International Journal of Biosciences (IJB)
ISSN: 2220-6655 (Print) 2222-5234 (Online)
Vol. 2, No. 6, p. 151-158, 2012
http://www.innspub.net

RESEARCH PAPER OPEN ACCESS

Serum adiponectin is related to resistin independent of adiposity

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Received: 12 May 2012
Revised: 25 May 2012
Accepted: 02 June 2012

Key words: Obesity, adiponectin, resistin, anthropometrical markers.

Abstract

Adipocytokines secreted by adiposity and other tissues in known to have inflammatory and anti-inflammatory property. Adiponectin and resistin are two important adipokines and they have important role in obesity and chronic related diseases. This study was designed to determine the relationship between serum adiponectin as an anti-inflammatory cytokine with resistin as a pro-inflammatory cytokine in thirty six sedentary adult men aged 38-44 years and body mass index, 32.56 ± 4.54 Kg/m2. For this purpose, participants fasted overnight to provide blood specimens and venous blood samples were collected of subjects. Blood samples were analyzed for measuring serum adiponectin and resistin. All anthropometrical variables were also measured. Serum adiponectin was not related with each anthropometrical marker ($p \geq 0.05$). In contrast, we observed that serum resistin was positively related anthropometrical indexes ($p < 0.05$). Serum adiponectin concentrations were negatively correlated with resistin, independent of BMI or fat tissue ($P=0.000$, $r=0.77$). Based on these data, we conclude the relationship between adiponectin and resistin levels were independent of adiposity in obese men.

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Introduction

It is repeatedly reported that obesity is associated with systemic inflammation (Hansen *et al.,* 2010; Gnacińska *et al.,* 2010). Adipokines or adipocytokines secreted by adipocytes may be involved in the underlying biological mechanism linking obesity due to their potential effects on insulin resistance, systemic inflammation and endothelial function which are important pathways involved in atherosclerosis and hence the pathogenesis of cardiovascular disease(Rabe *et al.,* 2008; Li *et al.,* 2007; Knudson *et al.,* 2008). In addition to a main source of triglyceride, adipose tissue functions as an endocrine organ (Pajvani *et al.,* 2003; Sell *et al.,* 2006), thermal insulation, and mechanical protection, releasing biologically active and diverse cytokines, termed adipokines (Pajvani *et al.,* 2003; Aldhahi *et al.,* 2003).

Adipokine (adipocytokine) is a general term of adipose-specific cytokines, such as leptin, resistin, adiponectin, visfatin, and omentin, and nonadipose-specific cytokines such as IL-6, IL-1*β*, and TNF-*α* (Ahima, 2006; Bassols *et al.,* 2009). Depending on their roles on body tissue, some cytokines are protective, others can be detrimental. Adiponectin, as anti-inflammatory cytokine, is a 30-kDa protein that is predominantly expressed in adipocytes (Maeda *et al.,* 1996; Scherer *et al.,* 1995). Review of research evidence shows that adiponectin plays a important role in metabolic disorders, such as obesity, type 2 diabetes, coronary heart disease, and metabolic syndrome (Salmenniemi *et al.,* 2004). Adiponectin is found in high concentrations in the peripheral circulation (Tsao *et al.,* 2002), and its circulating levels are decreased in obesity and type 2 diabetes (Arita *et al.,* 1999). In contrast, resistin is an inflammatory cytokine and its levels increased in the presence of obesity and chronic related diseases (Steppan *et al.,* 2001).

Although resistin has structural similarities to proteins involved in inflammatory processes (Holcomb *et al.,* 2000), circulating resistin levels have never been studied in relation to inflammatory or anti-inflammatory markers in humans. Review of research evidence shows a wide variability of adiponectin levels even in subjects having similar BMI (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). On the other hand, the mechanisms underlying the relationship between adiponectin and resistin have not been fully established yet. Therefore, we evaluated the association of baseline circulating levels of adiponectin and resistin in middle-aged obese or overweight men and in case there is any relationship between them, is this relationship dependant on the body fat level or other anthropometrical indexes determining obesity, or independent from them.

Material and methods

Study population

In present study, we determined the relationship between serum adiponectin and resistin in thirty seven sedentary but healthy adult obese or overweight males aged 38 – 44 years and body mass index (32.56 ± 4.54 Kg/m2) that selected for participle in this study by accidentally. All subjects were otherwise in good health were taking no medications. Obesity or overweight was diagnosed by BMI and body fat percentage. All subjects had a body mass index (BMI) greater than 28 kg/m^2 and they have body fat percentage higher than 27 (%).The ethics approval was taken from Islamic Azad University of Iran ethical committee. After the nature of the study was explained in detail, informed consent was obtained from all participants.

Inclusion or exclusion criteria

Subjects were excluded if they had a known history of cardiovascular disease, stroke or transient ischemic attack, uncontrolled hypertension, liver disease, renal disease, diabetes or asthma, or any other serious chronic disease requiring active treatment. All subjects

were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months.

Anthropometrical and laboratory measurements

We measured height, weight, and waist circumference by using a standardized protocol. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m2). Waist and hip circumferences were measured and a waist-to-hip ratio (WHR) was calculated. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Percentage body fat was measured using body composition monitor (OMRON, Finland).

After anthropometrical measurements, venous blood samples were collected of subjects. Participants fasted overnight to provide blood specimens. Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. Blood samples were analyzed for measuring serum adiponectin and resistin. Adiponectin concentrations were measured by immunosorbent assay (ELISA; Biovendor, Czech) (Intra-assay CV: 5.9%; Inter-assay CV: 6.3%). Serum resistin 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 3.4% and 0.033 ng/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 and resistin 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

Table 1 show the descriptive anthropometric and biochemical features of the study groups. Data were expressed as individual values or the mean ± SD. Significant levels of each anthropometrical index with serum resistin and adiponectin are also presented in Table 1. The data of statistical analysis indicate serum adiponectin was negatively correlated with serum resistin in studied subjects (P=0.000, r=0.77, Fig 1). The significant correlation between adiponectin and resistin were independent of adiposity markers such as BMI and other markers of anthropometric. There was no significant relationship between serum adiponectin with all anthropometrical indexes (see Table 1). But we observed that serum resistin was positively correlated with BMI (Fig. 2), body weight, abdominal obesity and body fat percentage (Fig. 3).

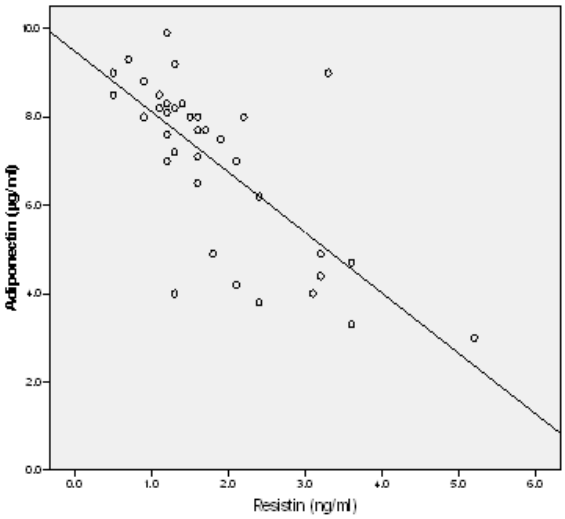

Fig. 1. The correlation pattern between serum adiponectin and resistin in obese subjects.

Discussion

Our study finding supports negative relation between serum resistin as a pro-inflammatory cytokine in obese individuals. These findings point out that increased circulating adiponectin is associated with lower systemic inflammation in obese subjects. In accordance with our observations, in a recent study by Barnett et colleagues, Resistin levels had an inverse correlation with adiponectin levels, indicating an

inverse relationship between pro-inflammatory cytokines and adiponectin (Hanif *et al.,* 2006).

Review of research evidence shows that Adiponectin and resistin are two adipose secreted signals with apparently different, opposite functions regarding the control of insulin sensitivity (Ribot *et al.,* 2008). Adiponectin is also known as Acrp30, AdipoQ, apM1, or GBP28, and it is only expressed in mature adipocytes, in both white adipose tissue (WAT) and brown adipose tissue (Ahima, 2006; Kadowaki *et al.,* 2006). Adiponectin is highly conserved across species, and it is the most abundant protein secreted by adipose tissue (Ahima, 2006; Kadowaki *et al.,* 2006). Adiponectin has been postulated to have efects on energy homeostasis, glucose and lipids, and diferent studies suggest that such effects would be mediated through phosphorylation and activation of adenosine monophosphate–activated protein kinase, an enzyme typically activated by cellular stress (Ahima, 2006). This antiinflammatory cytokine can also increase fatty-acid oxidation and energy consumption in part via peroxisome proliferator-activated receptor-α (PPARα) activation (Kadowaki *et al.,* 2006).

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

Variable	Mean ± SD	Significant level with Adiponectin	Significant level with Resistin
Age (years)	40 ± 3.4	P=0.022, r=0.41	P=0.013, r= 0.43
Weight (kg)	99 ± 11	P=0.332, r=0.18	P=0.021, r=0.45
Height (cm)	177± 6.11	P=0.114, r=0.28	P=0.339, r=0.17
Abdominal circumference (cm)	105 ± 8.12	P=0.076, r=0.31	P=0.042, r=0.39
Hip circumference (cm)	103 ± 7.35	P=0.035, r=0.37	P=0.032, r=0.42
WHO	1.02 ± 0.21	P=0.533, r=0.14	P=0.001, r=0.55
Visceral fat	14.27 ± 2.68	P=0.314, r= 0.19	P=0.032, r=0.38
Body fat percentage (%)	32.56 ± 4.54	P=0.325, r=0.22	P=0.023, r=0.41
Body mass index (kg/m²)	31.93 ± 6.18	P=0.412, r=0.19	P=0.032, r=0.43
Serum resistin (ng/ml)	2.1 ± 1.44	P=0.000, r=0.77	-----
Serum adiponectin (µg/ml)	6.97 ± 1.93	-----	P=0.000, r=0.77

Although recently readers have described the relationship between adiponectin and obesity in several human populations (Meilleur *et al.,* 2010), the precise mechanisms of any association between them are still not completely elucidated. Circulating adiponectin is known to affected by gender, aging, and lifestyle; interestingly, female humans and rodents have higher plasma adiponectin levels than males (Kadowaki *et al.,* 2006). Although in present study, serum adiponectin was not related with all anthropometrical indexes of obese subjects, suggesting serum adiponectin is independent of adiposity in these subjects.

Resistin is a putative adipocyte-derived signaling poly-peptide first described in 2001 (Steppan *et al.,* 2001). This inflammatory cytokine belongs to a family of cysteine-rich proteins (Meilleur *et al.,* 2010; Steppan *et al.,* 2001). Although the expression of resistin in mice was originally restricted to adipocytes (Steppan *et al.,* 2001), the principle origin of human resistin has remained somewhat contentious. Unlike the mouse gene, the human homologue of resistin was sparsely

detectable in human adipocytes (Nagaev and Smith, 2001); this was confounded further by confusion over the proposed sites of resistin production (Nagaev *et al.,* 2001; Janke *et al.,* 2002). Unlike the expression of resistin in mouse, a number of studies have demonstrated that human resistin is expressed primarily in macrophages but not in adipose (Tomaru *et al.,* 2009). Diferent studies showed that resistin was upregulated in rodent models of obesity (usually in models of well-developed obesity); thus it was characterized as a potential etiological link between obesity and diabetes (Kusminski *et al.,* 2005).

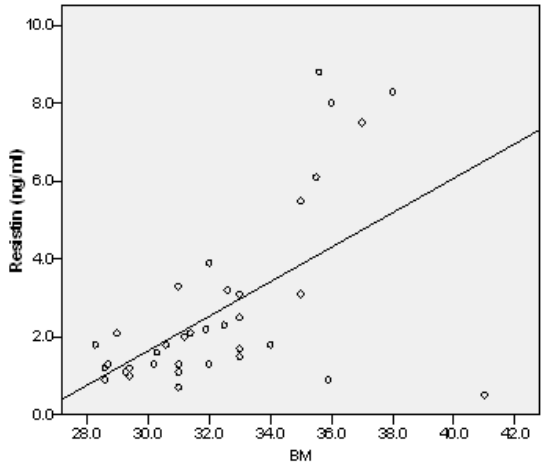

Fig. 2. The correlation pattern between serum resistin and BMI in obese subjects.

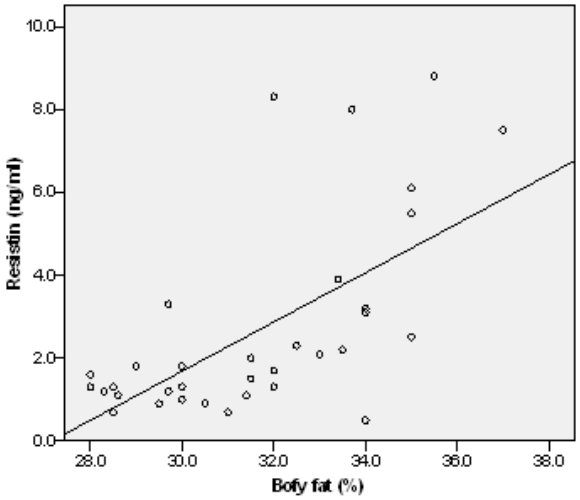

Fig. 3. The correlation pattern between serum resistin and body fat percentage in obese subjects.

Growing bodies of literature have highlighted increased resistin expression in adipose tissue (Savage *et al.,* 2001), particularly abdominal depots (McTernan *et al.,* 2002; McTernan *et al.,* 2002); furthermore, positive correlations between serum resistin and body fat content have also been reported (Zhang *et al.,* 2002). In comparison with mouse models, human resistin expressed in adipose tissue is significantly lower and is also expressed in other tissues (Pang *et al.,* 2006), although different human obesity studies have highlighted increased resistin expression in adipose tissue particularly in abdominal depots and positive correlations between serum resistin and body fat content (Kusminski *et al.,* 2005). These observations are consistent with the findings of our study. In present study, serum resistin is strongly and positively associated with adiposity markers such as BMI, abdominal obesity and body fat percentage. These data supports the hypothesis that circulating resistin is strongly influenced by body fat levels.

To sum up, the findings of the present study suggest that serum adiponectin and resistin levels of obese people are inversely related and the relationship is significant. However, based on the results of this study alone it is not possible to conclude with certainty that increase in resistin levels of obese subjects causes a cut in adiponectin level. In fact there is the possibility that changes in serum adiponectin and resistin levels of obese subjects or other healthy or unhealthy populations are influenced by other hormonal or inflammation mediators. Nonetheless, these findings in line with previous studies, point to an indirect linear relationship between level of adiponectin and resistin in serum of the obese individuals. Moreover, this indirect relationship was observed while no significant relationship was found between anthropometrical indexes and adiponectin level. Also, a significant relationship was observed between resistin level and each of the body fat level markers. Evidently, absence of relationship between adiponectin and adiposity has already been reported in previous studies (Weyer *et al.,*

2001; Snehalatha *et al.,* 2008; Lindsay *et al.,* 2002; Retnakaran *et al.,* 2006). These same studies have even reported the relationship between serum adiponectin levels and other blood metabolic factors independent of body fat levels. In fact, in recent study researchers found that the relationship between adiponectin and insulin sensitivity is independent of BMI or other anthropometrical indexes (Martin *et al.,* 2008; Bacha *et al.,* 2004). This was also reported in earlier studies (Weiss *et al.,* 2004). Considering these research findings, the present study suggests that despite a close relationship between serum resistin and other anthropometrical indexes, adiponectin levels in serum are not influenced by body fat. Therefore, it seems that the relationship between adiponectin and resistin levels of obese individuals under study were independent of body fat levels. Finally, it should be acknowledged that a comprehensive understanding of the mechanisms of the relationship between these cytokines and the nature of their interactions deserves more studies and laboratory experiments.

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