RESEARCH PAPER

Interleukin-1 beta response to an acute incremental cycling in obese men

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Abstract

To compare of circulating levels of IL-1b as an inflammation cytokine between obese and none obese men and also to investigation its response to an acute exercise test. Fasting blood samples were obtained of adult obese (n=15) and none obese (n=14) men aged 40 ± 5 year in order to measuring serum IL-1b and glucose. In addition, blood samples were repeated immediately after a session cycling exercise in order to determine these variables responses to exercise test. Statistic analysis was done with SPSS 15.0 for Windows by using Student's t-tests for independent and paired samples. At baseline, serum IL-1b level, glucose and insulin resistance in obese men were higher than those with normal weight ($p < 0.05$). Acute cycling test increased IL-1b ($p = 0.037$) and decreased glucose concentration ($p = 0.024$) without changes in insulin resistance ($p = 0.126$) on obese subjects. Obesity is associated with systemic inflammation. Despite the decrease in glucose concentration, but a session exercise does not lead to improved systemic inflammation in obese men.

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Introduction

Aging and Obesity is associated with chronic systemic inflammation. Obesity also may further contribute to the age-related increase in the production of inflammatory cytokines (Trayhurn *et al.,* 2004). Inflammatory activation with increased serum cytokine levels has been described as an important factor in progression as chronic diseases such as chronic heart failure (Anker *et al.,* 2004; Gielen *et al.,* 2003). Recent evidence has shown that sarcopenic obesity is associated with increased levels of circulating inflammatory markers (Cesari *et al.,* 2005). It has been demonstrated that, cytokines act as catabolic factors involved in the pathogenesis of muscle wasting and cardiac cachexia (Anker *et al.,* 2004). 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, 1998). Interleukin-1 beta, proinflammatory cytokine, plays important roles in inflammation (Matsuki *et al.,* 2003). However, the role of this cytokine under physiological conditions has not drawn much attention. It was found that secretion of IL-1β have been related not only to various autoimmune and auto-inflammatory diseases, but also to metabolic dysregulation (Dinarello, 2009). 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). Recently, it has been hypothesized that IL-1β plays an important role in glucose concentration and obesity and its related diseases. On the other hand, it was reported that IL-1beta may drive tissue inflammation that impacts on both beta cell functional mass and insulin sensitivity in type 2 diabetes (Kathrin *et al.,* 2009). Some authors noted that exercise training as a none-pharmological lead to improvement in inflammation cytokines profile in obese or its related chronic diseases (Gielen *et al.,* 2003). In this area, a recent study indicated that serum IL-1b decreased by long-term exercise training (Gomez-Merino *et al.,* 2007). In contrast, the finding of another study shows no significant change in serum IL-1b by long-term study (Bonyadi *et al.,* 2009). Despite mentioned contradictory findings, an effect of a single bout exercise on serum IL-1b levels has received limited attention. Therefore, the primary aim was to determine effect a session graded cycling test on serum IL-1b in obese men.

Material and methods

We compared the concentrations of IL-1b, glucose and insulin in fifteen adult obese and fourteen none-obese men (40 +/- 5 years; 175 +/- 7.2 cm) after an overnight fast that participated in this study bay randomly. A medical history to retrieve information about health status, current medications and alcohol consumption s; a physical examination including height, weight, waist circumference and blood pressure were performed of all participants. Subjects with a history or clinical evidence of impaired fasting glucose or diabetes, orthopedic abnormalities, recent myocardial infarction, congestive heart failure, active liver or kidney disease, growth hormone deficiency or excess, neuroendocrine tumor, anemia, or who were on medications known to alter insulin sensitivity were excluded. Subjects had neither used any medication 6 weeks prior to the study nor participated in any regular physical exercise/diet. Body weight and height were measured with a standard physician's scale and a stadiometer, respectively when subjects were in a fasting state when the participant had thin clothes on and was wearing no shoes. Visceral fat and body fat percentage was determined using body composition monitor (OMRON, Finland). Systolic and diastolic blood pressure was measured using the left arm after the subject had been sitting comfortably for 5 min, using an oscillometric device (Alpikado, Japan). Two measurements were made every 1 minute and the average of two measurements was used for analysis. Body mass index (kg/m²) was

calculated as weight (kg) divided by squared height (m²). Before the examination, all participants fasted for at least 12 hours and signed a written informed consent. Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. Then, 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 to measuring serum IL-1b and glucose. In addition, blood samples were repeated immediately after a session cycling exercise in order to determine these variables responses to exercise test. Insulin resistance (HOMA-IR) = [fasting insulin (μ/ml) × fasting glucose (mmol/l)] / 22.5. Cycling exercise test was a YMCA standard test on leg ergometery cycle (Tunturi, made in Finland). This protocol was performed in 5 continues stage without rest between stages. Each stage lasted 3 minute (Mullis *et al.,* 1999). 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 all variables between obese and none-obese subjects. Student's t-tests for paired samples were performed to determine significance of changes in variables by exercise test in obese subjects. P value of <0.05 was accepted as significant.

Results

In this study, we initially compared IL-1b, glucose and insulin resistance between healthy adult men with obesity and none-obese men. All anthropometrical in obese men were higher significantly than non-obese men (Table 1).

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)	40 ± 5	39 ± 6
Weight (kg)	101 ± 13	72 ± 8
Height (cm)	175 ± 7.2	174 ± 6
Body Fat (%)	31.9 ± 3.22	21 ± 2.28
Body mass index (kg/m²)	33.00 ± 3.24	24.50 ± 2.11
Abdominal circumference (cm)	107 ± 11	90 ± 8
Systolic blood pressure (mmHg)	127 ± 10	113 ± 6
Diastolic blood pressure (mmHg)	88 ± 7	77 ± 5

At baseline, serum Il-1b level in obese subjects was significantly higher than none obese subjects (2.03 ± 0.36 vs 1.48 ± 0.23 pg/ml, p = 0.031). This data have demonstrated that obesity is associated with systemic inflammation. Obese participants have higher fasting glucose when compared to normal weight men (101 ± 14 vs 91 ± 11 mg/dl, p = 0.023). In addition, insulin resistance index in obese men was significantly higher than those with normal weight (2.09 ± 0.31 vs 1.62 ± 0.23, p = 0.037). High fasting glucose and insulin resistance in obese men compared to none-obese men may indicate risk for diabetic prevalence in obese subjects.

The second aim of our study was to investigation the effect of a session incremental cycling on Il-1b, glucose and insulin in obese subjects. Our study finding showed that serum IL-1b increased significantly in response to exercise test (2.03 ± 0.36 vs 2.24 ± .33 pg/ml, p = 0.024). On the other

hand, exercise test led to significantly decrease in glucose concentration (101 ± 14 vs 96 ± 11 mg/dl, p = 0.023). But, insulin resistance index remained without change following cycling exercise when compared to pre-test (2.09 ± 0.31 vs 2.21 ± 0.33, p = 0.126).

Discussion

The initial finding of our study showed higher levels of serum IL-1b, glucose and insulin resistance in obese men when compared to normal-weight subjects. 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.,* Meier). 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).

Interleukin-1Beta (IL1B) gene, part of a cluster of genes on chromosome 2 coding for a family of IL-1 proteins, has been shown to be an important modulator of inflammatory pathways, with potential involvement in the pathogenesis of atherosclerosis and other cardiovascular diseases (Maruyama *et al.,* 2003). Based on the role of IL-1B gene on adipose tissue regulation, investigators have explored potential interrelationships between obesity, IL1B genotype (Um *et al.,* 2009; Markovic *et al.,* 2004). 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.,* 2009) and its Expression of IL-1β, the

human gene encoding IL-1β, is increased in the visceral adipose tissue of obese subjects (Meier *et al.,* Meier). 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). It is generally accepted that inflammation plays a key role in insulin resistance (Dandona *et al.,* 2004). On the other hand, there exists a statistical significant association between elevated serum cytokine levels and exercise intolerance (Gielen *et al.,* 2003). Exercise training has been known to improve the inflammatory profile by inhibition of cytokine-chemokines production, regulation of monocyte activation and adhesion, inhibition of inflammatory cell-growth signals and growth factor production, reduction of soluble apoptosis signaling molecules (Adamopoulos *et al.,* 2002). Although the mechanisms underlying this response are a matter of some debate. Some studies have been demonstrated that exercise training led to low inflammation cytokines such as TNF-α and IL-1b (Larsen *et al.,* 2002; Smart *et al.,* 2011). In contrast, our study finding showed that a session cycling increases serum IL-1b and decreases glucose concentration without changes in insulin resistance in obese men. To support these findings, the findings of a recent study have also observed a notable increase in concentration of IL-1b following a single bout treadmill exercise in obese subjects (Damirchi *et al.,* 2011). However, although IL-1 beta has traditionally been understood to be a main inducer cytokine of acute phase reactions, the majority of studies have shown that the circulating concentration of this cytokine is either unchanged following exercise, or exhibits relatively small, delayed increments (Suzuki *et al.,* 2002).

Of course this point must also be considered that although it is expressed in most studies, that a single-session exercise is associated with instantaneously increased levels of inflammatory cytokines or with their remaining unchanged, it is likely that the effect of exercise is more associated

with levels of gene expression of these cytokines with. Or in other words, this type of exercise leads to reduced levels or numbers of the receptors of these cytokines in the muscle or in other tissues (Smart *et al.,* 2011; Conraads *et al.,* 2002).

Accumulating evidence suggests that alterations in levels of the cytokines are not necessarily uniform. So, some studies have been demonstrated that increments in physical capacity following exercise training may be unrelated to changes in cytokine levels (Smart *et al.,* 2011). Moreover, changes in particular cytokines appear to be independent of one another. On the other hand, it is likely the levels of systemic cytokine responses to exercise to be independent of their skeletal muscles (Gielen *et al.,* 2003).

However, given the increased serum levels of IL-1b and the absence of any significant changes in insulin resistance in this study, it appears that a significant reduction in blood glucose levels in response to this single-session exercise is independent of the relationship between IL-1b and insulin resistance. In fact it appears that lowered blood glucose in response to a single-session exercise in this study does not depend on symptoms associated with insulin-related signals and exercise may also affect the absorption exercise leads to a decrease in blood glucose concentration by other signs affecting blood glucose intake or glucose metabolism such as reactions associated with the activity or mechanism of AMPK (Bergeron *et al.,* 1999) and the proof of this hypothesis requires further studies in this field.

Also, It was reported that decreasing in glucose concentration after exercise even a session may be due activation of an immune response during acute exercise that enhances lipid and glucose metabolism (Damirchi *et al.,* 2011). Further studies are needed to clarify possible mechanisms by which Il-1b or other cytokines can be affecting by exercise.

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