Dramatic Improvement of Blood Glucose Control after Pioglitazone Treatment in Poorly Controlled Over-weight Diabetic Patients with Myotonic Dystrophy

HIROKO ABE, TOMOYA MITA, KYOKO KUDO, TAKASHI FUNAYAMA, MASAKO TOKORO, HIDEYOSHI KAGA, FUKI IKEDA, AKIO KANAZAWA, TAKAHISA HIROSE, RYUZO KAWAMORI AND HIROTAKA WATADA

Abstract. Insulin resistance is mainly present in skeletal muscle in non-obese patients with myotonic dystrophy. Thiazolidinediones are reported to reduce insulin resistance in these patients. However, the effects of pioglitazone in over-weight patients with myotonic dystrophy and type 2 diabetes mellitus have not been established. Here, we evaluated the effect of pioglitazone in two poorly-controlled over-weight diabetic patients with myotonic dystrophy. Case 1 was a 41-year-old women (BMI 27.8 kg/m²) with myotonic dystrophy and type 2 diabetes had been treated with 3 mg/day glimepiride and 500 mg/day metformin, but the treatment failed to achieve good glycemic control (HbA₁c 11.8 %). Following admission to the hospital, she was treated with low-dose insulin and 30 mg/day pioglitazone. At 10 days after initiation of therapy, glycemic control was improved, serum IL-6 and hs-CRP decreased, and adiponectin level increased rapidly. Case 2 was a 47-year-old women (BMI 29.2kg/m²) with myotonic dystrophy and type2 diabetes mellitus had been treated with insulin without successful glycemic control (HbA₁c 10.3 %). After admission, she was treated with 15 mg/day pioglitazone. This improved glycemic control, reduced daily insulin requirement, decreased IL-6 and hs-CRP levels rapidly and increased adiponectin level at 10 days after initiation of therapy. In both cases, pioglitazone rapidly improved glycemic control, enhanced adiponectin production, and reduced inflammatory cytokines. These results suggest that pioglitazone may be suitable for these patients.

Key words: Thiazolidinediones

NOTE

MYOTONIC dystrophy (DM1) is a neuromuscular disease characterized by myotonia, muscle weakness, cataract, cardiac conduction defects and insulin resistance. The genetic mutation is an expansion of CTG-repeat in the 3-prime untranslated region of a myotonic dystrophy protein kinase (DMPK). In DM1 skeletal muscle, alternative splicing of the insulin receptor pre-mRNA is aberrantly regulated, resulting in predominant expression of the lower-signaling nonmuscle isoform [1]. In addition, it was demonstrated that DMPK itself is a positive modulator of insulin action in muscle [2]. These findings support the presence of insulin resistance specifically in DM1 skeletal muscle in patients with DM1. In fact, it is reported that insulin sensitivity in skeletal muscle is decreased by 70% in patients with DM1 [3], while whole body glucose disposal is reduced by 15-25% following insulin infusion [4]. Due to focal insulin resistance in muscle, the incidence of diabetes is only 5-9% in these patients [5]. However, since the obesity induces insulin resistance in adipose tissue and liver in addition to skeletal muscle, glucose intolerance may be more severe in overweight patients with DM1.

Thiazolidinediones (TZDs) are effective in the treatment of diabetes associated with insulin resistance. A few reports show its usefulness in the management of insulin resistance in skeletal muscle in
non-obese DM1 patients [6]. However, there is little or no information on the effect of pioglitazone in overweight diabetic patients with DM1. We report here the effect of pioglitazone treatment in over-weight diabetic patients with DM1.

**Case Reports & Discussion**

**Case 1.**

A 41-year-old woman (BMI 27.8 kg/m²) with DM1 and type 2 diabetes mellitus was followed at our outpatient clinic. Although she had been treated with 3 mg/day glimepiride and 500 mg/day metformin, glycemic control was very poor (HbA1c 11.8%). The patient was admitted to our hospital in April 2008 for further management. Although she received diet therapy (1400 kcal/day), glycemic control was not improve at all. Accordingly, she was placed on low-dose insulin therapy (18 U/day insulin aspart plus 6 U/day insulin detemid; Novo Nordisk) and 30 mg/day pioglitazone in addition to the existing drug treatment. After 10 days on this treatment, fasting plasma glucose improved from 219 to 95 mg/dL. Although insulin aspart was discontinued at discharge, the metabolic control was well maintained (HbA1c 6.8% at 6 months). Serum levels of iL-6 and hs-CRP decreased from 11.5 to 4.0 pg/mL and from 32.8-34.4 to 0.3-0.34 mg/L, respectively. Adiponectin level also increased rapidly from 6.2 to 21.6 µg/mL at 2 months.

**Case 2.**

A 47-year-old woman (BMI 29.2 kg/m²) with DM1 and type 2 diabetes mellitus had been treated with 44 U/day Novolin 70/30 (Novo Nordisk) without achieving good glycemic control (HbA1c 10.3%) at our outpatient clinic. After admission in May 2008, she received diet therapy (1400 kcal/day), but glycemic control remained poor. Treatment was supplemented with 15 mg/day pioglitazone. Only 10 days after pioglitazone administration, fasting plasma glucose was improved from 155 to 80 mg/dL and daily requirement of insulin fell to 32 U. Furthermore, IL-6 and hs-CRP levels decreased rapidly from 5.4 to 2.3 pg/mL and from 3.26 to 1.26 mg/L, respectively. Adiponectin level also increased rapidly from 4.9 to 7.9 µg/mL. Although the diet therapy was not accepted well after discharge, the blood glucose control was maintained remarkably better than before (HbA1c 7.9% at 6 months after discharge).

This is the first study to report that pioglitazone rapidly and dramatically ameliorates glycemic control in poorly controlled over-weight diabetic patients with MD1. The improvement was accompanied with enhanced adiponectin production and reduction of inflammatory cytokines.

TZDs have various effects on glucose and lipid metabolism, and cardiovascular disease. One of the important mediators of this effect is adiponectin that enhances insulin sensitivity and improves glucose metabolism [7]. While serum adiponectin level are low in the patients with type 2 diabetes, it has been shown that TZDs increase circulating adiponectin level in diabetic subjects, probably by activating peroxisome proliferator-activated receptors (PPARs) [8]. Unexpectedly, it was reported that newly diagnosed patients with DM1 have high adiponectin levels compared with general control [5]. This finding may be due to the compensatory reaction for deterioration of insulin sensitivity in non-obese subjects with mild glucose intolerance. It has also been reported that TZDs improve peripheral insulin resistance even in lean DM1 patients with normal to mild diabetes and insulin resistance [6]. In over-weight patients such as the present cases, we reasonably observed more dramatic effect of TZDs on glycemic control than lean subjects.

A previous report support the usefulness of low dose metformin in the patients with DM1 and lean diabetes mellitus [9]. In our first case, the addition of metformin to glimepiride in out patients clinic did not alter her glucose control level. On the other hand, addition of pioglitazone rapidly improves glycemia control. This may suggest that thiazolidinedione treatment is superior to metformin in over-weight diabetic DM1 patients.

A previous report suggests that TZDs improve not only hyperglycemia, but also myotonia in DM1 patients. However, in our cases, we have not observed any significant improvement of myotonia after the commencement of pioglitazone. Taken together, the effect of TZDs on myotonia is not always observed in DM1 patients. On the other hand, the dramatic effect of pioglitazone on hyperglycemia is widely observed in DM1 patients and it appears to be especially suitable for poorly controlled over-weight diabetic patients with DM1.
References