

Hyperinsulinemia and insulin resistance in a patient with type 2 diabetes complicated with myelofibrosis

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Abstract

Inflammation induces insulin resistance and hyperinsulinemia due to elevation of serum cytokines such as tumor necrosis factor- α and interleukins. Chronic myeloproliferative diseases including myelofibrosis show higher serum interleukin levels than healthy subjects, which has been suggested to be the useful markers for disease activity. However, an association between myelofibrosis and insulin resistance has not ever been discussed anywhere. Here we report a case of type 2 diabetes showing remarkable hyperinsulinemia and insulin resistance possibly due to myelofibrosis.

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Key words: Cytokines; Hepatosplenomegaly; Hyperinsulinemia; Insulin resistance; Myelofibrosis

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INTRODUCTION

Chronic inflammation induces insulin resistance and hyperinsulinemia due to elevation of inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukins^[1]. Chronic myeloproliferative diseases show higher serum interleukin levels than healthy subjects, recently, which has been suggested to be the useful clinical markers for disease activity of myeloproliferative diseases^[2]. However, an association between chronic myeloproliferative diseases including myelofibrosis and insulin resistance has not ever been discussed anywhere. Here we report a case with type 2 diabetes showing hyperinsulinemia and insulin resistance possibly due to myelofibrosis.

CASE REPORT

A 71-year-old man was diagnosed as having type 2 diabetes and myelofibrosis in 1998 and 2001, respectively. His diabetes was treated by α -glucosidase inhibitor, voglibose (0.6 mg/d) from 1998 to 1999, and his HbA1c levels were 7.0%-7.7%. He was treated by nateglinide (270 mg/d) from 1999 to 2003, and his HbA1c levels were 6.5%-7.4%. After the basal supported oral therapy using nateglinide (270 mg/d) and 4-5 units of NPH-insulin (from 2003-2004) and insulin glargine (from 2004) at bedtime, his HbA1c levels were 6.0%-6.9%. Recently, his diabetes has been treated by using nateglinide (270 mg/d) and 4 units of insulin glargine at bedtime. His myelofibrosis progressed since June, 2011, and the counts of leukocyte and platelets were 2000/ μ L and 2.8×10^4 / μ L, respectively, and hemoglobin concentration was 73 g/L on July 1, 2011. At the same time, his blood glucose control became

worse. His plasma glucose and HbA1c were 1500 mg/L and 5.8%, respectively, on July 1, 2011. In September, 2011, fasting plasma glucose and HbA1c levels increased to 2020 mg/L and 7.2%, respectively. He was admitted to our hospital. His body height, body weight and body mass index were 169 cm, 56 kg and 19.6 kg/m², respectively. We started the intensive insulin therapy, and his blood glucose levels were 1460-2480 mg/L by using 10, 8 and 10 units of insulin aspart before breakfast, lunch and dinner, respectively, and 8 units of insulin glargine at bedtime, showing a significantly increased requirement of insulin dose. However, unexpectedly, his urinary C-peptide level was remarkably elevated (248 µg/d; normal, 29.2-167 µg/d). Anti-insulin antibody (¹²⁵I-insulin binding rate, 1.5%; normal, < 0.4%) level was slightly elevated, and anti-insulin receptor antibody was not detected. Abdominal computed tomography showed severe hepatosplenomegaly. We measured his serum inflammatory cytokines. Serum levels of TNF-α (6.3 pg/mL; normal, 0.6-2.8 pg/mL), interleukin-1 (11 pg/mL; normal, < 10 pg/mL) and interleukin-6 (5.9 pg/mL; normal, < 4.0 pg/mL) were significantly elevated. However, interleukin-2 (0.8 U/mL; normal, < 0.8 U/mL) and interleukin-8 (< 2.0 pg/mL; normal, < 2.0 pg/mL) were not elevated.

DISCUSSION

Myelofibrosis is myeloproliferative disease which induces fibrosis of the bone marrow and leads to hepatosplenomegaly, which may cause portal hypertension and portosystemic shunt^[3]. To our knowledge, the association between myelofibrosis and hyperinsulinemia in humans has not ever been studied. The insulin metabolism in rats with portal hypertension has been previously reported^[4]. The metabolic clearance rate of insulin in the portal-hypertensive rats was significantly reduced in comparison with the control rats^[4]. The control of blood glucose levels when he was diagnosed as having diabetes is dealt with the long-term influence of early metabolic control on clinical outcomes, also known as “metabolic

memory”, and where a long-term receptor for advanced glycation end products activation is a crucial element in the maintenance of a low-grade systemic chronic inflammation, which is a very well-known feature of diabetes mellitus^[5,6]. His plasma glucose control was poor (HbA1c, 6.5%-7.7%) from 1998 to 2003, before the start of the basal supported oral therapy using nateglinide and insulin. We have to mention that early poor glycemic environment might also possibly affect his diabetes aggravation.

We also have to mention that we should have measured cytokine levels on this patient before the onset of the acute progress on June 2011, and we used the cut-off values for cytokines from healthy individuals, however, comparisons should be made in reference to cytokines serum levels on tightly controlled diabetic patients.

In conclusion, the decrease of insulin clearance due to portosystemic shunt, and elevated serum levels of TNF-α interleukin-1 and interleukin-6, strongly associated with insulin resistance^[1], may induce hyperinsulinemia and insulin resistance in our patient with type 2 diabetes complicated with myelofibrosis.

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