that plays important roles in systemic inflammation (Matsuki *et al.,* 2003). However, the physiopathological mechanisms of this cytokine on obesity or type II diabetic are largely unknown. According to the population studies, it has been indicated a positive association between IL-1 beta +3953 (C>T) gene polymorphism (rs 1143634) and obesity, suggesting functional effects on fat mass, fat metabolism and body mass (Manica-Cattani *et al.,* 2010).

The main cytokines involved in the pathogenesis of T2D are interleukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), and IL-6, considered as the main regulators of inflammation, leptin, and several others, such as resistin, adiponectin with either deleterious or beneficial effects in diabetic pathogenesis (Alexandraki *et al.,* 2006). Several studies have suggested that IL-1beta is a regulator of the body's inflammatory response and is produced after infection, injury, and

antigenic challenge. It plays a role in various diseases, including autoimmune diseases, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and type 2 diabetes (Juge-Aubry *et al.,* 2004).

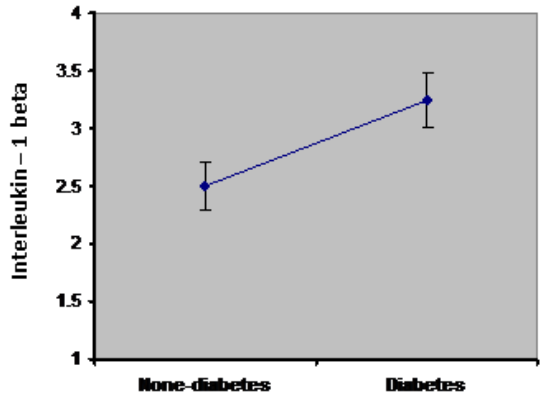

Fig. 1. Mean and standard deviation of serum IL-1b in two groups.

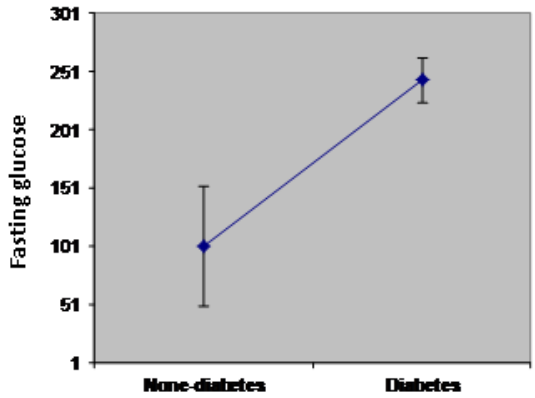

Fig. 2. Mean and standard deviation of fasting glucose in two groups.

IL-1beta production and secretion have also been reported from pancreatic islets (Maedler et al., 2009). Emerging evidence from animal and human studies suggests that IL-1b is elevated in obese individuals and rodents and it is implicated in impaired insulin secretion, decreased cell proliferation and apoptosis of pancreatic beta cells (Osborn *et al.,* 2008). In accordance with this suggestion, our study finding showed a significant negative correlation between serum IL-1b and Beta-cell function in bout diabetic and none-diabetic obese subjects. These findings point out that increased circulating IL-1b is associated with pancreatic Beta-cell dysfunction in either diabetic or non-diabetic obese.

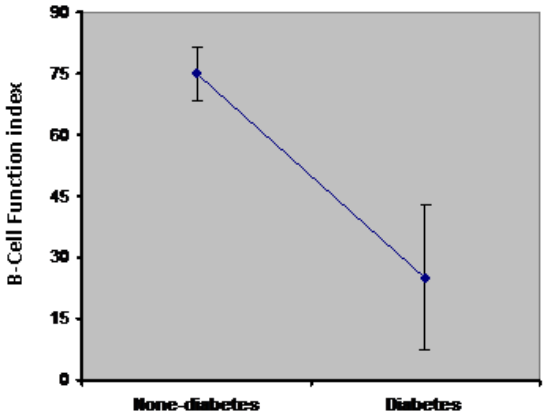

Fig. 3. Mean and standard deviation of Beta-cell function in two groups.

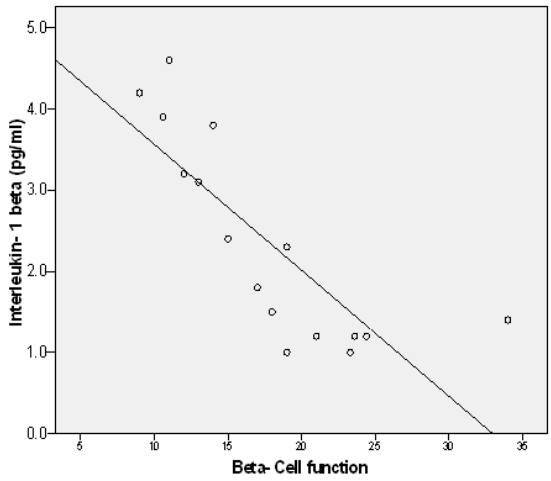

Fig. 4. The correlation pattern between serum Il-1b and Beta cell function in patients. This illustration indicates a significant negatively association between serum IL-1b and beta cell function in patients.

Recent studies have established that IL-1b affects both beta cell functional mass and insulin sensitivity in type 2 diabetes (Ehses *et al.,* 2006). *B-cell* dysfunction and apoptosis by IL-1b are involved in the pathogenesis of pancreatic *β*-cell dysfunction and type 2 diabetes (Wang *et al.,* 2010). It is also important to make a note here that islet-produced IL-1*β* may be involved in glucotoxicity on islet *β* cell (Wang *et al.,* 2010). In accordance with these observations, IL-1*β* expression is shown to be increased in islets from type 2 diabetic patients (Boni-Schnetzler *et al.,* 2008). The data of a resent study suggests that reduced IL-1beta activity by blockade of its receptor with anakinra or neutralizing anti-IL-1beta antibodies is sufficient for

correcting dysfunctional beta-cell production of insulin in type 2 diabetes, including a possibility that suppression of IL-1beta-mediated inflammation in the microenvironment of the islet allows for regeneration (Dinarello *et al.,* 2010). In a recent study, 13 weeks of treatment the IL-1beta antibody showed reduced glycated hemoglobin, reduced serum levels of proinsulin, reduced levels of insulin and smaller islet size relative to the control antibody treated group (Osborn *et al.,* 2008).

Our study was also showed that serum IL-1b was positively related with glucose concentration. In this area, a recent study suggests that prolonged IL-1b treatment induces an inhibition of insulin effect on glucose uptake as also recently published (Lagathu *et al.,* 2006). In addition to the essential role of glucose in mediating insulin secretion and proliferation, a decreased circulating of IL-1b also stimulates insulin release and proliferation in rat and human islets (Schumann *et al.,* 2007; Maedler *et al.,* 2006). Disturbance in secretion of IL-lb not only does not reduce insulin secretion, but also it leads to beta cell apoptosis and improves the destructive effect of TNF-α on beta cells (Eizirik, 1988; Pukel *et al.,* 1988).

Generally, accumulation of fat tissue in healthy or unhealthy populations is accompanied with an increased inflammation cytokines levels and drop in anti-inflammation markers. It is observed that in addition to genetic factors and sedentary life style, increase in inflammation cytokines levels in obese people paves the way for chronic inflammation diseases. In general, it is observed that increase in the body fat percentage, especially abdominal obesity, increases inflammation cytokines levels. However, it seems that in obese patients such as those suffering from diabetes or cardiovascular disease, in addition to obesity, the type of illness also affects inflammation or anti-inflammation mediators' levels. In fact, some recently published research studies have reported the rise in inflammation cytokines in obese patients compared with healthy people (Dasu *et al.,* 2007). In line with these studies, the present study showed that despite the same body fat levels and body mass index in diabetic and non-diabetic subjects, Il-lb levels in diabetics were significantly higher than those in non-diabetic obese subjects. There is also the possibility that the rise in levels of these inflammation cytokines of the diabetic subjects in the present study is due to the serum changes of other inflammation mediators affecting directly or indirectly IL-lb. These hypotheses need more studies laboratory experiments.

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