Ind J Clin Biochem (Apr-June 2013) 28(2):158–163
DOI 10.1007/s12291-012-0246-3

ORIGINAL ARTICLE

# Hypoadiponectinemia in Obesity: Association with Insulin Resistance

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Received: 29 May 2012 / Accepted: 21 July 2012 / Published online: 17 August 2012
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**Abstract** Obesity is risk factor for insulin resistance, diabetes, and other chronic diseases. Adiponectin, an adipose-specific protein with antiatherogenic and antiinflammatory effects, were found to be associated with obesity, type 2 diabetes, and insulin resistance. Our aim to identify possible relationships between circulating adiponectin and obesity as well as obesity related phenotypes. A total of 642, obese and non-obese individuals were included in this cross-sectional study. Hormone and glucose levels were estimated using standard protocols. The adiponectin levels showed a significant decrease with increasing quartiles of insulin resistance index. Subjects in lowest quartile of adiponectin level had a significantly higher risk than those in the highest quartile, with higher body mass index, waist circumference, blood pressure, percentage body fat, fat mass, fasting insulin, insulin resistance index, total cholesterol ($p < 0.001$), low density lipoprotein–cholesterol ($p = 0.001$), very low density lipoprotein–cholesterol ($p = 0.002$), and Triglyceride ($p = 0.002$). The present study indicates that adiponectin is significantly associated with obesity, insulin resistance and other obesity related phenotypes.

**Keywords** Adiponectin · Insulin resistance · Obesity · Phenotypes · Body mass index

## Introduction

Obesity is commonly associated with insulin resistance and hyperinsulinemia and is often associated with high blood pressure and various metabolic abnormalities, such as dyslipidemia and elevated plasma glucose [1].

Adiponectin is the most abundant serum adipokine that has been recognized as a key regulator of insulin sensitivity, tissue inflammation, endothelial function, and lipid metabolism [2]. Moreover, a growing body of evidence suggests that hypoadiponectinemia may play a significant role in the development of Metabolic Syndrome [3]. However, little is known about the significance of circulating adiponectin as a surrogate marker for obesity itself and development of obesity related phenotypes in general population.

Adiponectin is the only adipose-derived cytokine that is decreased in individuals with obesity, type 2 diabetes, and coronary artery disease [4]. Hypoadiponectinemia has been demonstrated to be linked with insulin resistance [5], while increased adiponectin levels by supplementation of adiponectin attenuated the insulin resistance [6]. Moreover, the effect of adiponectin was supported by human cohort study in which hypoadiponectinemia apparently predicted the development of type 2 diabetes [7]. A low level of adiponectin was also associated with a higher risk for myocardial infarction and mortality after stroke [8].

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Hypoadiponectinemia is common in obese adults [9], and subjects having insulin resistance [10]. Low adiponectin is shown to be predictive of future diabetes, in many populations, including the Asian Indian [11].

Therefore, we sought to address this question and to identify potential relationships between circulating adiponectin concentration and obesity as well as obesity associated phenotypes.

## Methods

### Subjects

This study is a population-based cross-sectional study, designed to evaluate the effects of adiponectin on obesity and obesity related phenotypes. A total of 821 subjects were enrolled initially from the out patients department of Chatrapati Shahuji Maharaj Medical University, Lucknow, and community centers for routine preventive care in Lucknow city (North India).

Out of these subjects, only 309 obese (BMI $> 30$ kg/m$^2$) and 333 non obese (BMI $\leq 30$ kg/m$^{2)}$ individuals were selected on the basis of the strict inclusion criteria. In all individuals, body height, body weight, waist circumferences and hip circumferences were measured for calculation of BMI and WHR. Hypertension was diagnosed when the systolic or diastolic BP was $\geq$140/$\geq$90 mm Hg on a repeated single-day measurements or when the individual was a known hypertensive. Diabetes was diagnosed when a subject provided history of previously diagnosed diabetes or the fasting blood glucose was $\geq$126 mg/dL.

Subjects with established diabetes mellitus, coronary artery disease, congestive heart failure, and pregnant women were excluded. Informed consent was obtained from each participant and the study was carried out in accordance with the local ethics committee. All study participants were subjected to a thorough screening program that included assessment of a detailed personal and family history, physical examination, determination of anthropometric indices and measurement of various biochemical parameters.

### Estimation of Body Fat Composition

The Body fat analyzer (Bioelectrical impedance was obtained using a device, Tanita-TBF-310, Tanita, Tokyo, Japan; calibrated to suit Indian population) was used for assessing the percentage body fat and fat mass.

### Biochemical Parameters

Venous blood was collected after an overnight fast, and plasma and serum samples were either used immediately for analysis or were stored frozen at $-80$ °C. Commercial enzymatic test kits were used for determining high density lipoprotein–cholesterol, triglyceride concentrations and total serum cholesterol, low density lipoprotein cholesterol was calculated by the formula of Friedewald (low density lipoprotein–cholesterol = total cholesterol − high density lipoprotein cholesterol − triglyceride/5 mg/dl). The inter assay coefficient of variation was less than 5.0 % for high density lipoprotein–cholesterol, less than 2.5 % for triglycerides.

Insulin level was determined by enzyme-linked radio immunosorbent assay (Linco Research, Inc.). The intra- and the inter assay coefficients of variation for the insulin assay were 5.7 and 8.9 %, respectively. The lowest detection limit of insulin assay was 0.5 μU/ml. Laboratory measurements.

The degree of insulin sensitivity/resistance was calculated according to the homeostasis model assessment (HOMA) which is a good index for assessing insulin sensitivity/resistance. Insulin resistance (IR) was calculated as follows: IR = FI × g/22.5; where FI = fasting insulin ($\mu$u/ml) and g = fasting glucose (mmol/1) [12]. Adiponectin was assayed with enzyme linked immunosorbent assay. The fasting glucose concentration was measured by Glucose oxidase–Peroxidase (GOD-POD) method [13].

### Statistical Analysis

Quantitative variables are expressed as mean (standard deviation) or as mean (range). An independent $t$ test was performed to assess differences between the two groups in terms of biochemical parameters. Groups were also compared by one-way analysis of variance. A two-tailed probability value of $p < 0.05$ was considered statistically significant. Pearson correlation coefficient ($r$) analysis was used to evaluate the correlation of Adiponectin with obesity and parameters of obesity. All statistical analysis was performed with Statistical Package for the Social Sciences 15.0 software.

## Results

Basic metabolic and clinical characteristics of all subjects in non-obese, overweight and obese groups are summarized in (Table 1). There was statistically insignificant age difference between three groups, the non-obese subjects proved to be within the physiological parameters in all the tests performed and there were significant difference between non-obese group to overweight and obese group for insulin, HOMA of insulin resistance index, adiponectin, fat mass, percentage body fat, total cholesterol while systolic, diastolic blood pressure, very density lipoprotein

**Table 1** Basic metabolic and clinical characteristics of subjects

| | Non-obese (136) | Over-weight (197) | Obese (309) |
|---|---|---|---|
| Sex (male/female) | 86 (63.2)/50 (36.8) | 108 (54.8)/89 (45.2) | 153 (49.5)/156 (50.5) |
| Waist to hip ratio | 0.94 (0.09) | 0.95 (0.08) | 0.96 (0.09) |
| Systolic blood pressure (mm Hg) | 119.75 (9.96) | 121.04 (12.73) | 128.39 (15.19)*** |
| Diastolic blood pressure (mm Hg) | 80.47 (6.74) | 80.95 (8.27) | 86.23 (8.05)*** |
| Fat mass (kg) | 18.84 (7.12) | 21.81 (8.62)** | 30.59 (8.33)*** |
| Percentage body fat | 26.68 (5.80) | 28.67 (6.21)** | 37.28 (6.16)*** |
| Insulin (μU/ml) | 8.66 (5.05) | 11.38 (6.37)** | 15.00 (9.73)*** |
| Adiponectin (μg/ml) | 8.18 (1.45) | 7.56 (1.66)** | 6.52 (1.88)*** |
| Homeostasis model assessment of insulin resistance index | 2.37 (1.50) | 3.15 (1.97)* | 4.15 (2.87)*** |
| Total cholesterol (mg/dl) | 153.69 (42.08) | 167.25 (45.69)** | 213.54 (35.72)*** |
| High density lipoprotein cholesterol (mg/dl) | 47.43 (10.24) | 44.67 (9.85) | 42.82 (7.13)** |
| Very low density lipoprotein cholesterol (mg/dl) | 20.94 (3.63) | 21.76 (4.07) | 26.06 (5.78)*** |
| Triglyceride(mg/dl) | 104.69 (18.16) | 108.80 (20.37) | 130.28 (28.88)*** |
| Low density lipoprotein (mg/dl) | 96.16 (29.80) | 102.12 (41.26) | 151.29 (30.440*** |
| Fasting glucose (mg/dl) | 108.96(15.67) | 109.41 (16.15) | 109.64 (18.62) |

The variables are presented as mean values (standard deviation) or number (%)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (comparison with healthy subjects)

cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride show significant difference between overweight and obese groups. The obese subjects had higher value of systolic and diastolic hypertension, insulin, fat mass, percentage body fat, HOMA of insulin resistance index, lipid profile concentrations and lower value of adiponectin concentration (Table 1).

We also evaluated level of serum adiponectin levels in male and female groups. There were significant sex-specific differences in adiponectin levels between different groups.

Table 2 shows interrelationships between serum adiponectin levels and HOMA of insulin resistance index in both genders. A significantly linear decrease in adiponectin levels was observed according to increasing quartiles of HOMA of insulin resistance index in both men and women. Using the HOMA of insulin resistance index, we also estimated the indices of insulin resistance among all subjects. The serum adiponectin levels showed a significantly linear decrease with increasing quartiles of HOMA of insulin resistance index in both men and women ($p$ trend $< 0.001$). The median serum adiponectin levels in men with 1st quartile, 2nd quartile, 3rd quartile, and 4th quartile were 7.83, 7.50, 6.47, and 5.85, respectively ($p$ trend $< 0.001$), while those in women were 8.34, 8.25, 7.52, and 6.07, respectively ($p$ trend $< 0.001$).

The relationship between adiponectin quartiles and various Clinical and biochemical variables are summarizes in Table 3. Subjects with baseline adiponectin levels in the lowest quartile had a significantly higher adverse risk factor profile than those in the highest quartile, with higher

**Table 2** Distribution of serum adiponectin levels among the cohort according to lean, over weight and obese subjects and quartile of homeostasis model assessment of insulin resistance index in men (347) and women (295)

| | Adiponectin, μg/dL Men (347) | p trend | Adiponectin, μg/dL Women (295) | p trend |
|---|---|---|---|---|
| Lean | 7.96 (7.69–8.23) | <0.001 | 8.56 (8.08–9.04) | <0.001 |
| Over weight | 7.12 (6.81–7.43) | | 8.10 (7.77–8.42) | |
| Obese | 6.41 (6.12–6.69) | | 6.62 (6.31–6.94) | |
| Homeostasis model assessment of insulin resistance index | | | | |
| 1st quartile (<1.66) | 7.83 (7.49–8.17) | <0.001 | 8.34 (7.92–8.77) | <0.001 |
| 2nd quartile (1.67–2.71) | 7.50 (7.20–7.81) | | 8.25 (7.72–8.77) | |
| 3rd quartile (2.72–4.55) | 6.47 (6.13–6.81) | | 7.52 (7.15–7.90) | |
| 4th quartile (>4.55) | 5.85 (5.51–6.20) | | 6.07 (5.73–6.41) | |

The variables are presented as mean (range)

**Table 3** Associations between serum adiponectin levels and baseline characteristics ($n = 642$)

| Parameter | 1st quartile 161 (25.1) | 2nd quartile 161 (25.1) | 3rd quartile 161 (25.1) | 4th quartile 159 (24.7) | $p$ value |
|---|---|---|---|---|---|
| Body mass index | 32.30 (31.47–33.14) | 29.73 (29.14–30.32) | 27.45 (26.60–28.31) | 27.03 (26.14–27.92) | <0.001 |
| Waist to hip ratio | 0.99 (0.97–1.00)* | 0.98 (0.97–0.99) | 0.95 (0.93–0.96)* | 0.92 (0.91–0.93)* | <0.001 |
| Systolic blood pressure (mm Hg) | 131.02 (128.71–133.33) | 125.93 (123.85–128.00) | 120.34 (118.22–122.46) | 119.87 (118.13–121.62) | <0.001 |
| Diastolic blood pressure (mm Hg) | 87.35 (86.06–88.65) | 84.39 (83.09–85.68) | 80.60 (79.53–81.66) | 81.21 (79.96–82.46) | <0.001 |
| Fat mass | 31.92 (30.38–33.45) | 26.66 (25.50–27.82) | 21.34 (20.14–22.54) | 21.69 (20.24–23.15) | <0.001 |
| Percentage body fat | 36.60 (35.46–37.74) | 33.69 (32.61–34.77) | 29.40 (28.27–30.54) | 29.84 (28.73–30.96) | <0.001 |
| Insulin (μU/ml) | 17.85 (16.16–19.54) | 13.98 (12.83–15.13) | 10.32 (9.38–11.25) | 7.97 (7.36–8.58) | <0.001 |
| Homeostasis model assessment of insulin resistance index | 5.02 (4.52–5.51) | 3.88 (3.54–4.23) | 2.79 (2.52–3.06) | 2.17 (1.97–2.36) | <0.001 |
| Total cholesterol | 200.17 (193.37–206.97)* | 185.68 (178.37–192.99) | 180.83 (172.85–188.82)* | 179.86 (172.33–187.38)* | <0.001 |
| High density lipoprotein cholesterol (mg/dl) | 44.51 (43.32–45.70) | 45.04 (43.55–46.53) | 45.09 (43.63–46.55) | 43.87 (42.41–45.32) | 0.587 |
| Very low density lipoprotein cholesterol (mg/dl) | 24.64 (23.79–25.48)$ | 24.24 (23.36–25.12) | 23.16 (22.30–24.03) | 22.56 (21.81–23.31)$ | 0.002 |
| Triglyceride(mg/dl) | 123.18 (118.96–127.41)$ | 121.19 (116.80–125.59) | 115.82 (111.50–120.13) | 112.81 (109.06–116.56)$ | 0.002 |
| Low density lipoprotein (mg/dl) | 135.60 (128.87–142.34)* | 123.38 (117.01–129.74) | 120.41 (113.81–127.02)* | 118.61 (111.96–125.25)* | 0.001 |
| Fasting glucose (mg/dl) | 111.55 (108.55–114.55) | 111.12 (108.32–113.93) | 107.90 (105.42–110.38) | 107.10 (104.71–109.48) | 0.043 |

The variables are presented as mean (range)

*$p < 0.05$ (comparison with 1st quartile to 3rd and 4th quartile), $ $p < 0.05$ (comparison with 1st quartile to 4th quartile), (1st quartile 0–5.68, 2nd quartile 5.69–7.4, 3rd quartile 7.41–8.70 and 4th quartile 8.71–16)

body mass index, percentage body fat, fat mass, Total cholesterol, low density lipoprotein–cholesterol, very low density lipoprotein–cholesterol, Triglyceride, systolic and diastolic blood pressure, waist circumference, fasting insulin, and insulin resistance index (as assessed by HOMA of insulin resistance index) ($P < 0.05$ for all parameters).

Pearson correlation coefficient ($r$) analysis was used to determine the correlation of Adiponectin with obesity (define by BMI) and several parameters of obesity (Table 4). In obese and non-obese subjects, Adiponectin significantly negatively correlated with obesity (defined by BMI) ($r = -0.378$, $p < 0.001$), and other parameters of obesity like WHR, SBP, DBP, Percentage body fat, fat mass, insulin, HOMA of insulin resistance index, Total Cholesterol, Triglyceride, LDL-C, and Fasting Glucose (Table 4).

## Discussion

In the present study adiponectin level is significantly lower in morbid obese subjects in comparison to over-weight and non-obese subjects while insulin and HOMA of insulin resistance index are significantly higher in morbid obese subjects in comparison to over-weight and non-obese subjects.

Data were also analyzed according to gender, and mean serum adiponectin levels in men were lower than women but the levels were typically lower in morbid obese subjects in comparison to over-weight to non-obese subjects in both sexes. Also, mean serum adiponectin levels were found to be associated significantly with the HOMA of insulin resistance index quartiles. Lower mean serum adiponectin levels were significantly associated with highest quartile of HOMA of insulin resistance index.

Our results thus confirm that adiponectin is negatively regulated in obesity ($r = -0.378$, $p < 0.001$). Previous report on Japanese individuals has shown that the plasma adiponectin concentration is negatively correlated with body mass index (BMI) [14].

In this study, we confirm the relationships between adiponectin and various parameters of obesity. Lowest adiponectin Quartile was found to be associated significantly with higher body mass index (obesity), central obesity measured by waist to hip ratio and obesity related phenotypes like lower Systolic, Diastolic blood pressure, lower insulin, lower HOMA of insulin resistance index, lower fasting glucose, percentage body fat and fat mass.

**Table 4** Correlations of leptin with several parameters of obesity and circulating levels of adipokine

| Factor | Plasma adiponectin | |
|---|---|---|
| | Correlation coefficient ($r$) | $P$ value |
| BMI | −0.378** | <0.001 |
| Waist to hip ratio | −0.301** | <0.001 |
| Systolic blood pressure (mm Hg) | −0.326** | <0.001 |
| Diastolic blood pressure (mm Hg) | −0.303** | <0.001 |
| Percentage body fat | −0.372** | <0.001 |
| Fat mass (kg) | −0.435** | <0.001 |
| Insulin (μU/ml) | −0.475** | <0.001 |
| Adiponectin (μg/ml) | – | – |
| Homeostasis model assessment of insulin resistance index | −0.466** | <0.001 |
| Total cholesterol (mg/dl) | −0.146** | <0.001 |
| High density lipoprotein cholesterol (mg/dl) | −0.013 | 0.741 |
| Very low density lipoprotein cholesterol (mg/dl) | −0.128** | 0.001 |
| Triglyceride(mg/dl) | −0.138** | 0.001 |
| Low density lipoprotein (mg/dl) | −0.132** | 0.001 |
| Fasting glucose (mg/dl) | −0.115** | 0.004 |

**Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed)

Previous study has reported an inverse correlation between serum adiponectin concentration and body fat content, BMI, and fasting glucose [15], we also repot the same correlations.

Central obesity measured by waist to hip ratio significantly associated with adiponectin quartile, an inverse association between adiponectin concentrations and central obesity has been well established and confirmed in earlier study [16]. On the other hand, we have confirmed that systolic and diastolic blood pressures were associated with serum adiponectin levels, our results were in agreement with the previous cross-sectional study [17]. In previous animal study, adiponectin-knockout mice on a high salt diet developed hypertension, which was ameliorated by adiponectin replenishment [18]. Rahmouni et al. [19] reported that elevated free fatty acid levels in obese subjects appear to participate in obesity related hypertension, via sympathoactivation. Because adiponectin can reduce circulating fatty acid levels via enhanced fatty acid oxidation and reduced fatty acid synthesis [20], hypoadiponectinemia may increase the risk of hypertension in obese subjects through its adverse effects on fatty acid metabolism. Chow et al. [21] observed that hypoadiponectinemia associated with hypertension in prospective study.

The adiponectin was also recognized as an independent predictor for insulin resistance. The negative relationship was reported between adiponectin and insulin resistance in type 2 diabetes [22] and in insulin-resistant subjects [23]. The role of adiponectin on the pathogenesis of insulin resistance is at this time not well understood. Although in epidemiological and experimental studies, the association between low adiponectin levels and insulin resistance were reported but it has not been known whether decreased adiponectin levels are the cause of insulin resistance or decreased adiponectin levels are due to the insulin resistance. It has been shown that adiponectin directly or indirectly affects insulin sensitivity through modulation of insulin signaling and the molecules involved in glucose and lipid metabolism [24] and insulin resistance might be major determinants of the hypoadiponectinemia in obesity [9]. One of possible mechanisms for is overproduction of tumor necrosis factor-α by adipose tissue. Tumor necrosis factor-α is a cytokine which has direct effects on the insulin signaling cascade by improved release of free fatty acids by adipocytes and decrease of adiponectin synthesis [25]. In numerous obesity–diabetes models, tumor necrosis factor-α over expressed in adipose and muscle tissues and tumor necrosis factor-α blocks the action of insulin in cultured cells [26]. In humans, tumor necrosis factor-α also over expressed in the adipose and muscle tissues of obese insulin resistance subjects [27]. The production and action of tumor necrosis factor-α, both has been shown to inhibit by adiponectin [28]. Because hypoadiponectinemia may accelerate the tumor necrosis factor-α reaction, so the insulin resistance may be induced by hypoadiponectinemia.

The insulin resistance could be improved by replenishment of adiponectin in lipoatrophic and obese diabetic mice [6]. However, hyperinsulinemia down regulate adiponectin gene expression in 3T3-L1 adipocytes [29] and decreased adiponectin secretion in the insulin-resistant state might be induced by hyperinsulinemia.

In the present study, lowest adiponectin quartile were significantly associated with total cholesterol, triglyceride, LDL cholesterol, and VLDL cholesterol while results also showed that serum adiponectin was not associated with HDL cholesterol.

A significant negative correlation between plasma adiponectin and triglyceride levels were reported in previous studies [14, 15]. Adiponectin influences plasma lipoprotein concentrations by altering the expression and activity of key enzymes (i.e., lipoprotein lipase and hepatic lipase) responsible for the catabolism of triglyceride-rich lipoproteins [30].

In summary, the present study indicates that adiponectin is significantly and independently associated with obesity, insulin resistance and other obesity related phenotypes.

**Acknowledgments** Authors acknowledge Indian Council of Medical Research, New Delhi, for the financial support to carry out this research work.

**Conflict of Interest** It is declared that none of the authors have any conflict of interest.

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