The Role of Adiponectin as a Compensatory Mediator for the Primary Secretory Defect in Latent Autoimmune Diabetes in Adults

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ABSTRACT

Background: Increased adiposity in patients with newly diagnosed type 2 diabetes mellitus (DM), as well as in patients who do not have DM, affects the regulation of insulin sensitivity and the metabolic effects of adiponectin.

Objective: The goal of this study was to investigate the relationship between plasma adiponectin levels and obesity in patients developing DM mainly due to an early decline in β-cell function.

Methods: We studied 29 patients with latent autoimmune diabetes in adults (LADA), 38 patients with type 1 DM, and 55 healthy volunteers.

Results: Plasma adiponectin levels, adjusted for body mass index (BMI), were higher in patients with type 1 DM than in controls ($P < 0.001$) and similar to those in patients with LADA ($P = 0.464$). Plasma adiponectin levels were higher in LADA patients compared with controls ($P < 0.001$). In LADA patients, plasma adiponectin levels, adjusted for BMI, correlated significantly with insulin resistance (β coefficient, –6.453 [2.772]; $P = 0.028$). Interestingly, this relationship in LADA patients was significant in more overweight patients (β coefficient, –7.142 [3.249]; $P = 0.048$) but not in leaner patients ($P = 0.571$), a finding that was not confirmed through the results in the controls ($P = 0.520$ and $P = 0.992$, respectively).

Conclusions: In patients with LADA, increases in plasma adiponectin levels, after adjustment for BMI, could act as a mediator for improvement in insulin sensitivity and thus compensate for the primary secretory defect. This effect seems more profound in more overweight subjects than in leaner subjects.

(*Clin Ther*. 2013;35:1016–1024) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: adiponectin, insulin sensitivity, LADA, type 1 diabetes mellitus.

INTRODUCTION

Adiponectin is a collagen-like circulating protein secreted by adipocytes that has important insulin-sensitizing and antiatherogenic properties.[1–3] In healthy individuals, plasma adiponectin levels have been found to be more increased in women than in men and also negatively associated with adiposity and insulin resistance.[1,2,4–6] Furthermore, these levels predict type 2 diabetes mellitus (DM)[6–9] and cardiovascular disease.[10,11] Underlying mechanisms include direct effects of adiponectin on fat oxidation and the vasculature.[1,2] Plasma adiponectin concentrations are also positively associated with favorable plasma lipid profiles and decreased concentrations of inflammatory markers, suggesting that adiponectin may affect cardiovascular disease by modulation of plasma lipids and low-grade, chronic inflammation.[12,13]

Results of several animal and human studies suggest that the beneficial effect of adiponectin on metabolism becomes stronger with increasing adiposity. Adiponectin knockout mice exhibit severe insulin resistance only when fed a high-fat/high-carbohydrate diet.[14] In humans, an adiponectin-encoding gene haplotype leading to low plasma adiponectin concentrations was

Accepted for publication June 1, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.06.001
0149-2918/$ - see front matter

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associated with type 2 DM in obese and in morbidly obese patients but not in lean individuals.[15] Furthermore, the association of plasma adiponectin level with insulin resistance, HDL cholesterol, and triglycerides was found to be strengthened with increasing adiposity.[16] Obese individuals, particularly those with accumulated visceral fat, have reduced plasma levels of adiponectin[17] and are at increased risk for hypertension, type 2 DM, and atherosclerotic events.[18,19]

These data suggest that lifestyle and pharmacologic interventions aimed at increasing insulin sensitivity and reducing the risk of atherosclerotic vascular disease by increasing plasma adiponectin concentrations may be more effective in obese patients than in lean patients. In the current study, we addressed the relationship between plasma adiponectin levels and insulin resistance in patients developing DM, predominantly due to an early decline in β-cell function, by studying patients with latent autoimmune diabetes in adults (LADA) and type 1 DM.

PATIENTS AND METHODS

Patients

The study population consisted of 3 groups of patients who were followed up in the 2nd Department of Internal Medicine at the "Attikon" University General Hospital, Athens, Greece. The first group consisted of 29 patients (16 men and 13 women) with LADA. Diabetes was determined according to the 1997 World Health Organization diagnostic criteria.[20] LADA was defined by the following criteria: diagnosis at age ≥35 years, no insulin requirement for at least 6 months after diagnosis, and presence of glutamic acid decarboxylase (GAD65) autoantibodies.[21,22] At the time of the study, the patients in the LADA group were not receiving insulin therapy. The patients receiving oral antidiabetic drug therapy had to have stopped their medication for at least the last 24 hours before blood sample collection. The second group consisted of 38 individuals (12 men and 26 women) who were diagnosed with type 1 DM. For diagnosis confirmation, all patients underwent a C-peptide test. Patients had been instructed not to take any basal insulin for the last 24 hours and any short-acting insulin for the last 12 hours before testing. According to their medical history and the physical examination, none of the patients with type 1 DM had late complications of DM or other pathologic conditions, and were not taking any medication. In particular, they had no microalbuminuria or macroalbuminuria, and serum creatinine levels were within the normal range. The third group consisted of 55 healthy individuals (controls), 29 men and 26 women, with no family history of DM.

The research was conducted in accordance with the 2000 Declaration of Helsinki of the World Medical Association. Informed written consent was obtained from all participants, and the local medical ethic committees approved the protocol.

Body Composition and Insulin Sensitivity Assessment

Body mass index (BMI) was calculated as weight divided by the square of the height. Insulin sensitivity was estimated by using the homeostasis model assessment of insulin resistance (HOMA-IR) from fasting. Insulin was measured by using a radioimmunoassay (RIA) kit (Linco Research, St. Charles, Missouri).

Detection of GAD65 Antibodies

Serum GAD65 antibodies were detected by the use of a commercially available RIA kit using ^{125}I-labeled human recombinant GAD65 (CentAK anti-GAD65; Medipan Diagnostica, GmbH). This assay has a specificity of 97% and functional sensitivity of 0.6% U/mL.

Analytical Procedures

Blood glucose was determined by using a bedside glucose analyzer (Yellow Springs Instruments, Yellow Springs, Ohio). In all patients, fasting C-peptide levels were measured with an RIA kit (Byk-Santec, Dietzenbach, Germany) with an analytical sensitivity of 5 pM. For this assay, interassay %CV was 3.8% and intraassay %CV was 3.9%. Serum samples were frozen immediately after collection and stored at –20°C for determination of adiponectin by using an RIA kit (Linco Research), and interleukin (IL-6) and tumor necrosis factor (TNF)-α according to an enzyme-linked immunosorbent assay (Quantikine high-sensitivity kits for human IL-6 and human TNF-α; R&D Systems, Minneapolis, Minnesota).

Statistical Analysis

We performed ANOVA with generalized linear models of plasma adiponectin, BMI, age, fasting plasma glucose, fasting C-peptide, HOMA-IR, IL-6

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