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Clinical characteristics of high plasma adiponectin and high plasma leptin as risk factors for arterial stiffness and related end-organ damage

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ABSTRACT

Objective: The relationship between plasma levels of adiponectin and cardiovascular events is inconclusive. We evaluated the clinical characteristics of people with high plasma adiponectin and high plasma leptin levels.

Methods: Thousand seven hundred participants recruited from visitors to the Anti-Aging Doc were divided into four groups by combining the bipartiles of plasma adiponectin and leptin levels in men and women separately: AL, high adiponectin and high leptin; Al, high adiponectin and low leptin; al, low adiponectin and low leptin; aL, low adiponectin and high leptin. Body composition, including visceral fat area and thigh muscle cross-sectional area (CSA), brachial-ankle pulse wave velocity (baPWV), periventricular hyperintensity, and urinary albumin excretion, were determined.

Results: Twenty percent of the studied population fell within the AL group. This group had a significantly higher visceral fat area than the Al group. Thigh muscle CSA was lowest in the AL group among groups. baPWV, brain white matter lesions, and albuminuria findings in the AL group were significantly higher than those of the Al group. Multiple and logistic regression analyses with confounding parameters further confirmed that plasma adiponectin was not an independent determinant for brain and renal small vessel-related disease.

Conclusion: These findings suggest that the plasma level of adiponectin alone is not enough for the risk stratification of cardiovascular disease. Leptin resistance associated with skeletal muscle loss in addition to obesity may need to be addressed to identify high risk people with high plasma adiponectin levels.

1. Introduction

Adiponectin is one of the major adipokines and is present in abundance in the circulation [1–3]. Plasma levels of adiponectin decrease with increasing fat, especially visceral fat, accumulation [1–3]. Adiponectin has numerous physiological properties, including the improvement of insulin resistance, an antiatherosclerotic action, and is therefore thought to have a protective cardiovascular function [1–3]. However, the relationship between plasma adiponectin and cardiovascular events is inclusive [4,5]. Several epidemiological studies, including our own observations, suggest that higher plasma levels of adiponectin are associated with an increased risk of cardiovascular events and mortality [6–8]. However, the underlying mechanism of the "adiponectin paradox" has not been elucidated.

Leptin is another well-characterized adipokine. Plasma levels of leptin have been reported to increase with adiposity [9–11]. High plasma levels of leptin that are associated with obesity cause leptin resistance, resulting in blood pressure elevation, insulin resistance, and metabolic syndromes [9–11]. Leptin, through these functions, is thought to be anatherogenic adipokine [9–11], although its association with cardiovascular events is not conclusive [12]. We observed that plasma levels of leptin were associated with not only visceral fat, but also with muscle mass; the thigh muscle cross-sectional area (CSA) was negatively associated with plasma leptin levels [13].

Adiponectin and leptin are reciprocally regulated via adipocytes; however, their association is not strong [14]. We speculated

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that skeletal muscle mass may underlay the dissociation between plasma adiponectin and leptin levels. Sarcopenia, the age-related loss of muscle mass and muscle strength, is related to physical dysfunction, a decline in activities of daily living, and frailty in the elderly [15,16]. Furthermore, sarcopenia has been shown to be associated with arterial stiffness and cardiovascular death [17,18]. From these findings, we hypothesized that alterations in skeletal muscle mass and leptin resistance could be the underlying mechanism responsible for the "adiponectin paradox".

We investigated the clinical characteristics of people with dissociation between plasma levels of adiponectin and leptin. To isolate the dissociation between the levels of the two adipokines, participants were divided into bipartiles at the median of both adiponectin and leptin in men and women separately. The entire population was then divided into four groups by combining the bipartiles of plasma adiponectin and leptin levels. Clinical characteristics, including thigh muscle CSA, of the group with high adiponectin and high leptin levels were compared with the other groups. Furthermore, small vessel-related end-organ damage was compared among the four groups for any associations with plasma adiponectin.

2. Materials and methods

2.1. Study participants

Participants were middle-aged to elderly persons recruited from those consecutive visitors to the Anti-Aging Center at Ehime University Hospital between March 2006 and February 2013. They participated in the voluntary medical check-up program titled "Anti-Aging Doc", a program provided to residents of Ehime Prefecture, Japan and specifically designed to evaluate age-related disorders including atherosclerosis, cardiovascular disease, physical function, and cognitive impairment [13,17–21]. A total of 1700 people gave written consent to participate in the study and had no history of symptomatic cardiovascular events, including peripheral arterial disease, stroke, coronary heart disease, and congestive heart failure. All participants were functionally independent in their daily lives. Among them, about 90% of participants had their visceral fat area, thigh muscle CSA, and end-organ damage determined. The series of studies to which the present study belongs were approved by the Ethics Committee of Ehime University Graduate School of Medicine.

2.2. Measurement of thigh muscle cross-sectional area and visceral fat area

Thigh muscle CSA was measured using computed tomography (LightSpeed VCT; GE Healthcare, Tokyo, Japan) at the mid-thigh, measured as the midpoint from the inguinal crease to the proximal pole of the patella [13,17]. The muscle CSA (in cm squared), excluding intramuscular fat, was computed using an attenuation range of 0–100 Hounsfield units. The visceral fat area was measured using computed tomography at the level of the umbilicus, with an attenuation range of −150 to −50 Hounsfield units. Images were obtained with a minimal slice width of 5 mm and analyzed using OsiriX software (OsiriX Foundation, Geneva, Switzerland) [13,17].

2.3. Pulse wave velocity

Pulse wave velocity (PWV) was measured using a volume plethysmograph (PWV/ABI; Omron Healthcare Co., Ltd., Kyoto, Japan). A detailed explanation of this device as well as the validity and reproducibility of its measurements have been provided previously [15,16]. The brachial-ankle PWV (baPWV) was calculated from the time interval between the wave fronts of the brachial and ankle waveforms (DTba) and the path length from the brachium to the ankle. The path length from the suprasternal notch to the brachium (Lb) or ankle (La) was obtained using the following formulae: $Lb = 0.2195 \times height + 2.0734$; and $La = 0.8129 \times height + 12.328$. The baPWV was then obtained using the equation $(La - Lb)/DTba$. The intra-measurement and between-measurement reproducibility (coefficient of variation) of baPWV in our laboratory were $2.1\% \pm 1.8\%$ and $2.2\% \pm 1.5\%$, respectively [17,19].

2.4. Plasma adiponectin and leptin measurements

Plasma samples were obtained from each participant after an overnight fast. The samples were immediately frozen and stored at −80 °C until measurements were taken. The plasma concentration of leptin was determined using a commercially available radioimmunoassay kit (Leptin HL-81K; Linco Research Inc., St. Charles, MO, USA) [13,20]. Total plasma adiponectin levels, including high- to low-molecular-weight adiponectin, were measured using commercially available ELISA kits (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) [20]. Inter-assay and intra-assay reproducibility were evaluated using samples with concentrations from 4 to 18 ng/ml, and from 2 to 9 μg/ml, respectively. The coefficient of variation of the inter-assay of leptin and adiponectin was 7.2% and 11.5%, and the intra-assay variation was 4.1% and 4.0%, respectively.

The study participants were divided into four groups by combining the bipartiles of plasma adiponectin and leptin levels in men and women separately: AL ($n = 354$) high adiponectin and high leptin; Al ($n = 499$) high adiponectin and low leptinal ($n = 336$) low adiponectin and low leptin; and aL ($n = 511$) low adiponectin and high leptin (Suppl. Fig. 1)

2.5. Evaluation of risk factors

Lifestyle, medical history, and prescribed drugs were evaluated by questionnaire. Anthropometric measurements were performed by a trained nurse. Venous blood was collected for measurement of lipid, insulin, and glucose levels. Low-density lipoprotein cholesterol was calculated using the Friedewald formula: Total cholesterol − high-density lipoprotein cholesterol − triglyceride/5. Homeostasis model assessment-insulin resistance was calculated as an index of insulin resistance. Physical activity frequency was assessed using a questionnaire that evaluated the frequency of a participant's daily physical activities into the following categories: every day or sometimes, not so often, and none.

2.6. End-organ damage

Two types of small vessel-related, end-organ damage were evaluated.

2.6.1. Periventricular hyperintensity (PVH)

Brain magnetic resonance imaging (MRI) was performed with a 3-T scanner (Sigma Excite 3.0T; GE Healthcare, Milwaukee, WI, USA). PVH was defined as white matter hyperintensity depicted on T2-weighted and FLAIR images [21] in contact with the ventricular wall. PVH was further classified into five grades according to the Japanese Brain Dock Guidelines 2003 [22], namely: grade 0, absent or only a "rim"; grade 1, limited lesion-like "caps"; grade 2, irregular "halo"; grade 3, irregular margins and extension into the deep white matter; and grade 4, extension