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Circulating adiponectin regulates serum C - reactive protein and Interleukine-6 in obesity

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Abstract

Impaired adiposity-secreted adipocytokines is known to be associated with obesity and related diseases. The aim of this study was to assess the association between antiinflammatory cytokine adiponectin with C-reactive protein and interleukine-6 as two important pro-inflammatory cytokine in thirty nine sedentary healthy obese men aged 35 – 45 years. For this purpose, venous blood samples were collected from each subject after overnight fast in order to measuring serum adiponectin, CRP and Il-6. All anthropometrical variables were also measured. Pearson correlations were used to establish the relationship between adiponectin concentration with CRP and Il-6 in studied subjects. A significant negative correlation was observed between adiponectin ($p = 0.022$, $r = 0.37$) and Il-6 ($p = 0.009$, $r = 0.41$). Our data suggests that high adiponectin is associated low pro-inflammatory cytokine. We can say Serum adiponectin may affects circulating CRP an Il-6 as two inflammatory mediators and markers of increased cardiovascular risk.

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Introduction

Aging is known to be associated with chronic systemic inflammation (Grimble, 2003). Review of research evidence also shows that Obesity induces chronic inflammation and may further contribute to the age-related increase in the production of inflammatory cytokines (Tan *et al.,* 2006). In addition to a major source of fat reserves, adipose tissue is a major regulator of the metabolic adaptation through the secretion of different hormone-like peptides, named adipocytokines such as leptin, adipsin, TNF-α, adiponectin, resistin and interleukins (Saltiel, 2001; Spiegelman *et al.,* 2001; Steppan *et al.,* 2001). Cytokines are inflammatory mediators produced primarily by peripheral blood mononuclear cells, adipocytes, hepatocytes, and skeletal muscle (Charles *et al.,* 2008). Not only does adipose tissue release cytokines, but also skeletal muscles express cytokines that have direct autocrine and paracrine effects (Saghizadeh *et al.,* 1999).

Adiponectin has antidiabetic and antiatherogenic properties that are believed to be related to its inverse relationship with body fat mass and insulin resistance (Maeda *et al.,* 2002; Yamauchi *et al.,* 2003). Although, a number of studies have demonstrated that that adiponectin's biological effect may be independent of fat mass and insulin resistance (Maeda *et al.,* 2002; Tschritter *et al.,* 2003). Elevated levels of C-reactive protein and serum IL-6 is known to be strongly predict mortality and functional decline in older persons (Reuben *et al.,* 2002). The American Heart Association and the Centres for Disease Control and Prevention in the USA suggests that CRP is the best and most clinically useful of the markers of inflammation currently available, with the following cut-off points for assessing CVD risk (Pearson *et al.,* 2003). Other pro-inflammatory cytokines such as IL-6, IL-1b and TNFa, are often included in the panel of inflammatory markers and accumulating evidence suggests that these cytokines have been associated with obesity and components of the metabolic syndrome (Julia *et al.,* 2010).

Accumulating evidence indicates a wide variability of adiponectin levels even in subjects having similar BMI (Baratta *et al.,* 2004; Arita *et al.,* 1999; Weyer *et al.,* 2001) and may be attributed to a number of factors that influence adiponectin synthesis and secretion (including hormones like glucocorticoid, TNF-α intracellular mediators like cAMP) (Stefan *et al.,* 2002). Although the role of other cytokines such as C-reactive protein and interleukine-6 on circulating adiponectin are not completely understood. The objective of this study was to determine relation between adiponectin as antiinflammatory cytokine with serum IL-6 and CRP in obese men.

Subjects and methods

Thirty nine none-trained adult obese men (age, 40 ± 5 years; BMI 30–36 kg/m2, mean ± standard deviation) were enrolled in this study. All subjects were otherwise in good health were taking no medications. All subjects had a body mass index (BMI) greater than 30 kg/m^2. The aim of our work was to study the relation of serum adiponectin with CRP and Il-6 in studied subjects. All participants gave informed consent before recruitment. The study protocol was approved by the ethics committee of Islamic Azad University, Saveh Branch, Iran. Subjects with a history or clinical evidence of impaired fasting glucose or diabetes, orthopedic abnormalities, congestive heart failure, active liver or kidney disease were excluded. Subjects had neither used any medication 6 weeks prior to the study nor participated in any regular physical exercise.

Height was measured without shoes on standing while the shoulders were tangent with the wall. Obesity was measured by body mass index (BMI) and body fat percentage. Body mass index was measured for each individual by division of body weight (kg) by height (m2). Body composition monitor (BF508-Omron made in Finland) with a precision error of less than 100 g was used to measure weight and body fat percentage of the subjects. Waist circumference was measured after a

normal expiration under the midline of the subject's armpit, at the midpoint between the lower part of the last rib and the top of the hip using a non-elastic cloth meter. Waist to hip circumference ratio was measured by dividing the abdominal circumference into that of the hip.

Table 1. The descriptive anthropometric and biochemical features of studied subjects

Variable	Mean	Standard deviation	Range
Age (years)	40	5	35 - 45
Weight (kg)	100	11.2	89 - 110
Height (cm)	175	6.3	168 - 181
Body mass index (kg/m^2)	32.68	3.11	30 - 36
Systolic blood pressure (mmHg)	129	13	120 – 142
Diastolic blood pressure (mmHg)	90	9	80 – 98
Abdominal obesity (cm)	106	12.6	95 – 116
Hip circumference (cm)	103	9.6	93 – 113
Visceral fat	15	4.6	10 - 17.8
WHO	1.03	0.21	0.98 – 1.05
Body fat (%)	32	4.3	29 - 36
C-reactive protein (ng/ml)	1528	314	1216 - 1935
Interleukine-6 (Pg/ml)	14.6	5.16	12 – 19.9
Adiponectin (µg/ml)	7.13	2.6	5.2 – 8.9

After anthropometrical measurements the individuals were asked to attend Hematology Lab following 12 hours of overnight fasting, between the hours of 8 to 9 am. Then, Venus blood samples were obtained of each subject for measuring serum adiponectin, CRP and IL-6.

Serum adiponectin was determined by ELISA method, using a Biovendor- Laboratorial kit made by Biovendor Company, Czech. The Intra- assay coefficient of variation and sensitivity of the method were 3.9% and 5-50 ng/mL, respectively. Serum CRP was determined by ELISA method (Diagnostics Biochem Canada Inc. High sensitivity C - reactive protein (Hs-CRP)). The Intra- assay coefficient of variation and sensitivity of the method were 8.3% and 7.8 ng/mL, respectively. Serum IL-6 was determined by ELISA method (Human IL-6 Platinum ELISA BMS213/2 / BMS213/2TEN). The Intra- assay coefficient of variation and sensitivity of the method were 3.4% and 5.2 pg/mL, respectively.

Statistical analysis

Statistical analysis was performed with the SPSS software version 15.0. Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. The bivariate associations between changes in serum adiponectin with serum CRP and IL-6 e were examined with the Pearson rank correlation analysis in studied subjects. All statistical tests were performed and considered significant at a $P \leq 0.05$.

Results

Anthropometric and metabolic characteristics of the study participants are shown in Table 1. All values are represented as mean ± standard deviation.

A significant negative correlation was found between serum adiponectin and CRP (p = 0.000, r = 0.00, Fig 1). We also observed that serum adiponectin was negatively correlated with serum IL-6 (p = 0.000, r = 0.00, Fig. 2).

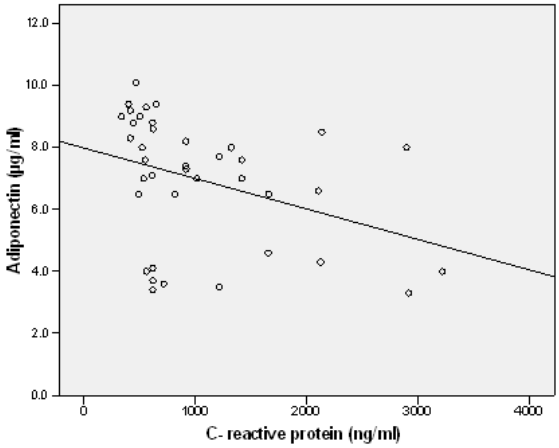

Fig 1. The correlation pattern between serum adiponectin and Iterleukin-6 in studied subjects. This illustration indicates a significant negatively association between serum adiponectin and Interleukin-6.

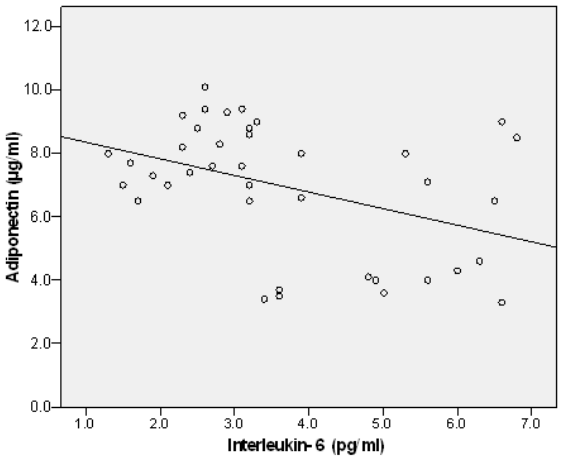

Fig 2. The correlation pattern between serum adiponectin and C-reactive protein in studied subjects. This illustration indicates a significant negatively association between serum adiponectin and C-reactive protein.

Discussion

Our study finding showed that adiponectin was negatively related with CRP and Il-6 as two inflammatory cytokines in obese men. Sedentary lifestyle, aging and obesity are also increasingly recognized as modifiable behavioral risk factors for a wide range of chronic diseases, and in particular for CVD (Pate *et al.,* 1995). It is repeatedly suggested that Obesity is associated with moderately raised levels of inflammation, and this observation has led to the view that obesity is characterized by a state of chronic low-grade inflammation (Trayhurn *et al.,* 2004).

The continued identification of bioactive proteins secreted by adipokines supports the theory that an excess of adiposity plays a central role in the metabolic syndrome (Gibbs *et al.,* 1973; Schwartz *et al.,* 2000). IL-6 and other cytokines have been suggested to be play important roles in chronic diseases and low-grade inflammation.

Expression of IL-6 a major pro-inflammatory cytokine is markedly regulated at the transcriptional level and increased in human fat cells from obese subjects and those with insulin resistance (Rotter *et al.,* 2003). It was reported that visceral adipose tissue releases around three times more IL-6 into the circulation than subcutaneous adipose tissue (Fried *et al.,* 1998). This is because adipose tissue is composed of many different cell types including adipocytes,pre-adipocytes, monocytes/macrophages, stromovascular cells and others. It has been suggested that adipocytes are a minor IL-6 source and cells retained in the tissue matrix after collagenase digestion are the major adipocytokines and IL-6 source (Philippou *et al.,* 2009). Altogether, it is now clearly established that both subcutaneous and visceral adipose tissues are major sources of IL-6 in human obesity (Moschen *et al.,* 2010). Activated macrophages secrete interleukin-1 and 6 which are powerful stimuli for production of CRP by the hepatocytes (Ryan *et al.,* 1998). These authors noted that CRP in combination with age, hypertension, and

diabetes were the most outstanding risk factors associated with CVD in this population (Panagiotakos *et al.,* 2008).

Adiponectin is an antiinflammatory cytokine and low circulating levels of it is associated with obesity, metabolic syndrome and obesity-induced chronic diseases. Decreased adiponectin expression in adipose tissue has been demonstrated in many clinical studies (Statnick *et al.,* 2000). Although recently researchers have described the relationship between adiponectin and obesity in several human populations (Meilleur *et al.,* 2010 of 66), the precise mechanisms of any association between them are still not completely elucidated. This antiinflammatory cytokine stimulates nitric oxide production and may mediate associations between visceral obesity and vascular dysfunction (Peña *et al.,* 2010 of 66). Initial studies suggested that adiponectin exerted anti-inflammatory effects on endothelial cells through the inhibition of son inflammatory cytokines (Ouchi *et al.,* 1999). It has been established that mRNA expression of adiponectin is negatively correlated with body mass index and expression of the pro-inflammatory cytokine IL-6 (Moschen *et al.,* 2010).

Circulating adiponectin level decreases in obesity and is inversely correlated with insulin resistance and C-reactive protein (Fantuzzi, 2005). There is considerable evidence that adiponectin is affected by, and is itself involved in, the regulatory pathway of many factors including tumor necrosis factor-α, interleukin-6, C-reactive protein, insulin, weight loss/gain, body composition, and disease (Simpson *et al.,* 2008). In the present study, we observed a close correlation between serum adiponectin and CRP. These finding demonstrates that increased serum adiponectin in obese subjects is associated with decreased CRP as well as Il-6. Consistent with our findings, Strong negative correlations of adiponectin concentrations with high-sensitivity C-reactive protein and, to lesser degree, with interleukin-6 concentrations were also repeatedly reported in some (Schulze *et al.,* 2004; Mantzoros *et al.,* 2005), although some recent studies does not confirm these data (Yamamoto *et al.,* 2002).

CRP is known to mainly produce by liver, and IL-6 is important in controlling hepatic CRP production (Yudkin *et al.,* 2000). This data supports that the association of adiponectin with CRP is similar to that of adiponectin with IL-6, becoming stronger with increasing adiposity (Kantartzis *et al.,* 2006). One study reported that central obesity plays a major role in the relationships of adiponectin with triglycerides, C-reactive protein, and tissue plasminogen activator (Shetty *et al.,* 2004). A growing body of literature suggests the mode of action of CRP, other cytokines and adiponectin and their specific roles in the regulation of inflammation. Population studies have reported important correlations between plasma levels of CRP and increased risk for heart disease. On the other hand, increased concentrations of plasma adiponectin are related to decreased risk for heart disease.

These observations are consistent with the findings that Several studies have suggested that adiponectin acts directly to increase adenosine monophosphate–activated kinase (Yamauchi *et al.,* 2002) and indirectly decreases levels of C-reactive protein and interleukin-6 through the dose-dependent, reciprocal inhibition of tumor necrosis factor-α (Ouchi *et al.,* 1999). On the other hand, data by a clinical study showed that treatment with adiponectin reduced secretion of the centrally active interleukin-6 from brain endothelial cells, a phenomenon that was paralleled by a similar trend of other proinflammatory cytokines (spranger *et al.,* 2006).

All together, recent evidence has shown that in obesity and its chronic related diseases such as diabetes and cardiovascular diseases, circulating adiponectin is inversely associated with CRP, suggesting that these two factors might reciprocally regulate each other. In was reported that

Adiponectin reduced IL-6-induced CRP mRNA levels in HepG(2) cells and CRP protein secretion (Sun *et al.,* 2011). More research is needed to further explore any pathophysiologic link between adiponectin and inflammatory cytokines.

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