The relationship between adiponectin levels and metabolic status in centenarian, early elderly, young and obese women

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Abstract

OBJECTIVES: Adipose tissue secretes proteins which regulate energy metabolism and insulin sensitivity. Adiponectin possesses anti-diabetic, anti-atherogenic and insulin-sensitizing properties. To assess the prognostic factors in prolonged survival and the potential protective role of adiponectin in aging, we examined the release of adiponectin in relation to the metabolic status of centenarians, compared with young, early elderly and obese subjects.

MATERIAL AND METHODS: The study was carried out on 122 women: 22 centenarians aged 100–102 yrs, 45 younger women aged 20–43 yrs, 19 early elderly women aged 64–67 yrs, and 36 obese women aged 26–54 yrs. Anthropometric data, clinical features and blood samples were obtained. Plasma adiponectin and insulin concentrations were measured by RIA methods. Fasting plasma glucose levels, lipid profile and creatinine concentrations were determined using routine laboratory procedures.

RESULTS: In centenarians we found that adiponectin concentrations were significantly increased, compared with young, early elderly and obese women. Insulin concentrations were lower than those in young and obese subjects. HOMA-IR was significantly lower than in obese women. Positive correlations were found between adiponectin and HDL, and negative correlations between adiponectin and HOMA-IR, total cholesterol, LDL, triglycerides, blood pressure and BMI.

CONCLUSION: Our results indicate that adiponectin may play a protective role that contributes to longevity.

ORIGINAL ARTICLE

Introduction

Adipose tissue is not only an energy storage organ, but it is also able to secrete protein factors, called adipocytokines, which are thought to regulate energy metabolism and insulin sensitivity [1, 2]. Deregulation of the secretion of adipocytokines, such as adiponectin, leptin, adipsin, TNF-α and resistin, may lead to insulin resistance [3, 4], which is a predisposing factor for the metabolic syndrome [5, 6].

Adiponectin is a 247-amino acid polypeptide that was first isolated during a study of adipocyte differentiation of 3T3-L1 and 3T3-F 442 A fibroblasts and its transcript identified by large-scale sequencing of a human adipose cDNA library [7].

Levels of adiponectin mRNA are reduced in adipose tissue of animals and humans with obesity and diabetes [8, 9, 10]. In humans, negative correlations between plasma adiponectin level and obesity, hyperinsulinemia, insulin resistance, diabetes, dyslipidemia and cardiovascular diseases have been demonstrated [11, 12, 13, 14, 15].

Adiponectin is an important factor in lipid and glucose metabolism. It induces a decrease in circulating FFA (free fatty acids) by increasing fatty acid oxidation in skeletal muscles [16, 17, 18]. Furthermore, adiponectin decreases liver FFA influx and stimulates glucose uptake in adipocytes and muscles through the activation of AMP-activated protein kinase [2, 19, 20]. The decrease in triglyceride content in the muscles and liver improves insulin sensitivity. In addition to its metabolic effects, adiponectin displays anti-inflammatory and atheroprotective activity in endothelia [21, 22].

These findings indicate that adiponectin possesses both anti-diabetic and anti-atherogenic properties.

Complex risk factors of the metabolic syndrome such as hyperinsulinemia, insulin resistance, glucose intolerance, dyslipidemia, hypertension and cardiovascular complications are strongly correlated with higher mortality.

The aim of this study was to examine plasma adiponectin and insulin levels in relation to metabolic status in the oldest-old humans (centenarians), compared with young, elderly and obese subjects.

Study subjects and methods

The study was carried out on 122 women: 22 extremely long-lived women, centenarians, aged above 100 yrs (100–102 yrs, mean 100.98 ± 0.98); 45 younger women aged 20–43 yrs (mean 26.04 ± 7.6); 19 early elderly women aged 64–67 yrs (mean 66.03 ± 0.85), and 36 obese women aged 26–54 yrs (mean 41.63 ± 12.42).

The centenarians and early elderly women were randomly selected from citizens living in the Mazowsze region of Poland. The obese women were recruited from outpatient clinics. The young women were volunteers.

Some exclusion criteria were established to ensure that all subjects were in good health, without relevant acute or chronic disorders including cardiovascular, respiratory and renal diseases. Any subjects with endocrine diseases, heart, respiratory, renal or hepatic failure, and those with neoplasm history were excluded from the study. Moreover, diabetic patients treated with oral therapy or insulin were also omitted. Additionally, none of the subjects had smoked for at least two years and they had no history of alcohol over-consumption.

Informed consent was obtained from all participants and the study was approved by the local Ethics Committee.

Table 1: Clinical and biochemical data (Mean ± SD)

	Centenarians	Young	Elderly	Obese
Age (yrs)	100.98 ± 0.98	26.04 ± 7.6***	66.03 ± 0.85***	41.63 ± 12.42***
BMI (kg/m^2)	23.19 ± 3.97	21.52 ± 1.77	26.31 ± 2.83	32.71 ± 4.1***
Systolic BP (mm Hg)	129.5 ± 18.8	119.8 ± 7.5	143. 4 ± 17.3	151.8 ± 21.4***
Diastolic BP (mm Hg)	80.9 ± 10.3	75.2 ± 7.5	87.6 ± 6.3	93.9 ± 10.5***
Cholesterol (mg/dl)	176.4 ± 35.2	176.1 ± 7.3	232.4 ± 30.4***	227.8 ± 34.7***
HDL(mg/dl)	61.4 ± 16.8	78.7 ± 7.2***	69.9 ± 15.6	58.3 ± 12.8
LDL (mg/dl)	96.0 ± 27.4	68.7 ± 7.3***	137.7± 38.4***	145.9 ± 29.4***
TG (mg/dl)	94.4 ± 44.47	75.5 ± 5.0	123.8 ± 55.5	130.2 ± 36.9***
Fasting insulin (μU/ml)	5.6 ± 3.8	14.12 ± 9.3***	7.8 ± 4.9	33.8 ± 25.9***
Fasting glucose mmol/l	5.5 ± 2.2	4.05 ± 0.5*	4.9 ± 0.5	6.72 ± 2.3
HOMA index	1.47 ± 1.4	2.33 ± 1.57	1.76 ± 1.25	11.18 ± 8.76***
Adiponectin (μg/ml)	17.15 ± 9.8	10.78 ± 5.8 ***	10.0 ± 6.0***	8.21 ± 3.0 ***

BMI-Body Mass Index, BP-blood pressure, HDL-High Density Lipoproteins, LDL-Low Density Lipoproteins, TG-triglycerides, HOMA-IR – Homeostasis Model Assessment of Insulin Resistance
* p< 0.05 between the centenarian group and the investigated group
** p < 0.01 between the centenarian group and the investigated group
*** p < 0.001 between the centenarian group and the investigated group

Table 2: The incidence of diabetes mellitus, hypertension and plasma lipid disturbances in the investigated groups

		Centenarians N = 22	Early elderly N = 19	Young N = 45	Obese N = 36
Diabetes mellitus		2 (9%)	4 (21%)	0	14 (39%)
Hypertension		4 (18%)	8 (42%)	1 (2%)	24 (67%)
Cholesterol, mg/dl	> 200	5 (23%)	14 (74%)	1 (2%)	28 (78%)
Triglycerides, mg/dl	> 150	1 (4.5%)	5 (26%)	0	19 (53%)

After overnight fasting, blood samples were taken from the subjects.

Plasma adiponectin concentration was measured by a RIA method using a commercial kit (Linco Research Inc.). The sensitivity of the assay was 1.0 ng/ml with an intra-assay coefficient of variation (CV) of 4.8%, and inter-assay CV of 6.5%. Plasma insulin levels were determined using a commercial RIA kit (Biosource) and the sensitivity was 1.0 μIU/ml, with intra-assay CV of 1.6% and inter-assay CV of 6.1%.

Fasting plasma glucose levels, lipid profile and creatinine concentrations were determined using routine laboratory procedures.

Insulin resistance was estimated from fasting plasma insulin and glucose values using a homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was calculated according to the formula: fasting plasma glucose mmol/l × fasting plasma insulin concentration μU/ml / 22.5. Insulin resistance was defined as HOMA-IR > 2.5.

The glomerular filtration rate (GFR) was calculated from serum creatinine measurements using the Cockroft-Gault formula: (140-age {yrs} × body mass {kg} × 0.85) / (serum creatinine concentration × 72).

Clinical and biochemical data from all groups are presented in Tables 1 and 2.

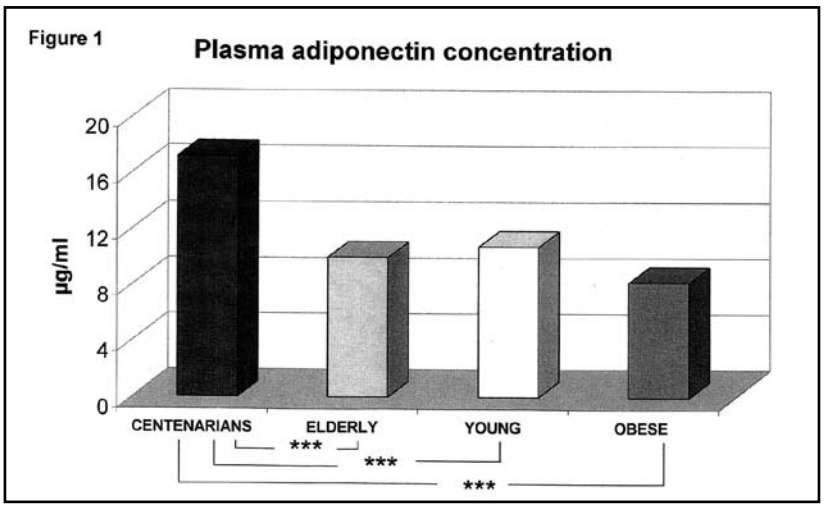

Figure 1: Plasma adiponectin concentration. ***p<0.001

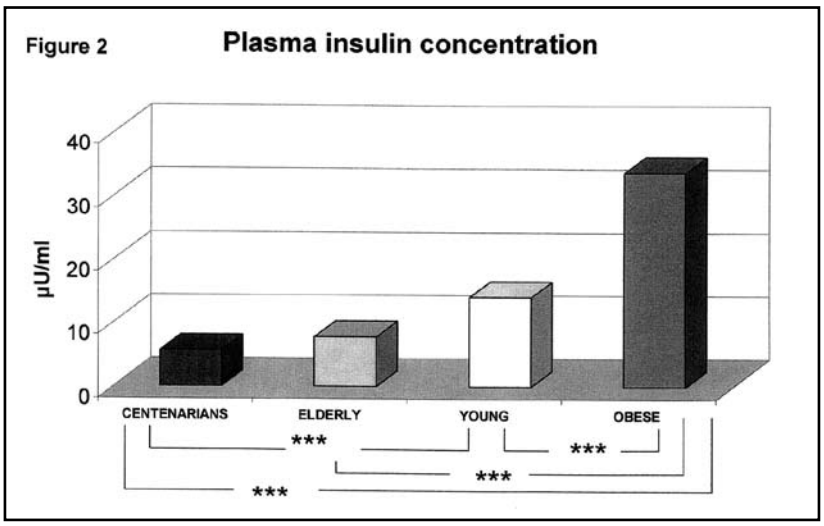

Figure 2: Plasma insulin concentration. ***p<0.001

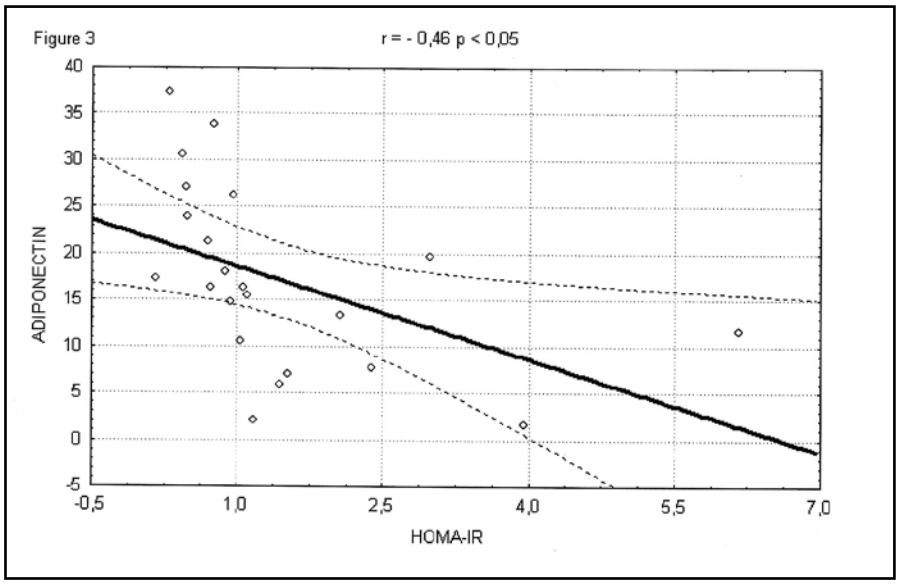

Figure 3: Correlation between adiponectin concentration and HOMA-IR. r – Spearman's correlation coefficient

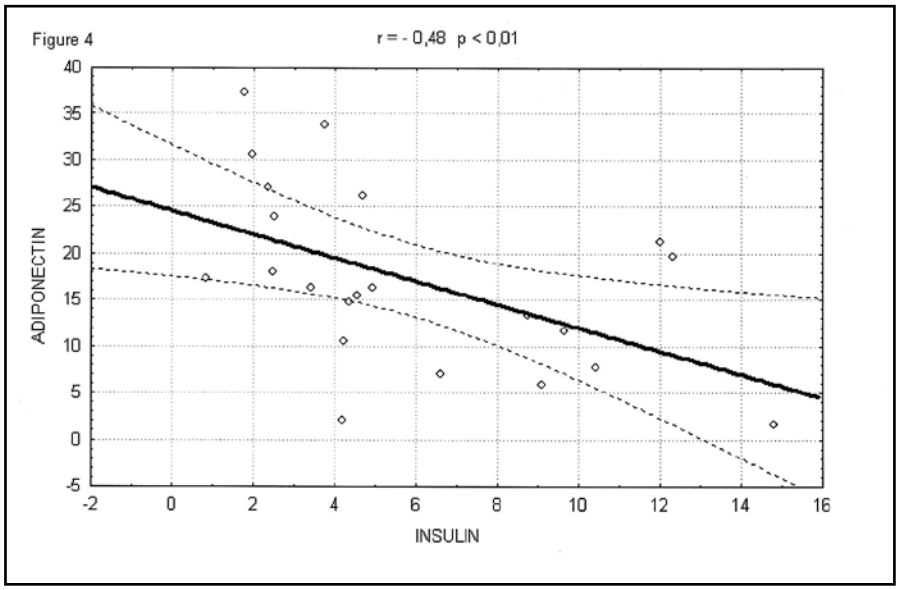

Figure 4: Correlation between adiponectin and insulin concentrations. r – Spearman's correlation coefficient

Statistical analysis

Statistical analysis was made using the ANOVA test followed by the Scheffe test (comparison of all groups).

In order to study the possible correlations between adiponectin and age, BMI, lipids and the indicator of insulin resistance, the Spearman test was performed.

Multiple regression analyses in the groups under study, with adiponectin as a dependent variable and age, BMI, diastolic and systolic blood pressure, cholesterol, HDL, LDL, triglycerides and HOMA index as independent variables, were performed.

All results are presented as mean ± SD. Statistical significance was accepted at $p < 0.05$.

Results

Plasma adiponectin and insulin concentrations in centenarians, early elderly, young and obese women are presented in Figures 1 and 2.

Plasma adiponectin levels were significantly higher in the centenarian group, compared with the other groups. There were no significant differences between the obese, elderly and young groups (Figure 1). The arithmetic mean of plasma adiponectin concentration in centenarians was found to be significantly higher than in early elderly subjects ($\bar{x}$ 17.15 μg/ml ± 9.8 vs. $\bar{x}$ 10.0 μg/ml ± 6.0; $p<0.001$ – Figure 1). Moreover, in centenarians, adiponectin concentrations were significantly increased, compared with young women ($\bar{x}$ 17.15 μg/ml ± 9.8 vs. $\bar{x}$ 10.78 μg/ml ± 5.8; $p<0.001$ – Figure 1). Plasma adiponectin levels in centenarians were also significantly higher than in obese women ($\bar{x}$ 17.15 μg/ml ± 9.8 vs. $\bar{x}$ 8.21 μg/ml ± 3.0, $p<0.001$ – Figure 1).

Serum fasting insulin concentrations were significantly lower in centenarians, compared with both the obese ($\bar{x}$ 5.6 ± 3.8 vs. $\bar{x}$ 33.8 ± 25.9; p<0.001) and the young groups ($\bar{x}$ 5.6 ± 3.8 vs. $\bar{x}$ 14.12 ± 9.3; p<0.001 – Figure 2), but did not differ from values found in early elderly women.

In the centenarian group, values for the insulin resistance index (HOMA-IR), total plasma cholesterol, LDL and triglycerides were significantly lower (p<0.001 for all measurements) than in obese subjects (Table 1).

We also observed that total cholesterol and LDL levels were significantly lower in centenarians than in early elderly subjects (p<0.001, p<0.001 respectively), but LDL levels were higher, in comparison with the young group. Moreover, HDL values in this extremely long-lived group were lower than those found in young subjects (p<0.001 – Table 1). Triglyceride concentrations in centenarians were lower, compared with the obese group (p<0.001). Consequently, the prevalence of hypertension, diabetes mellitus and dyslipidemia was markedly lower in centenarians than in the elderly and obese (Table 2).

Mean glomerular filtration rate (GFR) values in centenarians (28.6 mL/min) were below the normal range.

To examine possible correlations between the studied parameters, statistical analyses were performed using the Spearman test.

In all groups we identified negative correlations between adiponectin and BMI (R = –0.21; p<0.05), systolic blood pressure (R = –0.23; p<0.05), triglycerides (R= –0.24; p<0.01), insulin (R = –0.33; p<0.001) and HOMA-IR (R = –0.32; p<0.001). It should be emphasized that the strongest negative correlations were found with the indicator of insulin resistance.

In the centenarian group, negative correlations were identified between adiponectin and triglycerides (R = –0.58; p<0.01), HOMA-IR (R = –0.72; p<0.05 – Figure 3) and insulin (R = – 0.48; p<0.01 – Figure 4). A positive correlation was observed between adiponectin and HDL (R = 0.61; p<0.01).

Multiple regression analysis, with plasma adiponectin concentration as the dependent variable and BMI and age as independent variables, indicated that in this model (R^2 = 0.20), plasma adiponectin concentrations depended significantly on BMI (β = –0.25; p<0.01) and age (β = 0.37; p<0.001). The second model of multiple regression (R^2 = 0.18), with adiponectin as the dependent variable and age and triglycerides as independent variables, showed that plasma adiponectin concentrations depended on age (β = 0.38; p<0.001) and triglycerides (β = –0.25; p<0.01).

Discussion

The present study demonstrates that the process of aging in humans is associated with several changes in the neuroendocrine and biochemical status.

We have shown that plasma adiponectin concentrations in the oldest-old women (centenarians) are significantly increased, compared with young, elderly (below 70 yrs of age) and obese women. Although plasma adiponectin values found in the elderly group have a tendency to be higher, compared with obese women, and lower, compared with young women, the differences were not significant.

The issue of alterations in adiponectin concentration with age is highly contentious.

Ryan et al. [23] studied women aged 18–81 yrs and found that plasma adiponectin concentrations did not differ with age; although adiponectin was associated with the percentage of body fat, visceral fat, and insulin release. Daimon et al. [24] demonstrated a significant positive relationship between adiponectin and age, while Yamamoto et al. [25] found no such correlation. Arai et al. [26] have observed that high plasma concentrations of adiponectin in centenarians were associated with lower levels of C-reactive protein and E-selectin.

Adamczak et al. [27] did not observe significant changes in adiponectin levels with age in women; however, they found higher plasma adiponectin concentrations in elderly males, compared with younger ones.

It is known that healthy women have higher plasma adiponectin levels than men [28]. This gender difference might be connected with the inhibitory effects of androgens. The increase in plasma adiponectin values in elderly men may be related to the andropause [27].

Androgens have been shown to cause a decrease in plasma adiponectin, and hypoadiponectinemia may be related to the higher risk of insulin resistance and atherosclerosis in men [28].

We observed high adiponectin concentrations in long-lived women aged over 100 yrs and it may be speculated that women with higher adiponectin levels have an increased life span.

It is known that both the kidneys and the liver are involved in the process of degradation and elimination of adiponectin [27, 29]. Elevated adiponectin levels were observed in hemodialyzed patients with chronic renal failure [30]. Tietge et al.[29] demonstrated increased adiponectin levels in patients with liver cirrhosis.

We found no clinical or biochemical signs of renal or liver dysfunction in our centenarian subjects Although in centenarians, compared with the elderly, young and obese groups, GFR values were significantly lower and adiponectin levels were significantly higher, we strongly believe that the high adiponectin concentrations seen in this group are not due to renal insufficiency. All of the extremely long-lived subjects were in good health without any clinical and biochemical signs of renal failure. The low GFR index in this oldest-old group, which was estimated using the Cockroft-Gault formula, may be considered to be the result of inaccuracy in this calculation due to the low body mass and great age of these individuals entered into this formula. In addition,

we failed to find significant differences between the adiponectin concentrations in the elderly and young groups despite the variation in GFR. Furthermore, despite the low GFR values, the centenarian group showed low insulin concentrations.

It has been reported that aging in humans is associated with several hormonal and metabolic alterations [31, 32, 33], and it has been estimated that 15% to 20% of subjects over 70 yrs of age suffer from the metabolic syndrome. The metabolic syndrome directly leads to increased atherogenesis, cardiovascular complications and major risks of early death [34].

Adiponectin has been considered to be a biomarker of the metabolic syndrome because hypoadiponectinemia is closely connected with symptoms associated with this syndrome.

Our results demonstrate that plasma insulin concentrations in the oldest-old women are significantly lower than those in young and obese subjects. All centenarians were lean, with mean BMI of 23 kg/m^2, and their BMI values did not differ from those of young persons. The incidence of hypertension, dyslipidemia and diabetes mellitus in centenarians was markedly lower than that found in obese and elderly women. HOMA-IR was significantly decreased in centenarians, compared with obese subjects.

In obese women, we observed significantly lower plasma adiponectin concentrations, compared with the centenarian group, and significantly higher insulin levels in comparison with young, elderly and centenarian women.

The majority of obese women exhibited metabolic disturbances such as hypertension, diabetes, dyslipidemia and insulin resistance.

The elderly women (below 70 yrs) were overweight (mean BMI 26 kg/m^2).

The incidence of metabolic syndrome symptoms in early elderly women was higher in comparison with the centenarian group, but was markedly lower than that found in obese women.

It is well known that obesity, especially visceral obesity, is associated with metabolic abnormalities that increase the risk of type 2 diabetes and cardiovascular diseases [35]. Many studies have indicated that plasma adiponectin levels negatively correlate with BMI, fasting glucose, insulin, HOMA-IR, total cholesterol, triglycerides and LDL, and positively correlate with HDL [23, 25, 35, 36].

The findings of Yamamoto et al. [25] suggest that adiponectin is negatively related to HOMA-IR, independently of age, sex and BMI.

Baratta et al. [36] observed that in both non-obese and obese subjects low plasma adiponectin levels are associated with insulin resistance.

The positive effects on the lipid profile may explain the role of adiponectin in protecting against endothelial dysfunction and atherosclerotic vascular changes [37, 38].

The anti-atherosclerotic properties of adiponectin are mediated through its direct action on endothelial cells and by indirect effects that improve insulin resistance and the lipid profile.

It has been reported that obese subjects have reduced plasma adiponectin levels [12, 39].

Decreases in the plasma concentration of adiponectin have also been observed in people with type 2 diabetes [10, 39], insulin resistance [11] and cardiovascular diseases. Moreover, decreased serum adiponectin levels are considered to be an independent risk factor for the progression of type 2 diabetes [24].

These findings suggest that adiponectin plays an important role in insulin sensitivity and glucose metabolism.

Hypoadiponectinemia is also considered to be an independent risk factor for hypertension [40], and is an independent parameter of endothelial function.

Plasma adiponectin levels have been found to be decreased in subjects with essential hypertension [37]. Plasma adiponectin levels are strictly associated with the insulin resistance syndrome and an atherogenic lipid profile, which suggests that adiponectin may play a role in the pathogenesis of coronary atherosclerosis, especially in obese and insulin-resistant subjects. Our previous studies indicated the role of neuropeptides in the mechanisms of appetite control and hormonal secretion in obesity [41, 42, 43]. Obesity and related diseases such as glucose intolerance, hypertension and dyslipidemia, which are the symptoms of the metabolic syndrome, result in cardiovascular morbidity and mortality.

Thus, it may be suggested that adiponectin represents a promising target for future investigation, with the aim of reducing the morbidity and mortality of atherosclerotic diseases.

In conclusion, our findings indicate that adiponectin may play a protective role that promotes human longevity and its anti-obesity, anti-diabetic, anti-atherogenic, and insulin-sensitizing properties might be of use in a novel strategy for the treatment of the metabolic syndrome.

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