*Iranian J Publ Health, Vol. 37, No.2, 2008, pp.88-92*

**Original Article**

# Serum Level of Adiponectin and Its Association with Insulin Sensitivity in Overweight Diabetic and Non-Diabetic Iranian Men

**L Giahi [1], A Djazayery [1], A Rahimy [2], M Rahmany [3], B Larijani [3]*

[1]*Dept. of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Iran*
[2]*Dept. of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Iran*
[3]*Endocrine Laboratory of Endocrine and Metabolic Research Center, University of Medical Sciences, Iran*

**(Received 8 Nov 2007; accepted 27 May 2008)**

## Abstract

**Background:** Adiponectin is a protein produced exclusively by adipose tissue; the reduced level of which has been shown to be involved in a variety of obesity-related disorders, such as insulin resistance and diabetes, in different ethnic groups. This cross-sectional study was conducted to determine adiponectin level and its association with insulin sensitivity in 20 adult overweight type-2 diabetic and 20 healthy over-weight non-diabetic Iranian men for the first time.

**Methods:** Body fat mass (Bio-electric impedance), serum level of adiponectin (ELISA), fasting blood sugar and fasting insulin were measured. Insulin sensitivity was calculated using QUICKI.

**Results:** As expected, the mean adiponectin concentration was lower in diabetics (7.7 ±3μg/ml) than non-diabetics (8.1 ± 2μg/ml); however, the difference did not achieve statistical significance (*P*= 0.5). Adiponectin negatively correlated with fat mass. This correlation was stronger in diabetics with a higher fat mass (r= -0.3 in diabetics vs. r= -0.01 in non-diabetics; p: N.S.). Adiponectin positively related with insulin sensitivity in both groups, although this relation was only statistically significant in non-diabetics (r= +0.5; *P*= 0.04). The relation between insulin sensitivity and mean of adiponectin level was marginally significant even after adjustment for group (diabetic and non-diabetic), age and fat mass.

**Conclusion:** Our findings are consistent with the studies on different ethnic groups which have indicated lower adiponectin levels in diabetics. Also our results confirm the relationship between a low adiponectin level and insulin sensitivity reported in earlier studies.

**Keywords:** *Adiponectin, Insulin sensitivity, Over-weight, Diabetes, Iran*

## Introduction

Adiponectin is a 244-amino acid cytokine, discovered in 1996 (1), exclusively produced by mature adipocytes of white adipose tissue, and it occurs in remarkably high concentrations of about 5 to 30 μg/mL in human blood, accounting for 0.01% of the total serum protein (2). This novel protein appears to have a central role in the metabolic syndrome in addition to having anti-atherogenic and anti-inflammatory properties (3, 4). Interestingly, in sharp contrast to most adipokines, although adiponectin is exclusively synthesized by adipocytes, its expression and serum concentrations have been found to decrease in a variety of obese, insulin-resistance, hyper-insulinemia and hyperglycemia states. On the other hand, weight loss results in an increased adiponectin expression with accompanying improvements in insulin sensitivity in different ethnic groups (5, 6). The existing information indicate that reduced plasma levels of adiponectin may be an important factor in the issue of obesity and its associated inflammatory disorders, such as insulin resistance and type 2 diabetes (7-9).

Not much information is available about adiponectin in Iranians on the one hand, and its relation to insulin resistance on the other. The objectives of this study were to determine for the first time, the level of adiponectin and any relationship between adiponectin and insulin sensitivity, in two groups of overweight diabetic and non-diabetic Iranian men, who are at growing predisposition to insulin resistance and diabetes.



***Corresponding author:** Tel/Fax: + 98 21 44414473, E-mail:lgiahi@yahoo.com

## Materials and Methods

***Subjects*** The required sample size was calculated for the significant level of 95% with 80% power of test and including 15% possibility for attrition rate. A total of 40 overweight adult men (20 type 2 diabetics and 20 non-diabetics) were recruited for this cross sectional study. Diabetic subjects were selected from the over-weight (BMI= 25-29.9) patients of the Diabetes Clinic of Shariaty Hospital, Tehran, with a medical record from 2001 till 2005, consulting the Clinic for regular checkups. The patients were chosen if they were not receiving insulin, TZDs and any androgenic hormones. Healthy non-diabetic overweight (BMI= 25-29.9) adult men where chosen from the general population in autumn 2005. All the subjects gave their informed consent prior to any measurements and blood sampling.

***Anthropometric measurements*** Height was measured with Seca height rod (0.5 accuracy), without shoes, and weight with Seca weight scale (100 g accuracy), with light clothes and without shoes. Also fat mass and fat-free mass were measured with body stat 1500 (Britain).

***Blood sampling*** Fasting blood samples were collected from brachial vein in sitting position at the hormone laboratory of Endocrine and Metabolic Research Center (EMRC). Serums were immediately separated and stored at -80° until the assays were performed. Fasting blood sugar (FBS), and fasting insulin was measured using IRMA. Percent of insulin sensitivity was determined by the quantitative insulin-sensitivity check index, QUICKI= (1/l ogfastinginsulin (mU/ml)+logFBS (mg/dL)) (10). For measuring adiponectin levels ELISA (adipogene, Germany) was used.

***Statistical analyses*** Independent t-test was used to compare the means of variables between diabetic and non-diabetic groups. The correlations between variables were determined using the bivariate correlation test. Multiple regression was used to determine the simultaneous effect of group, age, fat mass and QUICKI on the mean of adiponectin level.

## Results

Table 1 shows the descriptive anthropometric and biochemical features of the study groups. The average duration of diabetes was 11 yr in the diabetic group. As expected, the mean adiponectin concentration was lower in diabetics (7.7±3μg/ml) than non-diabetics (8.1± 2μg/ml); however, the difference was not statistically significant (*P*= 0.5). Despite fairly similar BMIs of the groups, diabetics had a significantly higher fat mass than non-diabetics, which was independent of age (26.6± 2.3% vs. 22.9±2.6; *P*< 0.05) (Table 1).

The correlations between adiponectin and independent variables are shown separately in Table 2. Adiponectin negatively correlated with BMI and fat mass in both groups, however, not statistically significant. Interestingly, adiponectin related positively with insulin sensitivity in both groups, although this relation was only statistically significant in non-diabetics (r= +0.5; *P*= 0.04). After adjustment for group (diabetic and non-diabetic), age and fat mass coefficient of regression for QUICKI was 30.8 with standard error of 17.5, this coefficient was marginally significant with 90% confidence level, so that each 0.01 unit increase in QUICKI will result in 0.3 μg/ml rise in adiponectin level (Table 3).

**Table1:** Descriptive statistics of the study groups

| Variable | Diabetics (n=20) | Non-Diabetics (n=20) |
|---|---|---|
| Age (yr) | 47.5 (8.4) | 35.9 (6.4) |
| BMI(kg/m$^2$) | 27.7 (1.7) | 27.8 (1.3) |
| Fat mass (FM) % | 26.6 (2.3) | 22.9 (2.6) * |
| Fat Free mass% | 73.4 (2.9) | 77 (2.7) * |
| FBS (mg/ml) | 192.35 (56) | 96.5 (15.6) * |
| Fasting insulin (μIU/ ml) | 0.4(0.2) | 0.3(0.1) |
| QUICKI | 0.31(0.02) | 0.36(0.03) * |

Data are mean values (SD).
* *P*< 0.001 compared with diabetics

**Table 2:** Correlations between adiponectin and independent variables

| Independent variable | Diabetics | | Non-diabetics | |
|---|---|---|---|---|
| | r | *P* | r | *P* |
| BMI (kg/m$^2$) | -0.2 | 0.5 | -0.3 | 0.3 |
| FM% | -0.3 | 0.2 | -0.01 | 0. 9 |
| FBS(mg/ml) | +0.1 | 0.6 | -0.2 | 0.3 |
| Insulin(μIU/ ml) | -0.1 | 0.3 | -0.3 | 0.1 |
| QUICKI | +0.1 | 0.6 | 0.5 | 0.04* |

*Correlation significant at $P< 0.05$

**Table 3:** Regression result for adiponectin as dependent variable

| Independent variable | Coefficients | | Sig. |
|---|---|---|---|
| | B | Std. Error | |
| Group | .253 | 1.300 | .847 |
| Age | .127 | .061 | .044 |
| fat mass1 | -.213 | .163 | .199 |
| QUICKI1 | 30.817 | 17.583 | .088 |
| Constant | -2.558 | 8.350 | .761 |

## Discussion

This is the first study to report the adiponectin level in Iranian diabetic and non-diabetic men. We observed that diabetic subjects had relatively a lower level of adiponectin. This finding is consistent with the studies on different ethnic groups, such as Pima Indians, who have high propensity for obesity (11), Asian Indians (12) and Japanese population (13), all of which had revealed that type 2 diabetes mellitus is associated with lower plasma adiponectin levels.

As expected, adiponectin shows negative relations with BMI and fat mass, although, probably, due to the limited range of chosen BMI for this number of subjects (n= 20) in each group, this relation was not found to be statistically significant. Several clinical, epidemiological and animal studies have shown a decrease in adiponectin by increasing body weight and fat mass% (14-17), although adiponectin is exclusively synthesized by adipocytes. This property of adiponectin, as its other features, is in sharp contrast to other adipose tissue-derived proteins.

Interestingly, adiponectin positively relates with QUICKI, the relation being significant in non-diabetics ($P= 0.04$). This confirms the strong relationship between a low adiponectin level and insulin resistance and dyslipidemia reported in earlier studies (13, 16). On the other hand, animal studies on adiponectin knock out mice have shown severely reduced insulin sensitivity (18, 19). Decreased adiponectin levels, regardless of body fat mass, confer a substantially increased risk for diabetes and cardiovascular disease, suggesting that adiponectin may even contribute directly to the pathogenesis of these diseases (20).

These findings might be explained by the stimulatory effect of adiponectin on insulin receptor tyrosine kinase activity and the tyrosine phosphorylation of insulin receptor substrate-1 (21).

In turn, insulin has been shown to serve as an inhibitory regulator for circulating adiponectin based on in vivo and in vitro studies in humans and rodents. Our results also show a negative correlation between adiponectin and fasting insulin. On the other hand, experimental studies on mice have also revealed that adiponectin is a potent insulin enhancer, linking adipose tissue and whole-body glucose metabolism by enhancing the suppression of hepatic glucose production (22). Indeed, adiponectin might be involved in the improvement of glucose metabolism via stimulating fat oxidation and reducing plasma triglyceride (23, 24).

Due to our study design, which is a cross-sectional one, we can not determine the cause and effect relationship between adiponectin and inflammatory obesity-related conditions such as, type 2 diabetes, or judge whether a reduction in adiponectin precedes the disorder. Neither can we determine whether or not it has the potential to predict the development of the above disorders by interfering with the inter-regulatory pathways among adipocytokines, as it is claimed by some researches (20, 23).

We recommend strongly that prospective studies in a cohort of overweight and obese subjects with a high risk of diabetes be undertaken to establish what changes may occur in adiponectin levels in association with other adipocytic determinants of insulin sensitivity and glucose metabolism involved in development of diabetes.

In conclusion, our results are in accordance with the earlier findings which indicate adiponectin as one of the metabolic factors intertwined in the complex metabolic environment that characterizes insulin resistance. Further longitudinal studies may provide us with better understanding about the predictive role of adiponectin in development of insulin resistance, diabetes and other sub-clinical chronic inflammatory disorders.

## Acknowledgements

This research was financially supported by the Endocrine and Metabolic Research Center (EMRC) at Shariaty Hospital, TUMS, Tehran, Iran. All the technical personnel of EMRC are gratefully thanked.

The authors declare that they have no Conflict of Interests

## References

1. Maeda K, Okubo K, Shimomura I (1996). cDNA cloning and expression of a novel adipose specific collagen-like factor, APM 1(Adipose most gene transcript 1). *Biochem Biophys Res Commun*, 221:286-9.
2. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF (1995). A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem*, 270: 26746-749.
3. Trujillo ME, Scherer PE (2005). Adiponectin-journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med*, 257:167-75.
4. Koerner J, Kratzsch W (2005). Adipocytokines: leptin-the classical, resistin-the controversical, adiponectin- the promising, and more to come. *Best Pract & Res Clin Endocrinol Metab*, 19(4):525-46 A.
5. Hu E, Liang P, Spiegelman BM (1996). AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem*, 271:10697-703.
6. Statnick MA, Beavers LS, Conner LJ, Corominola H, Johnson D, Hammond CD, et al. (2000). Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. *Int J Exp Diabetes Res*, 1:81-8.
7. Haluzik M, Parizkova J, Haluzik MM (2004). Adiponectin and its role in the obesity induced insulin resistance and related complications. *Physiol Res*, 53:123-29.
8. Matsubara M, Katyose S, Maruoka S (2003). Decreased plasma adiponectin concentrations in nondiabetic women with elevated homeostasis model assessment ratios. *Eur J Endocrinol*, 148:343-50.

9. Nadler ST, Stoehr JP, Schueller KL, Tanmoto G, Yandell BS, Attie AD (2001). The expression of adipogenic genes is decreased in obesity and diabetes mellitus. *Proc Natl Acad Sci USA*, 97:11371-376.
10. Hrebicek J, Janout V, Malincikova J, Horakova D, Cizek L (2002). Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. *J Clin Endocrinol Metab,* 87(1):144-47.
11. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J (2002). Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet,* 360(9326):57-8.
12. Snehalatha C, Mukesh B, Simon M, Viswanathan V (2003). Plasma Adiponectin Is an Independent Predictor of Type 2 Diabetes in Asian Indians. *Diabetes Care*, 26:3226-29.
13. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y (2001). Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*, 86(5): 1930-35.
14. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. (2001). The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Med*, 7:941– 46.
15. Matsubara M, Maruoka S, Katayose S (2002). Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. *Eur J Endocrinol*, 147(2):173-80.
16. Yamamoto Y, Hirose H, Satto I, Tomita M, (2002). Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clinical Science*, 103:137-42.
17. Arita Y, Kihara S, Ouchi N (1999). Paradoxical decrease of obtain a better understanding of adiponectin's role in the adipose-specific protein, adiponectin in obesity. *Biochem Biophys Res Commun*, 257:79–83.
18. Ma K, Cabrero A, Saha PK, Kojima H, Li L, Chang BH, et al. (2002). Increased β-oxidation but no insulin resistance or glucose intolerance in mice lacking adiponectin. *J Biol Chem*, 277:34658-661.
19. Kubota N, Terauchi Y, Yamauchi T, Kubota T (2002). Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem*, 277(29):25863-866.
20. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE (2001). The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nature Med*, 7:947-53.
21. Vettor R, MILAN G, Rossato M, Federspil G (2005). Review article: adipocytokines and insulin resistance. *Aliment Pharmacol Ther*, 22(2):3-10.
22. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, et al. (2003). Adiponectin and protection against type 2 diabetes mellitus. *Lancet*, 361(9353):226-28.
23. Nedvidkova A, Smitka k, Kopsky V, Hainer V (2005). Adiponectin, an adipocyte-derived protein. *Physiological research*, 54(2):133-40.
24. Tschritter O, Fritche A, Thamer C, (2003). Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes*, 52:239-43.