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Increased interleukin-1 beta is associated with high fasting glucose in obese men

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Abstract

Interleukin-1 beat, a proinflammatory cytokine, plays important roles in systemic inflammation. The aims of present study were 1) to compare serum IL-1b between obese and none-obese me, 2) to determine serum IL-1b in relation to fasting glucose, insulin and beta-cell function in obese men. For this purpose, Venous blood samples were obtained after a overnight fast in order to measuring Il-1b, insulin, glucose in sedentary obese ($30 \leq BMI \leq 36$, $n = 41$) and none-obese ($20 \leq BMI \leq 25$, $n = 36$) men matched for age (370 ± 5, aged). Anthropometrical indexes were also monitored in two groups. Beta cell-function (HOMA-BF) was calculated by fasting insulin and glucose. Statistical analysis was performed by Independent sample T-test and Spearman rank correlation method. P value of <0.05 was accepted as significant. Serum IL-1b and glucose concentrations were significantly higher in obese men when compared with none-obese subjects ($p < 0.05$). Beat-cell function in obese men was lower than none-obese men ($p < 0.05$). IL-1b correlated negatively with the insulin and beta-cell function and positively with fasting glucose in obese men ($p < 0.05$). Based on this data, it was concluded that obesity is associated with systemic inflammation and Measurement of inflammatory indices may be represented glucose homeostasis in this population.

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Introduction

Recent evidence has shown that Adipose tissue inflammation has a key role in circulation glucose and is probably linked to high local levels of cytokines. This proinflammatory cytokine is elevated in obese individuals and rodents and it is implicated in decreased cell proliferation and apoptosis of pancreatic beta cells and impaired insulin secretion (Osborn *et al.,* 2008). It has been suggested that, Proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha) and IL-6 are important in the induction of inflammatory responses (Takizawa H, 1998). Among them, it was found that IL-1β is a regulator of the body's inflammatory response and is produced after injury, infection and antigenic challenge (Maedler *et al.,* 2009). Although macrophages are the primary source of IL-1, but epidermal, epithelial, lymphoid and vascular tissues also synthesize IL-1. IL-1beta production and secretion have also been reported from pancreatic islets (Maedler *et al.,* 2009). Recently, it has been hypothesized that IL-1β plays an important role in glucose concentration and type II diabetic prevalence. Macrophage-derived IL-1 beta production in insulin-sensitive organs, leads to progression of inflammation and induction of insulin resistance in obesity (Maedler *et al.,* 2009), although the molecular mechanisms for this are less understood. It was reported that IL-1β may drive tissue inflammation that impacts on both beta cell functional mass and insulin sensitivity in type 2 diabetes (Ehses *et al.,* 2009). On the other hand, Previously, IL-1beta secretion from Type 2 diabetic patients has been shown to be increased compared with controls (Dasu *et al.,* 2007). Additionally, some studies suggest that, under HG conditions, monocytes release significantly higher amounts of IL-1β through multiple mechanisms, further compounding the disease progression (Dasu *et al.,* 2007), although the molecular mechanisms for this are still not completely elucidated. Circulating levels of IL-1β are increased in overweight and obese compared with lean subjects (Um *et al.,* 2004) and its Expression of IL1B, the human gene encoding IL-1β, is increased in the visceral adipose tissue of obese subjects (Juge-Aubry *et al.,* 2004). On the other hand, recent evidence has shown those obese subjects have higher glucose concentration compared to those with normal weight. The question is that whether a significant relation between serum IL-1b and fasting glucose in obese subjects. Therefore, the objective of this study was to compare serum IL-1β between obese and normal weight men and determining the relationship between serum IL-1β and fasting glucose, insulin, beta cell function in obese men with type subjects.

Material and methods

The study protocol was approved by the ethics committee of Islamic Azad University. In this study, we compared the concentrations of serum IL-1β, glucose and insulin in sedentary obese ($30 \leq BMI \leq 36$, $n = 41$) and none-obese ($20 \leq BMI \leq 25$, $n = 36$) men and also we investigated IL-1β in relation to glucose, insulin and beta-cell function in obese subjects matched for age (370 ± 5, aged). Each participant received written and verbal explanations about the nature of the study before signing an informed consent form.

Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. Subjects were reported to be non-smokers, not currently taking supplements of any kind, and having no major health problems (i.e., diabetes, cardiovascular disease, etc.). Daily food records were kept for 48 h preceding each test session, and subjects were instructed to refrain from caffeine consumption for 24 h before testing. No difference was observed in the subjects' diets 48 h before each trial**.** We also excluded people who had any self reported physician diagnosed chronic disease (arthritis, stroke, hypertension, cancer, heart attack, chronic cough, or bronchitis).

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 by using the standard hospital scales. The Body Mass index (BMI) was calculated using the formula body weight/height2 in terms of kg/m². Waist circumference was measured half distance between the lower border of the last rib and the upper border of the iliac crest at the end of a normal expiration, using a non-stretchable tape measure. Waist circumference (WC) was measured with a non-elastic tape at a point midway between the lower border of the rib cage and the iliac crest at the end of normal expiration. The arterial systolic and diastolic blood pressures (BP) were calculated after they rested for 10 minutes with a mercury manometer with appropriate sleeves from the right and left arm, in sitting position on the condition that they had not eaten anything, had not taken any caffeine, had not smoked or exercised thirty minutes before the measurement, and then the averages were calculated.

All participants were asked to attend Hematology Lab for blood sampling. Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. A venous blood sample was collected from all the subjects who came after a 12-h overnight fast between the hours of 8 to 9 am. These blood samplings used for measuring of fasting serum IL-1β, glucose, insulin and beta-cell function. Beta-cell function (HOMA-BF) was calculated by the formula fasting blood glucose and insulin values [(20 × fasting insulin (μ/ml] / [Fasting glucose (mmol/l) – 3.5]. 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

All values are represented as mean ± SD. 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 the serum levels of all variables between obese and none-obese subjects. The bivariate associations between IL-1β concentration with glucose, insulin and beta-cell function were examined with the Spearman rank correlation analysis in obese subjects. A p-value less than 0.05 were considered statistically significant.

Results

Anthropometric and metabolic characteristics of the study participants in the normal and obese groups are shown in Table 1. Data were expressed as individual values or the mean ± SD for groups. The data of table1 shows that obese subjects have BMI, body fat percentage, hip and abdominal circumference and body weight higher compared to those with normal weight subjects. The data of Independent sample T-test Fasting serum IL-1β concentrations were higher in obese men than in none-obese men (P = 0.015). Beta-cell function was significantly lower in the obese men when compared with none-obese subjects (P = 0.021). In addition, obese subjects have fasting glucose concentration more than none-obese men (P = 0.028).

The finding of Pearson method in obese group showed a positive significant association between serum IL-1β and fasting glucose concentration (p = 0.011, r = 0.56). Referring to these findings, although we cannot conclude a Cause and effect relationship between Il-1b and glucose concentration, it is likely an increase in IL-1β is accompanied with high glucose concentration. Serum IL-1b concentrations were also negatively correlated with serum insulin in these participants (p = 0.026, r = 0.57). We have also observed a significant negative correlation between Serum IL-1β and beta-cell function in obese subjects (p = 0.19, r = 0.57). These

findings support of this hypothesis that increase in IL-1β lead to low insulin secretion of pancreas beta cells.

Table 1. Mean and standard deviation of Baseline level of anthropometric and metabolic characteristics of studied subjects

Variables	obese group	None-obese group
Age (year)	37 ± 5	36 ± 5
Weight (kg)	101 ± 13	70 ± 9
Height (cm)	174 ± 7	173 ± 6
Body Fat (%)	31.6 ± 3.14	21 ± 2.12
Body mass index (kg/m²)	33.35 ± 3.14	23.38 ± 2.44
Abdominal circumference (cm)	108 ± 14	91 ± 8
Glucose (mg/dL)	102 ± 11	92 ± 7
Systolic blood pressure (mmHg)	128 ± 11	116 ± 7
Diastolic blood pressure (mmHg)	89 ± 8	78 ± 6
Insulin (µIU/ml)	8.42 ± 2.14	6.81 ± 2.3
HOMA-BF	85 ± 14	96 ± 13
IL-1β (pg/ml)	2.09 ± 0.31	1.52 ± 0.19

Discussion

Our study findings showed that serum IL-1β in obese subjects was higher than normal weight participants. In addition, fasting glucose was higher and beta-cell function was lower in obese compared to normal weight participants. White adipose tissue secretes proinflammatory cytokines such TNF-a, interleukin-1 (IL-1), interleukin-1 receptor antagonist (IL-1Ra), and interleukin-6 (IL-6), and chemokines such as monocyte chemoattractant protein-1 (MCP-1), interferon gamma inducible protein 10 (IP-10), interleukin-8 (IL-8), RANTES, and peptides with hormone-like actions such as adiponectin, leptin and resistin (Meier *et al.,* 2007). Recent evidence has shown that inflammation cytokine plays a role in various diseases, including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and type 2 diabetes (Maedler *et al.,* 2009). It is generally accepted that that obesity is associated with a low-grade inflammation of white adipose tissue resulting from chronic activation of the innate immune system as IL-1β (Manica-Cattani *et al.,* 2010). Our study shows obesity is associated with both serum IL-1β and glucose concentration and a low beta-cell function. In accordance with these observations, some recent studies have demonstrated a positive association between IL-1β and obesity, suggesting functional effects on fat mass, fat metabolism and body mass (Manica-Cattani *et al.,* 2010). Circulating levels of IL-1β are increased in overweight and obese compared with lean subjects (Um et al., 2004) and its Expression of IL-1β, the human gene encoding IL-1β, is increased in the visceral adipose tissue of obese subjects (Juge-Aubry *et al.,* 2004). It was found that secretion of IL-1β have been related not only to various autoimmune and auto-inflammatory diseases, but also to metabolic deregulation (Dinarello, 2009). On the other hand, some study demonstrated a positive relation between fasting glucose with inflammation cytokines such as TNF-α and IL-1β in obese subjects (Samaras *et al.,* 2010).

Increased fasting glucose and IL-1β in obese men were observed compared to normal weight subjects. This question is always raised Whether or not increased inflammation cytokines such as IL-1β affects glucose or insulin concentrations. In response to this question, a positive significant correlation between fasting glucose and serum IL-1β was also observed in our study. On the other hand, it was reported that Insulin-producing beta-cells within pancreatic islets are specifically prone to IL-1β-induced destruction and loss of function (Maedler *et al.,* 2009). The specific mechanisms responsible for these observations are not obvious. It is also important to note that low systemic insulin is associated with hyperglycemia in obese men or

diabetic patients (Um *et al.,* 2004; Maedler *et al.,* 2009). It is likely that high glucose level in obese men or patients with hyperglycemia occur in response to possible mechanisms between insulin and IL-1β. To support this hypothesis, our study was also showed that IL-1β correlated negatively with serum insulin. The proinflammatory cytokine, interleukin (IL)-1beta, is known to induce vascular dysfunction and cell death (Vincent *et al.,* 2007). IL-1β Produced by activated macrophages, IL-1 stimulates thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, and fibroblast growth factor activity (Kathrin *et al.,* 2009). IL-1β production and secretion have also been reported from pancreatic islets (Kathrin *et al.,* 2009). It seems that increased serum IL-1β is associated with impaired insulin secretion of beta-cell function. IL-1β is upregulated in adipose tissue of obese and insulin-resistant mouse models and may play a key role in the growth of insulin resistance in murine and human adipose cells (Lagathu *et al.,* 2006). This is likely that IL-1b lead to beta-cell dysfunction. It has been suggested that Insulin-producing β-cells within pancreatic islets are specifically prone to IL-1β-induced destruction and loss of function (Kathrin *et al.,* 2009). These results were supported by other authors. Recent evidence also support In addition to impaired insulin secretion, IL-1β was found to induce β-cell death, which was potentiated by the cytokines IFNγ and TNF-a (Eizirik, 1998; Pukel *et al.,* 1988). The clinical and research evidence to date support the hypothesis that IL-1β production in insulin-sensitive organs, leads to progression of inflammation and induction of insulin resistance in obesity (Kathrin *et al.,* 2009). To support these findings, our study clearly showed a negative significant correlation between IL-1b and beta-cell function in obese subjects. Inhibition of IL-1b action by specific IL-1β-neutralizing antibodies conferred protection from the cytotoxic effects induced by activated-mononuclear-cell-conditioned medium (Bendtzen *et al.,* 1986), somehow supports the hypothesis that that IL-1β plays an important role in the molecular mechanisms underlying autoimmune β-cell destruction (Kathrin *et al.,* 2009).

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