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ORIGINAL ARTICLE

Weight gain and changes in plasma adiponectin and leptin concentrations after 12-month insulin intensive therapy for Chinese male patients with newly diagnosed type 2 diabetes

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KEYWORDS
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Summary
Aim: To examine the effects of intensive insulin therapy (IIT) in Chinese male patients with newly diagnosed type 2 diabetes in 12 months on plasma adiponectin and leptin levels and to assess whether changes in plasma adiponectin and leptin could be associated with subsequent weight gain or not.
Methods: Overall 84 patients were taken IIT. Total, and high-, and low-molecular-weight (HMW, LMW) adiponectin and leptin concentrations were measured at the time of study inclusion, days 7, and 1, 3, 6 and 12 months after IIT, respectively. Patients' body weight was recorded every time when adiponectin and leptin were measured.
Results: With improvement of diabetes control, plasma total and HMW adiponectin and leptin concentrations increased from inclusion to 3 months significantly and progressively, but remained steady after 6 months. Weight increased relatively modestly with a mean gain of 2 kg for 12 months. Moreover, higher increments of total and HMW adiponectin from inclusion to 12 months were associated with significantly less subsequent weight gain after adjustment for confounding factors: the patients in the

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lowest tertile of total adiponectin increased by 2.47 kg compared to patients in the highest tertile who increased by 0.56 kg (*P*-value = 0.006). Whereas, the higher increments of leptin levels under the same condition were linked with more subsequent weight gain significantly (*P*-value = 0.003).

Conclusions: Our researches suggest that glycaemic control with IIT increases total and HMW adiponectin and leptin in newly diagnosed type 2 diabetes male patients, the elevation of total and HMW adiponectin and leptin levels may predict weight gain after IIT.

Introduction

In patients with type 2 diabetes, tight glycaemic control with intensive insulin therapy (IIT) including subcutaneous injection of insulin 3 or 4 times daily, has been associated with weight gain, especially during the first year following initiation of treatment [1—3]. Several explanations for the mechanism(s) by which IIT causes weight gain have been discussed, including hyperphagia following hypoglycaemic stimuli, alteration of physical activity level, the anabolic and/or lipogenic actions of insulin, and/or decreased glycosuria [1,4—6]. However, it has been proven difficult to establish the mechanisms underlying weight gain in human studies due to the complex nature of potential mechanisms [7]. Recently, Balkau et al. [8] found that a high baseline A1 C and insulin dose requirements were independently associated with greater weight gain in people with type 2 diabetes starting on insulin. The overall conclusion has been that the cause(s) of weight gain associated with IIT remain unclear.

Adiponectin is exclusively expressed from adipocytes, and circulates in human blood as multiple isoforms, trimeric low molecular weight (LMW), hexameric middle molecular weight (MMW), and high molecular weight (HMW) forms. All these forms have shown distinct biological effects through differential activation of downstream signalling cascades [9]. Studies in humans have revealed that circulating adiponectin levels decreased in patients with type 2 diabetes and in most obese human subjects, and significantly increased in patients with type 2 diabetes following treatment with glimepiride, peroxisome proliferator-activated receptor-γ agonists and various hypoglycaemic therapy and antihypertensive agents and in patients with obesity with loss of weight [10—13]. Also, IIT for improving glycaemic control in type 2 diabetes patients resulted in a modest, but statistically significant, increment in adiponectin in the short-time [14]. However, few studies have examined whether long-term IIT would affect circulating adiponectin levels [15]. Particularly, little information was given in regard to the isoform(s) of adiponectin measured in the study. In addition, adiponectin is known to cause directly weight reduction by regulating lipid and glucose metabolism in mice [16]. Furthermore, both central and peripheral adiponectin administration have been associated with reduced body weight via either food intake suppression or increased energy expenditure [17], but very little attention has been directed toward possible weight-regulating functions in human. Recently, Hivert et al. [18] reported that adiponectin (total and HMW) levels are associated with subsequent weight gain in healthy women participating in the Nurses' Health Study over 4 years of prospective follow-up.

In humans, leptin, another adipokine, is produced predominantly by adipose tissue and plays a pivotal role in the regulation of appetite and body weight. In leptin-deficient obese mice and humans, administration of leptin reduces food intake and raises energy expenditure resulting in weight loss [19,20]. However, plasma leptin concentrations were shown to be elevated in obese individuals, implying the presence of leptin resistance, which is characterised by deficient regulation of energy balance of leptin [21] and can lead to aggravated weight gain in the condition of exposure to a high-fat diet [22]. Many studies have revealed that elevated leptin levels and body weight may occur after insulin-induced improved glycaemic control in subjects with type 2 diabetes, and the increments in leptin levels were correlated with the increments in weight and body mass index (BMI) in patients on insulin monotherapy [23—27]. Aas et al. suggested that the increase in serum leptin-levels (so called hyperleptinemia) observed during insulin treatment in type 2 diabetes may induce leptin resistance, contributing to weight gain [23].

Based on the background above, we hypothesised the changes in plasma adiponectin and leptin levels under the same condition are associated with subsequent weight change in patients with type 2 diabetes with long-term IIT. To test this hypothesis, we examined the effects of IIT in

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