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Plasma adiponectin distribution in a Mediterranean population and its association with cardiovascular risk factors and metabolic syndrome

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Abstract

Adiponectin may play an important role in the regulation of body weight, insulin resistance, and cardiovascular disease. The aim of this study was to evaluate the distribution of adiponectin in a Mediterranean adult population and its relationship with cardiovascular risk factors and metabolic syndrome. A cross-sectional study was performed in a representative sample of 1023 subjects from a Spanish Mediterranean population. Individuals with the metabolic syndrome were identified using the diagnostic criteria of the Adult Treatment Panel III. Anthropometric parameters were measured, and biochemical analyses were performed in fasting conditions. Plasma insulin levels were measured and homeostasis model assessment of insulin resistance was calculated. Plasma adiponectin levels were measured by a commercial radioimmunoassay. Median levels of adiponectin were significantly higher in women than in men after adjusting for differences in body mass index. However, no differences in adiponectin plasma levels were observed in relation to age. Significantly lower levels of adiponectin were also observed in women with obesity, abdominal obesity, hyperglycemia or diabetes, low high-density lipoprotein cholesterol, hypertriglyceridemia, or metabolic syndrome. In men, only those with obesity, abdominal obesity, low high-density lipoprotein cholesterol, hypertriglyceridemia, or metabolic syndrome showed significantly lower plasma levels of adiponectin. In a stepwise multivariate analysis, sex, waist circumference, serum C-reactive protein serum levels, and homeostasis model assessment of insulin resistance explained 23.4% of its variability. In conclusion, adiponectin plasma levels are more closely related to the components of the metabolic syndrome in women than in men in a Mediterranean population.

1. Introduction

Cardiovascular disease accounts for a high proportion of morbidity and mortality in patients with obesity, type 2 diabetes mellitus, or both. Recent work has elucidated several potential mechanisms by which increased adiposity leads to higher cardiovascular risk. Adipose tissue plays an important role in the pathogenesis of metabolic syndrome and type 2 diabetes mellitus. Free fatty acids and adipocytokines, such as tumor necrosis factor α, interleukin-6, or leptin, released from adipose tissue lead to the development of insulin resistance, and it has been proposed that they may also contribute to beta-cell dysfunction [1].

Adiponectin is an adipocytokine that is exclusively expressed in adipose tissue, and structurally related to collagen VIII and X and complement factor C1q. It circulates in plasma at high concentrations where it accounts for 0.01% of total plasma protein [2]. It has been shown to improve insulin sensitivity in muscle and liver by enhancing free fatty acid oxidation [3], and indirect evidence suggests that it may also protect the pancreatic beta-cell function [4].

Adiponectin plasma levels are significantly reduced in obese subjects [5] and in insulin-resistant and diabetic patients [6], so they increase after weight loss [7]. Apart from the antidiabetic effect, adiponectin has antiatherogenic properties, partly because of its inverse relationship with body fat mass and insulin resistance but also related to the atherogenic process [8]. In fact, adiponectin has been shown to suppress all processes involved in atherosclerotic vascular change, including the expression of adhesion molecules in vascular endothelial cells [9,10], the proliferation of vascular smooth muscle cells [11], and the formation of foam cells in vitro [12]. Adiponectin has

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also been related to endothelium-dependent vasodilatation, hypertension [13], and atherogenic dyslipidemia [14], all components of metabolic syndrome.

Therefore, the purpose of the present study is to make a cross-sectional survey in a healthy Mediterranean sample that represents the adult population of Catalonia (Spain) to evaluate, firstly, the distribution of plasma adiponectin and, secondly, the relation of adiponectinemia to adiposity, several cardiovascular risk factors, and metabolic syndrome.

2. Materials and methods

2.1. Subjects

The subjects included in this study are a representative sample of the Health Survey of Catalonia (Encuesta de Salud de Catalunya) performed in 2001 in a noninstitutionalized adult population from Catalonia. A total of 8000 subjects, from 18 to 74 years old, participated in the 2001 Encuesta de Salud de Catalunya. Of these, 1300 participated in a second-phase study in which additional health information and blood samples were obtained [15]. Methodological aspects of the survey have been described elsewhere [15]. In the present study, we have included a total of 1023 subjects (440 men and 583 women) for whom the adiponectin concentration could be measured. The Health Examination Study was approved by the Ethical Committee of the Department of Health of the Autonomous Government of Catalonia. All the subjects who participated in the study gave their informed written consent.

2.2. Methods

Body weight and height were measured with all subjects wearing light clothes and no shoes. Body mass index (BMI) was then calculated as the weight in kilograms divided by the square of height in meters. Waist circumference (in centimeters) was measured at the level of the iliac crest. Subjects were classified according to their BMI as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2) following the classification of the Spanish Society for the Study of Obesity [16]. Blood pressure was measured with a standard mercury sphygmomanometer. High casual systolic blood pressure and high casual diastolic blood pressure were defined as systolic blood pressure ≥135mm Hg and diastolic blood pressure ≥85 mm Hg in 2 different measurements.

Blood samples obtained in fasting conditions were immediately centrifuged, and serum was stored at −70°C until assayed. Plasma triglycerides, total and high-density lipoprotein cholesterol (HDL-C), fasting glucose, and uric acid concentrations were measured by routine laboratory tests using automatic analyzers. Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald formula, but only in patients with triglycerides less than 400 mg/dL [17]. Fasting insulin was measured by radioimmunoassay using a commercial kit (Amersham, Little Chalfont, UK). Insulin resistance was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) as follows: fasting plasma insulin (mIU/L) × fasting plasma glucose (mmol/L)/22.5 [18]. Serum levels of C-reactive protein (CRP) were measured by ultrasensitive immunoturbidimetry (Quantex XRP ultrasensitive, Biokit, Barcelona, Spain). The lower limit of detection was 0.1 mg/L. The intra- and interassay coefficients of variation were 0.9% and 1.7%, respectively. Serum adiponectin concentrations were measured by a commercial radioimmunoassay (Linco Research, St Louis, MO). The intra-assay coefficient of variation was less than 6.2% and the interassay coefficient of variation was less than 9.2%. Assay sensitivity was 1 μg/mL. All plasma samples were diluted 1:250 to yield an effective range of 0.2 to 50 μg/mL. The diagnostic criteria of the Adult Treatment Panel III were used to identify individuals with the metabolic syndrome [19]. Three or more of the following criteria had to be present: waist circumference ≥102 cm in male and ≥88 cm in female subjects; triglycerides ≥150 mg/dL; HDL-C <40 mg/dL in male and <50 mg/dL in female subjects or medication use; elevated blood pressure ≥130/85 mm Hg or medication use; fasting plasma glucose ≥100 mg/dL or medication use. All patients with a self-reported diagnosis of diabetes or hypertension were considered to fit the respective criteria independently of the measured values.

2.3. Statistical analyses

Data were first tested for normal distribution using the Kolmogorov-Smirnov test. Because the CRP and adiponectin concentrations were skewed, the values were log-transformed before data analysis. These log-transformed variables showed a normal distribution with the Kolmogorov-Smirnov test and were expressed as the geometrical means. Groups were compared by Student t test or the analysis of variance test. Qualitative clinical data were compared using the χ^2 test. Correlations between quantitative variables were tested using univariate analyses (Pearson or Spearman correlations where appropriate). A multiple stepwise regression analysis was conducted to identify the independent factors explaining the variability observed in plasma adiponectin concentrations. The variables considered to be independent were sex, BMI, waist circumference, fasting glucose, HOMA-IR, and CRP concentrations. All statistical analyses were made with the statistical software package SPSS, version 12.0 (SPSS, Chicago, IL). All tests were 2-tailed, and a P value of less than .05 was considered to be statistically significant.

3. Results

In the present study, we analyzed a total of 1023 subjects (440 men and 583 women) distributed over a wide range of age and weight. The general characteristics of the population and the prevalence of cardiovascular risk factors are shown

Table 1
General characteristics of the population studied

	Women (n = 583)	Men (n = 440)	Total (N = 1023)	*P*
Age (y)	44.28 ± 15.20	46.00 ± 15.72	45.07 ± 15.16	NS
BMI (kg/m^2)	26.72 ± 3.81	26.07 ± 5.60	26.35 ± 4.95	.039
Waist circumference (cm)	82.73 ± 13.45	92.26 ± 11.15	86.84 ± 13.85	<.001
Fasting glucose (mg/dL)	5.03 ± 1.08	5.50 ± 1,63	5.23 ± 1.36	<.001
Total cholesterol (mg/dL)	194.87 ± 38.97	197.79 ± 37.89	196.10 ± 38.51	NS
Triglycerides (mg/dL)	83.89 ± 52.92	113.78 ± 76.65	96.75 ± 65.86	<.001
HDL-C (mg/dL)	57.30 ± 14.35	46.18 ± 12.58	52.50 ± 14.68	<.001
LDL-C (mg/dL)	118.47 ± 35.61	127.48 ± 32.94	122.34 ± 34.76	<.001
HOMA-IR	2.80 ± 2.25	3.27 ± 4.25	3.00 ± 3.27	.025
Prevalence of criteria to define metabolic syndrome (%)				
Abdominal obesity	33.1	16.4	25.9	<.001
Hypertension or medication use	40.4	51.2	45.0	.001
Hyperglycemia, type 2 diabetes mellitus, medication use	20.6	31.2	25.1	<.001
Low HDL-C or medication use	29.7	30.5	30.1	NS
Hypertriglyceridemia	8.8	21.5	14.3	<.001
Overweight	28.4	50.2	38	<.001
Obesity	20.2	15.7	18.5	<.021
Metabolic syndrome	18.76	22.1	20.5	NS

Data are expressed as mean ± SD. NS indicates not significant.

in Table 1. Men and women were of equivalent age but differed in the degree of adiposity and body fat distribution. In addition, men showed a significantly higher prevalence of cardiovascular risk factors than women did. A total of 33.3% of the subjects were smokers (38.4% of men and 12.45% of women), 14% took aspirin regularly, 6.2% took lipid-lowering drugs, 10.4% antihypertensive agents, and 4.2% antidiabetic drugs. The prevalence of metabolic syndrome did not significantly differ between men and women.

The distribution of plasma adiponectin levels by sex and age groups is shown in Fig. 1 and Table 2, respectively. Plasma adiponectin was significantly higher in women than in men. The mean differences remain significant after adjusting for BMI (10.30 ± 1.51 vs 6.60 ± 1.62, $P < .001$ women and men, respectively). In contrast, no significant differences were observed in plasma adiponectin levels between age groups in the whole population. Adiponectin plasma levels were significantly higher in women older than 55 years than in their counterparts ($P < .05$). Less than 2% of women were undergoing hormone replacement therapy. Adiponectin values were not significantly different in women under hormone replacement therapy compared with nontreated women, even after adjustment for age.

In women, the adiponectin plasma levels were significantly lower in the presence of overweight and obesity, abdominal obesity, hyperglycemia or diabetes, low HDL-C, and hypertriglyceridemia. They were also lower in smokers (Table 3). No differences were observed in women in relation to hypertension. Similar results were observed in men, although no differences were found in relation to hyperglycemia, type 2 diabetes mellitus, or smoking status (Table 3). Plasma adiponectin levels were lower in patients with

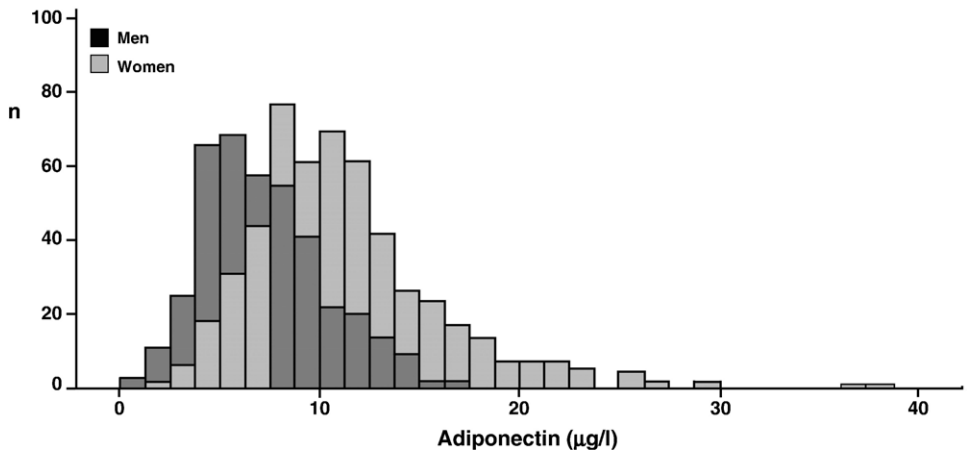

Fig. 1. Plasma adiponectin distribution in men (n = 440) and women (n = 583).

Table 2
Percentiles of adiponectin concentration (μg/mL) stratified by age for 440 men and 583 women between 18 and 74 years of age

	n	X	Percentiles				
			5	25	50	75	95
Total	1023		3.74	6.29	8.77	11.74	18.62
By age							
Women <40 y	239	11.39	5.62	8.12	10.54	13.18	19.95
Women 40-55 y	182	10.30 *	4.67	7.41	9.54 *	12.30	12.35
Women ≥55 y	157	12.05 **	4.89	8.31	10.96 **	14.79	23.44
Men <40 y	152	7.82	2.81	5.37	7.24	9.54	13.80
Men 40-55 y	140	7.19	2.69	4.57	6.16	8.70	12.30
Men ≥55 y	147	7.44	3.23	4.78	6.45	9.12	13.89

Values are expressed as geometric means. *X* indicates the arithmetic mean.
* $P < .05$ vs the group of subjects younger than 40 years.
** $P < .05$ vs the group of subjects 40 to 55 years old.

Table 4
Relationship between plasma adiponectin levels and cardiovascular risk characteristics

	Men		Women	
	r	*P*	*r*	*P*
BMI (kg/m^2)	−0.181	<.001	−0.139	.001
Waist circumference (cm)	−0.185	<.001	−0.201	<.001
Systolic blood pressure (mm Hg)	−0.087	.070	−0.009	.821
Diastolic blood pressure (mm Hg)	−0.165	.001	−0.074	.078
Glucose (mmol/L)	−0.077	.114	−0.106	.012
Insulin (mU/mL)	−0.128	.007	−0.273	<.001
Triglycerides (mg/dL)	−0.221	<.001	−0.188	<.001
Total cholesterol (mg/dL)	−0.064	.185	0.047	.261
HDL-C (mg/dL)	0.310	<.001	0.303	<.001
LDL-C (mg/dL)	−0.108	.031	−0.006	.886
HOMA-IR	−0.102	.035	−0.257	<.001
CRP (mg/L)	−0.139	.004	−0.134	.001

metabolic syndrome in both women (16.71 ± 1.48 vs 8.70 ± 1.58, $P < .001$) and men (6.91 ± 1.58 vs 5.62 ± 1.62, $P < .001$, absence or presence, respectively).

In Table 4, we show the relationship between selected cardiovascular risk factors and plasma adiponectin concentrations in both sexes. Body mass index, waist circumference, fasting insulin, HOMA-IR, triglycerides, and CRP were negatively and significantly related to adiponectin in both sexes. Diastolic blood pressure and LDL-C levels were also negatively related to adiponectin in men but not in women. Fasting glucose was also negatively related to adiponectin in women ($r = −0.106$, $P = .012$) but not in men ($r = −0.077$, $P = .114$).

To test the hypothesis that hormone changes caused by the aging process or treatment determine the adiponectin levels, we evaluated the effect of menopausal state

Table 3
Plasma adiponectin concentrations (μg/mL) in relation to the presence or absence of selected cardiovascular risk factors in women and men

	Women			Men		
	n	Adiponectin (μg/mL)	*P*	n	Adiponectin (μg/mL)	*P*
Hyperglycemia, type 2 diabetes mellitus, or medication use	579			439		
No	460	10.47 ± 1.47	.011	302	6.90 ± 1.02	.051
Yes	119	9.33 ± 1.58		137	6.16 ± 1.62	
Hypertriglyceridemia	579			437		
No	528	10.54 ± 1.47	<.001	343	6.91 ± 1.58	.001
Yes	51	8.12 ± 1.47		94	5.62 ± 1.69	
Low HDL-C or medication use	579			439		
No	407	11.19 ± 1.44	<.001	305	7.06 ± 1.62	<.001
Yes	172	8.51 ± 1.51		134	5.83 ± 1.59	
Current smoking	579			439		
Never	407	10.61 ± 1.51	.026	270	6.81 ± 1.58	.208
Occasionally	23	9.70 ± 1.51		11	7.74 ± 1.32	
Usually	149	9.54 ± 1.47		158	6.30 ± 1.69	
Hypertension or medication use	570			432		
No	340	10.32 ± 1.49	.842	211	6.88 ± 1.57	.143
Yes	230	10.23 ± 1.53		221	6.41 ± 1.67	
Overweight	567			432		
Normal-weight	283	10.73 ± 1.52	.066	142	7.63 ± 1.54	<.001
Overweight	166	10.16 ± 1.49		221	6.30 ± 1.60	
Obese	118	9.52 ± 1.52		69	5.74 ± 1.77	
Abdominal obesity	502			379		
No	336	10.71 ± 1.47	<.001	321	6.85 ± 1.58	.015
Yes	166	9.33 ± 1.57		58	5.83 ± 1.59	
Metabolic Syndrome	565			425		
No	459	16.71 ± 1.48	<.001	331	6.91 ± 1.58	<.001
Yes	106	8.70 ± 1.58		94	5.62 ± 1.62	

Data are expressed as geometric mean ± SD.

or hormone therapy replacement. No significant differences were observed in the adiponectin concentrations of premenopausal women and postmenopausal women older than 45 years. Likewise, no significant differences were observed in postmenopausal women using hormone replacement therapy.

In a stepwise multivariate analysis, waist circumference and HOMA-IR were independent predictors of adiponectin in women (r^2 = 0.086, $P < .001$). In men, BMI and CRP concentrations are independently associated to adiponectin (r^2 = 0.052, $P < .001$). However, when we analyzed the whole population, sex, waist circumference, CRP serum levels, and HOMA-IR were independent predictors of adiponectin plasma concentrations. All together they explained 23.4% of the variability ($P < .001$).

4. Discussion

This is the first study performed in a Mediterranean population that analyzes the distribution of plasma adiponectin levels and their relationship with anthropometric, biochemical, and clinical parameters in a wide sample representative of the adult population.

In accordance with other studies, we observed a sexual dimorphism in the adiponectin plasma levels, which are higher in women than in men. This effect of sex on adiponectin concentrations was independent of other potential confounding variables such as age, BMI, body fat distribution, or insulin resistance. Although some authors have reported a positive [14,20] or negative [21] relationship between age and adiponectin, in our study, no significant differences in adiponectin levels were observed between age groups in the whole population, and this variable was not an independent predictor of the variability of adiponectin plasma levels. Our results are similar to those of other studies that failed to find a correlation with age [22,23]. The reason for these discrepancies may be the heterogeneity of the samples between the different studies. In this respect, the fact that insulin resistance, diabetes, or abdominal fat accumulation are more prevalent in older subjects and related to lower adiponectin plasma levels could explain the negative association between low levels of this adipocytokine and age reported in some studies [24-27]. Otherwise, the decrease in testosterone and estrogens associated with the aging process could explain the positive relationship between age and adiponectin observed in other studies [28] because both hormones are potent inhibitors of adiponectin secretion, at least in cell cultures [29,30]. So, the fact that there are differences between many of the published results may be because of the equilibrium between the metabolic factors of the populations studied.

Adiponectin has been related to obesity, adipose tissue distribution, dyslipidemia, hypertension, and insulin resistance, all of which are factors in the metabolic syndrome cluster. More recently, adiponectin has been described as a biomarker of metabolic syndrome in a Japanese adult population.

In our study, we have found that central obesity was negatively associated with adiponectin concentrations in both men and women. Moreover, in the multiple regression analysis, waist circumference in women was an independent predictor of adiponectin. Results in women are in agreement with those obtained in cell cultures and show that adipocytes derived from intra-abdominal fat depots secrete adiponectin more actively than adipocytes derived from subcutaneous fat [31].

One of the main determinants of adiponectin plasma levels in our study was HOMA-IR, an indirect marker of insulin sensitivity. This association between adiponectin and different measures of insulin sensitivity has previously been reported in several studies [14,32]. However, in our study, as Cnop et al [14] have reported, this relationship is greater in women than in men. In fact, the relationship between fasting insulin or HOMA-IR and adiponectin disappears in men but remains significant in women after adjustment for adiposity.

Adiponectin also correlates with CRP, one of the most consistently inflammatory markers related to metabolic syndrome and to the risk of cardiovascular disease in a variety of populations [15].

In the present study, levels of adiponectin were significantly lower in women with hyperglycemia or type 2 diabetes mellitus and women with hypertriglyceridemia, low HDL-C, or smoking status even after adjusting for confounding variables such as BMI or age, but no significant differences were observed in relation to hypertension. Among men, hyperglycemia or type 2 diabetes mellitus; hypertriglyceridemia; or low HDL-C seem to be related to lower levels of plasma adiponectin, but no significant changes were observed in relation to the presence or absence of hypertension or smoking status. Hypoadiponectinemia has traditionally been closely related to insulin resistance and type 2 diabetes mellitus [5]. In fact, it has been demonstrated that the administration of thiazolidinediones, an insulin-sensitizing agent, increases adiponectin concentrations in both animals and humans [3,33], and adiponectin administration improves sensitivity to insulin in animal models of insulin resistance and type 2 diabetes mellitus [3]. In a group of Pima Indians, it was observed that a high adiponectin concentration was a protective factor against the development of type 2 diabetes mellitus [34]. The results of our study are in accordance with these findings and suggest that adiponectin may have a role in the development and progression of type 2 diabetes mellitus, particularly in women.

Finally, we also observed a strong, positive relationship between HDL-C and adiponectin plasma levels in both men and women. The relationship with triglycerides, however, was negative. These results have been previously described in other non-Mediterranean populations [22,23], suggesting that adiponectin acts as an anti-atherogenic or anti-atherosclerotic factor by improving the lipid profile.

Because adiponectin is related to several metabolic derangements, all of which are in the metabolic syndrome cluster, we used the diagnostic criteria of this syndrome described by the Adult Treatment Panel III to classify our population to explore the relationship between this syndrome and adiponectinemia. Furthermore, one of the limitations of our study is the fact that waist circumference was not measured in all samples, which led to an underestimation of the metabolic syndrome in our population. However, we do not consider that this has an important effect on the results of the study because levels of plasma adiponectin were observed to be significantly lower in both women and men with metabolic syndrome.

Taken together, the results of the present study of a Mediterranean population are very similar to those reported for other populations despite differences in lifestyle and nutritional habits, and lower rates of cardiovascular disease in the Mediterranean region. However, our results suggest that adiponectin plasma levels are more closely related to diabetes and cardiovascular risk factors in women than in men in a population that is representative of a Mediterranean area, although the causes of these sex differences should be explored in the future.

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References

[1] Bays H, Mandarino L, DeFronzo RA. Role of adipocyte, free fatty acids, and ectopic fat in the pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator–activated receptor agonists provide a rational therapeutic approach. J Clin Endocrinol Metab 2004;89:463-78.

[2] Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose-specific collagen-like factor, apM1 (Adipose Most abundant Gene transcript 1). Biochem Biophys Res Commun 1996;221:286-9.

[3] Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with lipoatrophy and obesity. Nat Med 2001;7:941-6.

[4] Yamauchi T, Kamon J, Waki H, et al. Globular adiponectin protected *ob*/*ob* mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem 2003;278:2461-8.

[5] 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;86:1930-5.

[6] Hotta K, Funahashi T, Arita Y, et al. Plasma concentration of a novel-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.

[7] Yang WS, Lee WJ, Funahashi T, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001;86:3815-9.

[8] Baratta R, Amato S, degano C, et al. Adiponectin relationship with lipid metabolism is independent of body fat mass: evidence from both cross-sectional and intervention studies. J Clin Endocrinol Metab 2004;89:2665-71.

[9] Ouchi N, Nihara S, Arita Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.

[10] Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kB signaling through a cAMP-dependent pathway. Circulation 2000;102:1296-301.

[11] Arita Y, Kihara S, Ouchi N, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB–binding protein and regulates growth factor–induced common post-receptor signal in vascular smooth muscle cell. Circulation 2002; 105:2893-8.

[12] Ouchi N, Kihara S, Arita S, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001;103:1057-63.

[13] Ouchi N, Ohishi M, Kihara S, et al. Association of hypoadiponectinemia with impaired vasoreactivity. Hypertension 2003;42:231-4.

[14] Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003;46:459-69.

[15] Juncá S, Guillén M, Aragay JM, et al. Methodological aspects in the evaluation of health and risk-reduction objectives of Health Plan for Catalonia for the year 2000. Med Clin (Barc) 2003;121(Suppl 1): 10-9.

[16] SEEDO'2000 consensus for the evaluation of overweight and obesity and the establishment of criteria for therapeutic intervention. Sociedad Española para el Estudio de la Obesidad. Med Clin (Barc) 2000;115: 587-97.

[17] Friedewald WT, Levy RI. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

[18] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 1985;28:412-41.

[19] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the 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). JAMA 2001;285: 2486-97.

[20] Adamczack M, Rzepkat E, Chudek J, Wiecek A. Ageing and plasma adiponectin concentration in apparently healthy males and females. Clin Endocrinol 2005;62:114-8.

[21] Vilarassa N, Vendrell J, Maravall J, et al. Distribution and determinants of adiponectin, resisitin and ghrelin in a randomly selected healthy population. Clin Endocrinol 2005;63:329-35.

[22] Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M, Matsubara K, et al. 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. Clin Sci 2002;103:137-42.

[23] Ryan A, Berman D, Nicklas B, et al. Plasma adiponectin and leptin levels, body composition, and glucose utilization in adult women with wide ranges of age and obesity. Diabetes Care 2003;26: 2383-8.

[24] DeFronzo RA. Glucose intolerance of aging. Evidence for tissue insensitivity to insulin. Diabetes 1979;28:1095-101.
[25] Chen M, Bergman RN, Pacini G, Porte D. Pathogenesis of age-related glucose intolerance in man: insulin resistance and decreased β-cell function. J Clin Endocrinol Metab 1985;60:13-20.
[26] Schwartz RS, Shuman WP, Bradbury VL, et al. Body distribution in healthy young and older men. Journal of Gerontology 1990;45:M181-5.
[27] Colman E, Katzel LI, Rogus E, Coon P, Muller D, Goldberg AP. Weight loss reduces abdominal fat and improves insulin action middle-aged and older men with impaired glucose tolerance. Metabolism 1995;44:1502-8.
[28] Ryo M, Nakamura T, Kihara S, et al. Adiponectin as a biomarker of the metabolic syndrome. Circulation Journal 2004;68:975-81.
[29] Nishizawa H, Shimomura I, Kishida K, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 2002;51:2734-41.
[30] Combs TP, Berg AH, Rajala MW, et al. Sexual differentiation, pregnancy, caloric restriction, and aging affect the adipocyte-specific secretory protein adiponectin. Diabetes 2003;52:268-76.
[31] Motoshima H, Wu X, Sinha MK, et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. Diabetes 2002;51 (Suppl 2):A-88.
[32] Kwon K, Jung SH, Choi C, Park SH. Reciprocal association between visceral obesity and adiponectin: in healthy premenopausal women. Int J Cardiol 2005;101:385-90.
[33] Maeda N, Takahashi M, Funahashi T, et al. PPAR-gamma ligands increase expression and plasma concentrations of adiponectin, and adipose-derived protein. Diabetes 2001;50:2094-9.
[34] Lindsay RS, Funahashi T, Hanson RL, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002;360:57-8.