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Assessment of adiponectin and its isoforms in Polish centenarians

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ABSTRACT

Background: The physiological mechanisms that promote longevity remain unclear. It has been suggested that insulin sensitivity is preserved in centenarians, whereas typical aging is accompanied by increasing insulin resistance. The oldest-old individuals display raised total adiponectin levels, despite the potential correlation between enhanced adiponectin and all-cause and cardiovascular mortality.
Aim: To evaluate the level of adiponectin and its isoforms in sera of centenarians and to assess associations between adiponectin and metabolic parameters.
Participants: A group of 58 Polish centenarians (50 women and 8 men, mean age 101 ± 1.34 years) and 68 elderly persons (55 women and 13 men, mean age 70 ± 5.69 years) as controls.
Measurements: Serum samples were analyzed to evaluate the following parameters: adiponectin array (total adiponectin, HWM-, MMW- and LMW-adiponectin; all by ELISA methods), insulin (by IRMA methods), glucose and lipid profiles. HOMA-IR was calculated. Clinical data were collected. Statistical analyses were performed.
Results: The concentrations of all adiponectin isoforms were significantly higher in the oldest-old participants. In the centenarian group, total adiponectin positively correlated with age and HDL-cholesterol, and HMW-adiponectin was negatively associated with insulin and triglycerides. The long-lived participants had a lower incidence of hypertension, type 2 diabetes, overweight and obesity, with lower concentrations of serum glucose and insulin, and reduced HOMA-IR.
Conclusion: Our findings support the thesis that centenarians possess a different adiponectin isoform pattern and have a favorable metabolic phenotype in comparison with elderly individuals. However, additional work is necessary to understand the relevance of these findings to longevity.

1. Introduction

The increasing lifespan of the human population has resulted in a growing number of centenarians. However, the mechanisms that promote longevity remain unclear. Data from the literature suggest that the oldest-old individuals have preserved insulin sensitivity, which contrasts with the increasing insulin resistance found in typical aging (Barbieri et al., 2001). Previous studies on the centenarian population have demonstrated that this particular group is characterized by increased total adiponectin levels (Adamczak et al., 2005; Bik et al., 2006).

Adiponectin is an adipocyte-derived protein composed of 247 amino acids. It is secreted into the periphery as three oligomeric forms including a trimer (LMW-low molecular weight), hexamer (MMW-medium molecular weight) and high molecular weight (HMW) form (12 to 18-mer) (Magkos and Sidossis, 2007). These three forms differ not only in the number of adiponectin molecules, but also in their biological activity. HMW adiponectin is thought to be the major active form since it possesses the greatest insulin sensitizing and cardioprotective activity (Kobayashi et al., 2004).

Adiponectin acts through two seven-domain transmembrane receptors named AdipoR1 and AdipoR2 (Yamauchi et al., 2003). The biological activity of adiponectin is mediated by activation of AMP kinase (AMPK), PPARα (peroxisome proliferators – activated receptor alpha) and p38 mitogen-activated protein kinase (MAPK) signaling pathways (Kadowaki et al., 2008). The fact that several signaling molecules are involved in the intracellular downstream signal transmission from adiponectin receptors may explain the wide range

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of adiponectin activities. APPL1 (adaptor protein containing pleckstrin homology domain, phosphotyrosine binding (PTB) domain and leucine zipper motif-1) is one such signaling molecule that interacts with both adiponectin receptors. This factor is involved in the insulin sensitizing mechanism of adiponectin action (Mao et al., 2006). Some intracellular signaling factors cooperate only with AdipoR1 and it has been demonstrated that the receptor for activated protein kinase C1 (RACK1), the regulatory subunit of protein kinase CK2 (CK2β), endoplasmic reticulum protein 46 (ERp-46) and lymphotoxin-β belong to this group (Hui et al., 2012). It has been suggested that lymphotoxin-β mediates the anti-inflammatory activity of adiponectin by suppressing NFkB (Xu et al., 2011).

Recently, a study by Holland et al. (2011) indicated that adiponectin may also modulate the metabolism of sphingolipids by stimulating ceramidase activity. It has been speculated that both receptors, AdipoR1 and AdipoR2, are involved in this function of adiponectin, since their absence results in ceramidase dysfunction.

Besides binding to AdipoR1 and AdipoR2, MMW-adiponectin and HMW-adiponectin, are also able to bind T-cadherin (Hug et al., 2004), and consequently exert a cardioprotective effect (Denzel et al., 2010).

In addition, data from experimental studies have suggested that adiponectin possesses anti-inflammatory, anti-atherogenic, vasoprotective and anti-apoptotic properties (Goldstein and Scalia, 2004). These beneficial effects of adiponectin were confirmed by the results of studies concerning the relationship between adiponectin and the risk of diabetes mellitus type 2, and its association with metabolic disturbances (Matsuzawa, 2010; Stenholm et al., 2010). A recent study found that increasing levels of total adiponectin HMW isoform were associated with a reduced risk of incident diabetes in the older cohort (Kizer et al., 2012). Furthermore, data from clinical studies indicated a link between hypoadiponectinemia and endothelial dysfunction, greater carotid intima media thickness and coronary artery disease (Gardener et al., 2012; Szmitko et al., 2007).

In contrast, another study revealed that hyperadiponectinemia was associated with cardiovascular disease (CVD) or all-cause mortality in patients with heart disease as well as in the general population, especially older adults (Poehls et al., 2009).

However, the findings of previous studies by our group, which are corroborated by the results of others, indicated that the oldest-old individuals have higher adiponectin levels than younger subjects (Arai et al., 2006; Atzmon et al., 2008; Bik et al., 2006).

The aim of the present study was to evaluate the serum concentrations of adiponectin isoforms in the elderly and extremely old, and to identify any correlations with indicators of glucose and lipid metabolism in these subjects.

2. Subjects and methods

2.1. Subjects

The study population consisted of 126 subjects of Polish descent: 58 extremely old individuals (50 women and 8 men) aged between 100 and 108 years (mean 101 ± 1.34 years), and 68 elderly persons (55 women and 13 men) aged between 63 and 86 years (mean 70 ± 5.69 years). The centenarians were selected mainly from citizens living in the Mazovia Region of Poland and were recruited from the study "Genetic and environmental factors of longevity". All elderly individuals were volunteers recruited from the General Practitioner Clinics.

To avoid confounding factors that could affect circulating adiponectin levels, certain exclusion criteria were established. These included relevant acute or chronic disorders including cardiovascular, pulmonary and renal diseases, history or evidence of endocrine dysfunction, neoplasm and heart, respiratory, renal or hepatic failure. In addition, subjects receiving treatment for systemic, infectious, inflammatory or malignant disorders at the time of the investigation or in the preceding 3 months were also excluded. The study was approved by the Ethics Committee of the Polish Academy of Science. All participants or their caregivers signed the informed consent form.

2.2. Medical examination

On the day of blood collection a medical examination was performed to assess the health status of the subjects and to collect clinical data including blood pressure, weight, height and body mass index (BMI).

2.3. Analytical methods

Blood samples were collected in the morning after a 6 to 12-h fasting period. Serum was separated by centrifugation at 4 °C and stored at −70 °C. The samples were not further aliquoted, nor were they repeatedly frozen and thawed.

The concentrations of total and multimeric adiponectin in the sera were measured by ELISA using commercial kits (ALPCO Diagnostics, Windham, NH, USA). The sensitivity was 0.075 ng/ml for all adiponectin assays. The insulin concentration was measured using IRMA (kits from Biosource, Europe, SA, Nivelles, Belgium). The sensitivity of the insulin assay was 1 μU/ml.

The inter- and intra-assay coefficients of variation were <10% for all investigated parameters.

Standard clinical laboratory tests were used for assessment of the creatinine, glucose and lipid profiles of the sera.

Insulin resistance was estimated using the homeostasis model assessment method (HOMA-IR) and defined as HOMA-IR >2.5.

2.4. Statistical analyses

Statistical analyses were performed using STATISTICA version 7.1PL. The normality of distributions within the groups was investigated using the Shapiro–Wilk and Kolmogorow–Smirnov tests with Lillefors corrections. The evaluation of differences between the two groups was performed using the Mann–Whitney U-test. The Spearman test was applied to calculate the correlations between the serum concentration of adiponectin or its isoforms with anthropometric measurements and biochemical parameters.

Three models of multiple regression analysis were used. In the first, total adiponectin was the dependent variable, and age and HDL cholesterol were independent variables. In the second, HMW adiponectin was the dependent variable, and age and HDL cholesterol were independent variables. In the third multiple regression model, the contribution of insulin and triglycerides as independent variables and HMW adiponectin as the dependent variable was determined.

All data were presented as mean ± SD.

Statistical significance was accepted at $p<0.05$.

3. Results

The clinical data and biochemical parameters are presented in Table 1A.

The analysis of body mass index revealed that elderly individuals had markedly higher values compared with centenarians ($p<0.05$). In the oldest-old group, the parameters of glucose metabolism (fasting serum glucose and insulin concentrations, HOMA-IR) were significantly lower ($p<0.001$ for all evaluated parameters) than those of elderly subjects. Moreover, values of total serum cholesterol, LDL-cholesterol and triglycerides differed significantly between the two examined groups, with lower concentrations found in the centenarians ($p<0.01$, $p=0.01$ and $p<0.001$, respectively). Interestingly, no differences were found when HDL-cholesterol levels were compared.

The results of evaluation of the adiponectin array are shown in Table 1A. A comparison between the oldest-old subjects and elderly individuals revealed that levels of total adiponectin and all multimeric