Int J Diabetes & Metabolism (2008) 16: 123-129

Hypoadiponectinemia in obese and diabetic subjects in the State of Qatar

N Rizk[1], R Awni[2], M Osman[2] and M Zirie[3]
Department of Health Sciences, University of Qatar,[1] Department of Clinical Chemistry,[2] Department of Endocrinology,[3] HMC, Doha, Qatar

Abstract
Background: Obesity is commonly associated with insulin resistance (IR), and is a common cause of type 2 diabetes. Adiponectin is an adipose tissue protein that enhances insulin sensitivity and has anti-atherogenic properties. **Objective:** This study was done to determine the adiponectin level and its relations to key components of the metabolic syndrome in obese diabetic (OD), obese non-diabetic (OB) and control [non-obese, non-diabetic (NOND)] Qatari subjects. **Research design and Methods:** We examined 64 (OD), 61 (OB) and 72 (NOND) male and female subjects. After a 12 h overnight fasting, blood samples were withdrawn for determination of plasma glucose, insulin, adiponectin, $HbA1_C$, uric acid, total cholesterol, triglycerides, HDL-C and LDL-C. **Results:** Plasma levels of adiponectin in OD (10.60 ± 3.64µg/mL) and OB (11.21 ± 3.41µg/mL) were significantly lower than NOND controls (14.73 ± 4.97µg/mL). Significant, inverse correlations were observed between adiponectin levels and BMI (r=-0.241, p<0.05), plasma glucose (r=-0.221, p<0.05), insulin (r=-0.280, p<0.05), C-peptide (r=-0.334, P<0.01), total cholesterol (r=-0.243, p<0.01,), triglycerides (r=-0.438, p<0.01), LDL-C (r=-0.214, p<0.05) and uric acid (r=-0.286, p<0.05). In addition, correlated positively with HDL-C(r=0.386, p<0.01). In multiple regression analysis, only TG was inversely associated with plasma level of adiponectin in all groups. **Conclusion:** This study provides the first evidence that adiponectin is reduced in Qatari obese subjects with and without diabetes. The measurement of circulating adiponectin among Qatari obese subjects is suggested to monitor cardiovascular disease (CVD) risks. Whether the plasma adiponectin level could be a suitable biomarker for following the clinical progress of CVD among Qatari obese and diabetic subjects warrants further investigation.

***Key words**: Adiponectin, obesity, diabetes, metabolic syndrome, CVD, Qatar*

Introduction

Obesity is commonly associated with insulin resistance, hyperinsulinemia and is a major risk factor for the development of type 2 diabetes mellitus and cardiovascular diseases.[1] The increased cardiovascular risk related to obesity has traditionally been ascribed to the presence of metabolic syndrome, which includes hypertension, insulin resistance, and dyslipidemia.[2]

Adiponectin is an adipose-specific plasma protein that has been shown to be an insulin-sensitizing hormone and has drawn substantial attention in research on metabolic syndrome.[3, 4] It suppresses hepatic glucose production, promotes lipid oxidation in muscle and may have a protective role against atherosclerosis.[5]

It has been showed that plasma adiponectin concentration is decreased in Caucasian, Pima Indians and Japanese subjects with obesity and type 2 diabetes.[6-9] Thus, given that low circulating adiponectin concentration is now considered as a cardiovascular disease (CVD) risk factor,[10] obese and type 2 diabetic subjects with low level of this peptide would have increased risk of developing atherosclerosis and coronary artery diseases (CAD).

The State of Qatar is a small country in the Arab Gulf area with a small population of approximately 820,000 inhabitants. The rapid transition in socioeconomic development after the discovery of oil has had a great impact on urbanization and life style of Qatar community. It results in an increase in the prevalence of obesity from 16.58% to 17.38% in males and from 27.92% to 29.31% in females from 2003 to 2005. Moreover, it is expected that the prevalence of obesity is going to increase to 18.7% and 31.6% among males and females of Qatari population in year 2010, respectively.[11] In addition, the International Diabetes Federation (IDF) estimated that ≈33% of Qatari people aged between 20 and 79 years has diabetes and impaired glucose tolerance (IGT) in 2003 and it is expected that the rate will increase among the Qatari population to ≈39% in 2025.[12]

There are currently no equivalent data on adiponectin levels related to metabolic syndrome criteria and CVD risks available for the Qatari population. This is an important omission, given the increased focus on the prevalence of

Received on: 3/8/2008
Accepted on: 12/11/2008

Correspondence to: Dr. Nasser Rizk, Department of Health Sciences, University of Qatar, 2713-Doha, Qatar. e-mail: nassrizk@hotmail.com

metabolic syndrome, diabetes and CVD in this region. Thus, we expect to determine the baseline level of adiponectin in this population. We therefore conducted a cross-sectional study to assess the plasma concentration of adiponectin and their correlation with various components of the metabolic syndrome among obese subjects with and without diabetes in State of Qatar.

Such study may be useful to unravel the complex interplay between adiponectin, and CVD risks among high risk obese and diabetic patients. The ultimate goal is to assist in early identification and management of patients with high propensity of developing coronary artery diseases.

Methods

Subjects

A total of 197 subjects [(97 males and 100 females); Table 1] were involved in this study. Obese and obese type 2 diabetic patients were recruited randomly from the Endocrine Outpatient Clinic at Hamad Medical Corporation (HMC), Qatar who received an annual health check-up for obesity and diabetes from March 2005 to June 2006. The non-obese non-diabetic subjects as a control group were recruited from healthy control volunteers from the Hematology Department HMC, Qatar and through posters and flyers. Interested persons were required to perform oral glucose tolerance test (OGTT) to exclude undiagnosed diabetes. The study was performed according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from each subject after full explanation of the purpose, nature, and risk of all procedures used.

The studied subjects were subdivided into three groups by gender based on the cut-off points for body mass index (BMI) according to World Health Organization (WHO) criteria,[13] and the presence of diabetes. Diabetes mellitus was diagnosed by the medical team of the diabetic unit (HMC). Group one, subjects with BMI < 25 kg/m^2 and had no diabetes, termed as "control group" with abbreviation (NOND). Group two, subjects with BMI ≥ 30kg/m^2 and had no diabetes termed as "obese group" with abbreviation (OB). Group three, subjects with BMI ≥ 30kg/m^2 and had diabetes termed as "obese diabetic group" with abbreviation (OD).

A standardized medical history was obtained. Patients were excluded from the study if they had CAD or history of CAD or clinical evidence of atherosclerosis. Also, subjects with renal, liver and immune disorders were also excluded from the study. A trained nurse with standard equipments measured height and body weight. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2).

Biochemical Measurements

After an overnight fasting, blood samples were withdrawn and analyzed for various metabolites and hormones. Aliquots of these samples were used for the biochemical analysis immediately, but aliquots for plasma adiponectin were stored at -80^{O}C until collection of the desired samples for study. Fasting glucose, uric acid, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were assayed by routine automated laboratory methods at the clinical chemistry laboratories at HMC using Hitachi-917 (Gmbh Diagnostic, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) level was estimated using the Friedewald formula.[14] HbA1c was evaluated by turbidimetric inhibition immunoassay technique (TINIA) for hemolyzed whole blood. Fasting insulin and C-peptide levels were measured by radioimmunoassay (RIA) using commercially available kits at the radioimmunoassay laboratory at HMC. The insulin resistance (IR) was assessed using fasting insulin and glucose concentrations in homeostatic model assessment (HOMA).[15] Plasma adiponectin was measured by ELISA with a commercially available kit (Linco Research, St Charles, MO, USA) as described by the manufacturer.

The cut-off points for the selected metabolic syndrome in our study were based on the NCEP ATP III criteria 2001.[16] DM was defined as fasting plasma glucose ≥7 mM or 2 h plasma glucose ≥11.1 mM measured during oral glucose tolerance tests (OGTT); dyslipidemia was measured as fasting TG ≥1.70 mM or specific treatment for this lipid abnormality and/or HDL-C <1.036 mM for males and <1.029 for females; insulin resistance index by HOMA formula was ≥ 2.5.[15]

Table 1: Characteristics of the study subjects

Characteristics	Males	Females
n	97 (49.2)	100 (50.8%)
Age (years)	39.11±12.56	39.94 ±11.37
Obesity (%)	62.89	64.00
Diabetes (%)	34.02	31.00
Body mass index (kg/m2)	29.93 ± 7.62	33.74 ± 8.97*
Fasting glucose (mmol/l)	7.06 ± 3.84	7.97 ± 4.26
HbA1c (%)	6.52 ± 1.81	7.26± 2.00
Fasting insulin (µIU/ml)	12.66 ± 8.63	12.20±7.68
Fasting C-peptide (µU/ml)	2.84 ± 3.00	2.88 ± 2.14
HOMA-IR	3.83 ± 1.81	4.32 ± 3.53
U.A(µmol/l)	347.6 ± 76.80	260.98 ± 72.88*
TC (mmol/l)	5.12 ± 1.18	5.15 ± 0.92
TG (mmol/l)	1.75 ± 1.33	1.66 ± 1.24
HDL –C (mmol/l)	1.19 ± 0.35	1.38 ± 0.33*
LDL –C (mmol/l)	3.26 ± 1.03	3.09 ± 0.87
TC/HDL	4.55 ± 1.32	2.39 ±2.15***
Adiponectin (µg/ml)	10.83 ± 5.85	13.46 ± 6.15*

Data are mean ± SD. *p<0.05, **p<0.01, ***p<0.001 for levels of significance between male and female patients

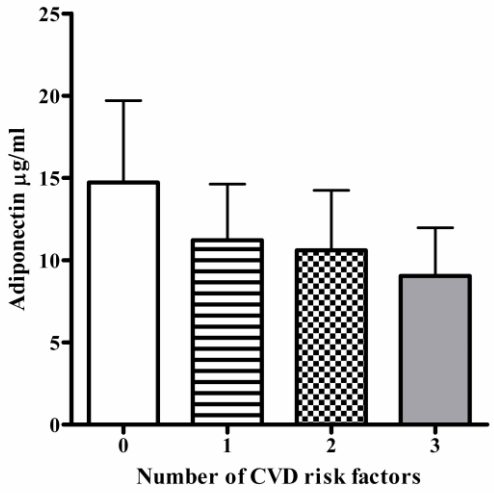

Figure 1: The mean ± SD plasma adiponectin levels among study subjects with various numbers of CVD risk factors. *P* value = 0.033 by ANOVA.

Statistical analyses

Data are expressed as mean ± SD. All statistical analyses were performed using the SPSS program for Windows (version 12 statistical software; Texas Instruments, IL, USA). Data was explored for outliers, skeweness, and normality and transformed when necessary if normality assumption was violated. Significant group differences in the parameters were compared by one-way ANOVA. Intergroup (within the same gender) and intra-group (between males and females of the same group) differences in the parameters were performed using student t, or Mann-Whitney/Wilcoxon test when appropriate.

The Pearson correlation coefficient was used to evaluate the strength association between two variables. Multiple linear regression analysis was employed to further quantify the strengths of associations between plasma adiponectin and the variables of interest; BMI, fasting glucose, insulin, triglycerides and HDL-C. The level $p < 0.05$ was considered as cut-off value for significance.

Results

Characteristics of the study subjects

Table I shows the characteristics for the study subjects. Females had a statistically significant higher; BMI, HDL-C and adiponectin than males. Meanwhile, males had significantly higher TC/HDL-C ratio and uric acid than females. No statistical significant differences were found for; fasting glucose, insulin, C-peptide, HbA1c, TC, TG, LDL-C, and HOMA-IR between males and females.

Plasma adiponectin levels in non-obese, non-diabetics (NOND), obese subjects without diabetes (OB), and with diabetes (OD)

The plasma level of the adipose-specific protein adiponectin was measured in 125 obese subjects with and without diabetes and in 72 healthy non-obese non-diabetic control subjects. Table 2 shows the characteristics for the studied groups by gender. Obese males had significantly higher plasma adiponectin levels than obese diabetic ($p<0.05$, Table 2). In females, OB and OD groups had a significantly lower plasma adiponectin concentrations than in NOND group ($p <0.05$, table 2).

In males, OD group exhibited a significantly higher; fasting glucose, HbA1c, insulin, C-peptide, HOMA-IR index and TG, than in OB and NOND groups. ($p<0.05$, Table 2). In addition, OD females exhibited a statistically significant higher glucose, HbA1c, HOMA-IR, and TG than in OB females, ($p<0.05$, Table 2). In comparison to NOND group in females, OD group had a statistically significant higher; glucose, HbA1c, insulin, C-peptide, insulin sensitivity index, uric acid, TG and TC/HDL ratio.

Because plasma adiponectin level was related to three major risk factors of CVD (obesity, diabetes and dyslipidemia), we categorized the subjects based on the number of CVD risk factors they had in order. The mean plasma adiponectin concentration was progressively lower with increasing numbers of such risk factors (14.73 ± 4.97, 11.21 ± 3.41, 10.60 ± 3.64 and 9.04 ± 2.93 µg/ml for 0, 1, 2, and 3 risk factors respectively, *p* value 0.001) as shown in figure 1.

Next, we analyzed the association between the plasma adiponectin and the other parameters including plasma variables in the complete cohort of subjects, as well as each group individually by Pearson's correlation coefficient (Table 3). In all subjects, plasma levels of adiponectin were negatively correlated with BMI, fasting glucose, insulin, C-peptide, and HOMA-IR index. The plasma concentration of adiponectin was correlated positively with HDL-C and inversely with TC, TG, LDL-C, and TC/HDL-C. The correlation between adiponectin levels and other variables based on the obesity state with and without diabetes are also shown in table 3. We observed also that plasma TG and TC/HDL-C ratio was constantly negatively correlated to plasma adiponectin concentration, while HDL-C is positively correlated in all groups. While plasma adiponectin correlated with different lipids and glucose homeostasis variables, the results of multivariate correlations (Table 4), showed only a relationship between adiponectin as dependent variable and TG as independent variables in all groups.

Discussion

The present data has shown that in a Qatari population (i) circulating adiponectin levels are lower in obese and obese diabetic patients than in non-obese non-diabetic control subjects in males and females, (ii) serum adiponectin levels were higher in obese than obese diabetics males, (iii) females have higher levels of plasma adiponectin than in males of their counterparts (iv) plasma adiponectin level has a significant negative relationship with triglycerides in control, obese and obese diabetic subjects, and (v) the mean plasma adiponectin concentration was progressively lower with increasing numbers of CVD risk factors. The implication of these findings in obesity and diabetic management are further explored.

Table 2: Study characters in male and female control "NOND", obese "OB" and obese diabetic "OD" subjects

	Males			Females		
Variable	**NOND**	**OB**	**OD**	**NOND**	**OB**	**OD**
	(n=36)	**(n=28)**	**(n=33)**	**(n=36)**	**(n=33)**	**(n=31)**
Age (years)	36.25 ± 9.38	38.70 ± 11.10	42.27 ± 9.49*	37.23 ± 7.34	40.31 ± 10.12*	42.29 ± 8.99 $^{\mu}$*
BMI(Kg/m2)	23.55±2.27	36.23 ± 7.06*	34.47 ± 5.39*$^{\neq}$	23.97±2.85	39.64 ± 6.26* $^{\Delta}$	39.87 ± 4.91*$^{\neq\Delta}$
Glucose (mmol/l)	4.86±0.50	5.33 ± 0.56	12.03 ± 3.86*$^{\mu\neq}$	4.86 ± 0.50	6.01 ± 1.39	11.25 ± 4.35* $^{\mu\neq}$
HbA1c (%)	5.28±0.3	5.0 ± 0.54	7.92 ± 1.72* $^{\mu\neq}$	5.22 ± 0.46	6.8 ± 1.53	8.26 ± 1.76* $^{\mu}$
Insulin (mIU/ml)	10.19±0.84	13.96 ± 0.97*	17.33 ± 3.40* $^{\mu\neq}$	8.52 ± 4.41≠	16.46 ± 7.4*	13.10 ± 8.7*$^{\mu\neq}$
C-peptide (ng/ml)	2.01±0.71	2.93 ± 0.54*	4.41 ± 2.23* $^{\mu\neq}$	1.83 ± 0.56	3.79 ± 3.70*≠$^{\Delta}$	3.30 ± 1.48*$^{\neq\Delta}$
HOMA-IR	1.99±0.84	3.36 ± 0.97*	7.33 ± 2.23* $^{\mu\neq}$	1.86 ± 1.12	4.90 ± 2.90*≠$^{\mu}$	6.09 ±3.92* $^{\mu\neq}$
U.A (mmol/l)	320.4±51.5	402.5 ± 78.2*	346.7±102.7	232.23±57.55	304.89 ± 103.79*	279.53 ± 61.06*$^{\neq\mu}$
TC (mmol/l)	5.37±1.11	5.16 ± 1.31	4.67±1.16	4.89±0.86	5.56 ±1.07	5.19 ± 0.85
TG (mmol/l)	1.44±1.18	1.47 ± 0.48	2.54 ± 1.85*$^{\mu}$	0.84 ± 0.37	1.57 ± 1.30*	2.53 ± 1.37* $^{\mu}$
HDL-C (mmol/l)	1.29±0.25	1.11 ± 0.33	1.11 ± 0.49	1.56 ± 0.30	1.43 ± 0.35	1.23 ± 0.28$^{\neq}$
LDL-C (mmol/l)	3.50±1.05	3.32 ± 1.1	2.80 ± 0.89	3.03 ± 0.88	3.57 ± 0.87	2.91 ± 0.79
TC/HDL	4.17±1.24	4.63 ± 1.01	4.67 ± 1.7	3.32 ± 0.88 $^{\Delta}$	4.02 ± 0.85*	4.49 ± 1.50*
Adiponectin (µg/ml)	12.83±4.7	10.81 ± 3.58*	7.21 ± 2.47* $^{\mu}$	15.83 ± 6.33 $^{\Delta}$	12.33 ± 5.45* $^{\Delta}$	12.07 ± 5.88*$^{\neq\Delta}$

$^{\neq}P<0.05$ for level of significance for ANOVA difference between all groups within the same gender $^{*}p<0.05$ is significantly different from NOND controls and $^{\mu}P<0.05$ is significantly different from OB group within the same gender. $^{\Delta}P<0.05$, is significantly different from the male gender of the same group.

Table 3: Correlation coefficient between fasting adiponectin and study characters in all subjects and in different groups

Variables	**All**	**NOND**	**OB**	**OD**
BMI	-0.241*	-0.049	-0.189	-0.191
Glucose	-0.221*	-0.101	-0.188	-0.131
Insulin	-0.280*	-0.056	-0.148	-0.239
C-peptide	-0.334**	-0.261	-0.272*	-0.211
HOMA	-0.228**	-0.262	-0.305*	-0.294
UA	-0.286*	-0.186	-0.408*	-0.376
TC	-0.243**	-0.367*	-0.094	-0.225
TG	-0.438**	-0.362*	-0.288*	-0.439*
HDL-C	0.386**	0.349*	0.292*	0.432*
LDL-C	-0.214*	-0.281	-0.174	-0.327
TC/HDL	-0.399***	-0.485**	-0.283*	-0.441**

*p<0.05, **p<0.01, ***p<0.001 for levels of significance of correlation coefficient at two tailed testing

Table 4: Multiple regression analysis showing the influence of independent variables (age, BMI, glucose, insulin, triglycerides and HDL-C) on plasma adiponectin in all, control, obese and obese diabetic subjects

	All		**NOND**		**OB**		**OD**	
Independent variable	B-coefficient	SE	B-coefficient	SE	B-coefficient	SE	B-coefficient	SE
Age	-0.137	0.053	-0.326	0.109*	-0.162	0.151	-0.086	0.163
BMI	-0.006	0.068	-0.026	0.228	-0.076	0.231	-0.005	0.228
Glucose	0.035	0.190	-0.010	0.854	-0.024	1.031	-0.028	0.329
Insulin	-0.125	0.035	0.004	0.048	-0.215	0.093	-0.106	0.164
TG	-0.451	0.727*	-0.281	0.961*	-0.461	3.266*	-0.348	1.002*
HDL-C	0.045	1.969	0.003	1.827	0.126	4.326	0.084	3.821

*p<0.05 for level of significance of β-coefficient at 2-tailed testing. SE= standard error.

The finding of lower adiponectin level in obese and obese diabetic male and female patients in comparison with control NOND male and female subjects is consistent with previous studies of different ethnic groups including

Caucasians, Pima Indians, Asian [6,7,17,18,] and Japanese.[8,9,19] A possible explanation of the observed results of adiponectin in OB and OD patients is due to the elevated HOMA-derived insulin resistance, low insulin and C-peptide levels. Insulin resistance appears to be the major common finding in individuals with obesity, glucose intolerance or type2 diabetes, high blood pressure and dyslipidemia.[20] Indeed, previous reports have shown that the adiponectin levels were suppressed during hyperinsulinemic euglycemic clamp study in both diabetic and non diabetic subjects.[21] Importantly, both *in vitro* and *in vivo* studies [22, 23] have demonstrated that insulin itself may lead to down-regulation of adiponectin secretion from fat cells. Also, previous reports have shown that C-peptide which reflects beta cell function of the pancreas is a negative modulator of circulating adiponectin in diabetic as well as non-diabetic subjects and support the presence of adipoinsular axis.[24] Moreover, several studies have reported that improving insulin resistance and reducing insulin levels with an insulin-sensitizing agent markedly increases adiponectin concentrations.[23, 25] Our findings of a further reduction of adiponectin levels in DO than OB male patients in this study could be explained by the several folds increase (2.5 folds) in HOMA-derived insulin resistance seen in OD compared to OB groups. Consistent with such result, several studies suggest that adiponectin concentrations are more closely related to differences in insulin-resistance than obesity.[26, 27]

In the current study, plasma adiponectin level was independently correlated with the serum triglyceride level by multiple regression analysis. Hyper-triglyceridemia is one of the major clinical features of the insulin resistance syndrome, which may take part in the development of atherosclerosis. Our observation of the association of adiponectin with HDL-C and TG metabolism (in particular) has been previously noted[28] and it was proposed as a useful marker/risk factor in CVD assessment.[29] In addition, the current study showed that plasma adiponectin was not only related to the key parameters of the metabolic syndrome such as BMI, glucose, insulin, C-peptide, HOMA-IR, uric acid, TC, TG and HDL-C levels, but also to the number of CVD risk factors the patients had (Fig. 1) and the atherogenic index; TC/HDL, suggesting that monitoring of plasma adiponectin may be a useful indicator in patients at risk of CVD [10]. Thus, the findings of the present study are consistent with several previous reports indicating that adiponectin correlated with various indices of metabolic syndrome.[30,31] Moreover, several studies have shown adiponectin to be a strong inverse independent risk factor for CVD [10, 30, 31, 32, 33] and hypoadiponectinemia was demonstrated in subjects with CVD.[34] The physiological nature of this correlation may be tied to the proposed functions of adiponectin at the vascular wall, which include modulation of endothelial function, inhibition of vascular smooth muscle proliferation, suppression of macrophage transformation and modulation of inflammation.[35]

In the current study, the plasma adiponectin concentrations were observed to be lowered in men than in women of their counterparts. The finding of gender-related differences in plasma adiponectin concentrations has been previously reported in Japanese diabetic patients without coronary artery disease.[12] Similarly, other studies in non diabetic subjects in Japanese, and North American populations have shown that women have higher adiponectin levels than men.[9,36] Sex hormones, including estrogen, progesterone and androgen may affect the plasma adiponectin level.[9] Androgens decreased the plasma adiponectin level and that androgen-induced hypoadiponectemia may be related to a high risk of insulin resistance and atherosclerosis in men.[8,37] It should be however, noted that previous studies indicating that the reported differences may not be entirely due to the possible effect of sex hormones as described in previous studies.[38] Further studies are needed to address the sexual dimorphism in plasma adiponectin levels.

A major limitation of our study is its cross sectional nature, which does not allow for inferring causality for our results. Although association between adiponectin and metabolic markers may be modified by the presence and type of cholesterol-lowering drugs and diabetic medications, we did not collect detailed medication data at the time of blood drawing in our study and therefore were unable to evaluate this. Further studies are needed to evaluate the role of medication and lifestyle on adiponectin in association with metabolic syndrome among Qatari subjects.

In conclusion, obesity with and without type 2 diabetes among Qatari subjects is associated with decreased plasma adiponectin level, particularly in males. Furthermore, decreased adiponectin level may be associated with increased risks for CVD. Lifestyle and pharmacological approaches that increase adiponectin levels might be valuable in decreasing CVD risk parameters.

References

1. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000; 106:473-481.
2. Haffner S, Taegtmeyer H. Epidemic obesity and the metabolic syndrome. Circulation 2003; 108:1541-1545.
3. Kondo H, Shimomura I, Matsukawa Y, et al. Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. Diabetes 2002; 51:2325-2328.
4. Yamauchi T, Hara K, Kubota N, et al. Dual roles of adiponectin/Acrp30 in vivo as an anti-diabetic and anti-atherogenic adipokine. Curr Drug Targets Immune Endocr Metabol Disord 2003; 3:243-254.
5. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002; 8:1288-1295.
6. Vasseur F, Helbecque N, Dina C, et al. Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. Hum Mol Genet 2002; 11:2607-2614.

7. Stefan N, Vozarova B, Funahashi T, et al. Plasma adiponectin levels are not associated with fat oxidation in humans. Obes Res 2002; 10:1016-1020.
8. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999; 257: 79-83.
9. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20:1595-1599.
10. Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: a new emerging biomarker of cardiovascular risk. Pharmacol Res 2007; 56:459-467.
11. WHO Global InfoBase. Retrieved July 25, 2008. Available on: http://www.who.int/infobase /report.aspx?rid=111&iso=QAT
12. International Diabetes Federation. Retrieved July 25, 2008. Available on: http://www.eatlas.idf.org /Prevalence.
13. WHO Expert Committee physical status. 1995. The use and interpretation of Anthropometry. WHO Technical Report Series, Geneva, no.854, WHO.
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499-502.
15. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
16. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002, 106:3143-3421.
17. Yang WS, Lee WJ, Funahashi T, et al. Plasma adiponectin levels in overweight and obese Asians. Obes Res 2002; 10:1104-1110.
18. Snehalatha C, Mukesh B, Simon M, et al. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. Diabetes Care 2003; 26: 3226-3229.
19. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86:1930-1935.
20. Goldstein BJ: Insulin resistance as the core defect in type 2 diabetes mellitus. Am J Cardiol 2002; 90:3G-10G.
21. Mohlig M, Wegewitz U, Osterhoff M, et al: Insulin decreases human adiponectin plasma levels. Horm Metab Res 2002; 34:655-658.
22. Fasshauer M, Klein J, Neumann S, et al. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochem Biophys Res Commun 2002; 290:1084-1089.
23. Yu JG, Javorschi S, Hevener AL, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. Diabetes 2002; 51:2968-2974.
24. Furuta M, Tamai M, Hanabusa T, et al. Serum adiponectin is associated with fasting serum C-peptide in non-obese diabetic patients. Diabetes Res Clin Pract 2006; 72:302-307.
25. Lin KD, Chang YH, Wang CL, et al. Thiazolidinedione addition reduces the serum retinol-binding protein 4 in type 2 diabetic patients treated with metformin and sulfonylurea. Transl Res 2008; 151:309-314.
26. Abbasi F, Chu JW, Lamendola C, et al. Discrimination between obesity and insulin resistance in the relationship with adiponectin. Diabetes 2004; 53:585-590.
27. Kim MJ, Yoo KH, Park HS, et al. Plasma adiponectin and insulin resistance in Korean type 2 diabetes mellitus. Yonsei Med J 2005; 46:42-50.
28. Buemann B, Astrup A, Pedersen O, et al. Possible role of adiponectin and insulin sensitivity in mediating the favorable effects of lower body fat mass on blood lipids. J Clin Endocrinol Metab 2006; 91:1698-1704.
29. Nishida M, Funahashi T, Shimomura I. Pathophysiological significance of adiponectin. Med Mol Morphol 2007; 40:55-67.
30. Rabin KR, Kamari Y, Avni I, et al. Adiponectin: linking the metabolic syndrome to its cardiovascular consequences. Expert Rev Cardiovasc Ther 2005; 3: 465-471.
31. Salas-Salvado J, Granada M, Bullo M, Corominas A, Casas P, Foz M. Plasma adiponectin distribution in a Mediterranean population and its association with cardiovascular risk factors and metabolic syndrome. Metabolism 2007; 56:1486-1492.
32. Eckel RH. Mechanisms of the components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD. Proc Nutr Soc 2007; 66:82-95.
33. Kuller LH, Grandits G, Cohen JD, et al. Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. Atherosclerosis 2007; 195:122-128.
34. Kumada M, Kihara S, Sumitsuji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003; 23:85-89.
35. Ouchi N, Kihara S, Funahashi T, et al. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 2003; 14:561-566.
36. Hanley AJ, Bowden D, Wagenknecht LE, et al. Associations of adiponectin with body fat distribution and insulin sensitivity in nondiabetic Hispanics and African-Americans. J Clin Endocrinol Metab 2007; 92:2665-2671.

37. Nishizawa H, Shimomura I, Kishida K, et al: Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 2002; 51:2734-2741.

38. Gui Y, Silha JV, Murphy LJ. Sexual dimorphism and regulation of resistin, adiponectin, and leptin expression in the mouse. Obes Res 2004; 12:1481-1491.