

A patient with Werner syndrome and adiponectin gene mutation

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Received 6 October 2005; received in revised form 20 April 2006; accepted 9 May 2006

Available online 27 June 2006

Abstract

Werner syndrome is a premature aging disease characterized by genomic instability and increased cancer risk. Here, we report a 45-year-old diabetic man as the first Werner syndrome patient found to have an adiponectin gene mutation. Showing graying and loss of hair, skin atrophy, and juvenile cataract, he was diagnosed with Werner syndrome type 4 by molecular analysis. His serum adiponectin concentration was low. In the globular domain of the adiponectin gene, I164T in exon 3 was detected. When we examined effects of pioglitazone (15 mg/day) on serum adiponectin multimer and monomer concentrations using selective assays, the patient's relative percentage increase in adiponectin concentration was almost same as that in the 18 diabetic patients without an adiponectin mutation, but the absolute adiponectin concentration was half of those seen in diabetic patients treated with the same pioglitazone dose who had no adiponectin mutation. The response suggested that pioglitazone treatment might help to prevent future Werner syndrome-related acceleration of atherosclerosis. Present and further clinical relevant to atherosclerosis in this patient should be informative concerning the pathogenesis and treatment of atherosclerosis in the presence of hypoadiponectinemia and insulin resistance.

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Keywords: Werner syndrome; Adiponectin mutation; Diabetes mellitus; Hypoadiponectinemia; Thiazolidine therapy

1. Introduction

Werner syndrome is an autosomal recessive hereditary disease characterized by premature aging, genomic instability, and accelerated atherosclerosis, and increased cancer risk [1,2]. The defective gene product in Werner syndrome belongs to the ReqQ family of DNA helicases [3]. Here, we report the first patient with

Werner syndrome found to have an adiponectin gene mutation as well. We examined changes in adiponectin secretion in response to pioglitazone therapy.

2. Case presentation

A 45-year-old man was diagnosed with diabetes when cataract developed at the age of 25 years. He did not seek further treatment until he was 39 years old, when he was admitted to another hospital. There he was given insulin and was noted to have abdominal fat accumulation. He was referred to our hospital in April 2004.

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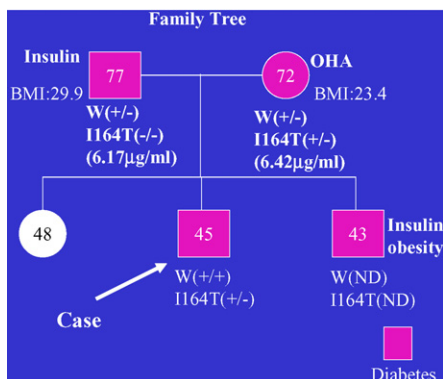


Fig. 1. The patient's father, mother, and uncle had diabetes; the father and uncle were treated with insulin, and the mother with oral hypoglycemic agents. Both parents were heterozygous for Werner syndrome type 4, and heterozygosity for the adiponectin gene mutation I164T was identified in the mother. Values shown are serum adiponectin concentrations ($\mu\text{g/ml}$).

The patient's father and uncle had diabetes; recently, his mother also had been diagnosed with diabetes. Fig. 1 shows the patient's family tree. His parents both were found to be heterozygous for the Werner mutation, while his mother was heterozygous for an I164T mutation in the adiponectin gene. No consanguinity was reported.

Height was 151.8 cm and weight was 38 kg. Blood pressure was 158/80 mmHg and the pulse was regular with a rate of 92 min^{-1} . The patient injected insulin before each meal (Penfil R 6U) and before sleep (Penfil N 6U). Hemoglobin (Hb) A1c was 6.7%; total serum cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were 208, 59, and 190 mg/dl, respectively. Urinary albumin excretion was 26.5 mg/g creatinine. The serum C-peptide concentration was 6.61 ng/ml with a simultaneous plasma glucose concentration of 156 mg/dl, suggesting that insulin secretory capacity was preserved and implying that insulin resistance was likely. The patient showed graying and loss of hair, skin atrophy, and juvenile cataract. We diagnosed him with Werner syndrome type 4 according to molecular analysis [4].

Yokote et al. [5], previously, reported serum adiponectin concentrations to be decreased in Werner syndrome (mean $3.1 \mu\text{g/ml}$); our patient's serum adiponectin concentration was particularly low ($2.24 \mu\text{g/ml}$; to adiponectin monomer assay kit, Otsuka, Tokyo, Japan). When we sequenced the adiponectin gene, heterozygous mutation representing I164T in exon 3 was seen in the globular domain, as was demonstrated in his mother. This mutation has been reported to be atherogenic and to promote insulin resistance, leading to ischemic heart disease [6]. As the

adiponectin and Werner genes are located on chromosome 3 and 8, respectively. We concluded that the two mutations were associated coincidentally.

To evaluate vascular atherosclerosis, carotid intima media thickness (IMT) was examined ultrasonographically. While this was only 0.6 mm, calcified plaques 2 mm in thickness were observed in right and left carotid arteries.

We next examined the effects of pioglitazone (15 mg/day) on adiponectin concentrations in the patient using separate adiponectin assay kits to detect the total monomers (Otsuka) and multimeric forms (Fujirebio, Tokyo, Japan). We compared his response to treatment with those in 18 diabetic patients whose adiponectin exon sequences were normal. Responses of serum adiponectin concentrations in the assay for monomers to 15 mg/day of pioglitazone in the other 18 diabetic patients were as follows: $5.68 \pm 0.67 \mu\text{g/ml}$ before pioglitazone, $11.76 \pm 1.85 \mu\text{g/ml}$ (at 1 month), and $11.81 \pm 2.20 \mu\text{g/ml}$ (at 2 months, mean \pm S.E.M.). In the Werner patient, the pretreatment adiponectin monomer concentration was $2.32 \mu\text{g/ml}$; the 1-month value, $6.07 \mu\text{g/ml}$; the 2-month value, $5.02 \mu\text{g/ml}$ (Fig. 2A). Expressed relative to basal concentrations, responses of adiponectin monomer concentrations in

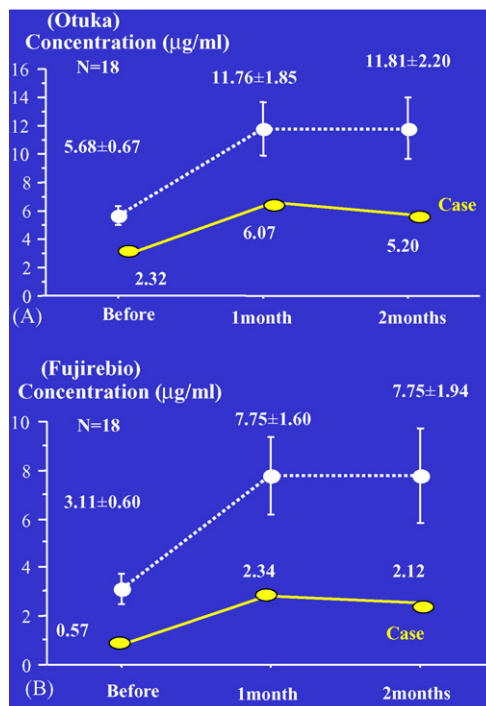


Fig. 2. A: Serum adiponectin concentrations (A, monomer; B, multimer) in response to 15 mg/day of pioglitazone. Data are shown for 18 diabetic patients without an adiponectin gene mutation (mean \pm S.E.M., broken line) and for the Werner patient (solid line).

the 18 patients with no mutation were $218.5 \pm 16.1\%$ (1 month) and $235.7 \pm 16.2\%$ (2 months). The Werner patient's relative responses were similar (261.6%, 1 month; 224.1%, 2 months). Serum adiponectin multimer concentrations in response to 15 mg/day of pioglitazone in the diabetic patients without an adiponectin mutation were as follows: $3.11 \pm 0.60 \mu\text{g/ml}$ (pretreatment), $7.75 \pm 1.60 \mu\text{g/ml}$ (1 month), and $7.75 \pm 1.94 \mu\text{g/ml}$ (2 months); in the Werner patient, these, respectively, were 0.57, 2.34, and $2.12 \mu\text{g/ml}$ (Fig. 2B). For the multimeric form, relative responses in the 18 patients were $284.8 \pm 25.9\%$ (1 month) and $326.4 \pm 35.7\%$ (2 months). In the Werner patient, these, respectively, were 410.5% and 371.9%.

3. Discussion

The adiponectin I164T mutation has been reported to interfere with adiponectin secretion in transfected cultured cells [7,8]. Kadowaki et al. reported that I164T adiponectin could not assemble into trimers, resulting in impaired secretion from the cell [7]. Another study using gel filtration reported that oligomerization was similar to that seen in wild-type adiponectin, but secretion from adipocytes into plasma was disrupted [8]. In our patient's response to pioglitazone, the serum adiponectin concentration was only half that seen in diabetic patients without mutation of the adiponectin gene, suggesting that secretion of mutant adiponectin from adipose tissues into plasma might be disturbed, and with only the wild-type adiponectin responding. The absolute change in serum concentration of adiponectin multimer, measured in response to pioglitazone, was slightly less than that of the monomer in the Werner patient compared with the other 18 diabetic patients, suggesting that processing of mutant adiponectin monomer to high-molecular-weight multimer might be compromised.

Here, we first reported a Werner syndrome patient with an additional mutation involving the adiponectin

gene. Our study suggested that despite some differences between monomeric and multimeric forms, serum concentrations of both forms of adiponectin could be increased by treatment with thiazolidine derivatives in patients with hypoadiponectinemia resulting from a heterozygous adiponectin gene mutation. These and future data concerning long-term effects on atherosclerosis in this patient may be informative concerning the pathogenesis and treatment of atherosclerosis associated with hypoadiponectinemia and insulin resistance.

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