Letter to the Editor

Alpha glucosidase inhibitor voglibose can prevent
pioglitazone-induced body weight gain in Type 2
diabetic patientsMayumi Negishi,^{1,2} Kenju Shimomura, Peter Proks,³ Yohnosuke Shimomura⁴ &
Masatomo Mori²

¹Medical Department of Diabetes, Heisei Hidaka Clinic and ²Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Gunma, Japan, ³Henry Wellcome Centre for Gene Function, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK and ⁴Gunma Prefectural College of Health Sciences, Gunma, Japan

Pioglitazone, a member of the thiazolidinedione (TZD) drug family, is widely used for the treatment of Type 2 diabetic patients. This antihyperglycaemic drug is a selective ligand of the nuclear transcription factor, peroxisome proliferator-activated receptor (PPAR) γ . It interacts with PPAR γ receptors that are located predominantly in adipose, hepatic and skeletal muscle cells. Modulation of these receptors adjusts the regulation of genes involved in metabolic control and also reduces insulin resistance [1]. However, pioglitazone is known to induce body weight gain [2–4]. Therefore, it is important to control the body weight in usage of PPAR ligands in the treatment of Type 2 diabetes.

Alpha glucosidase inhibitors (AGIs) such as voglibose are known to inhibit disaccharide hydrolysis in intestinal mucosa, thereby reducing the hydrolysis of disaccharides to monosaccharides. This impedes absorption of carbohydrate and therefore reduces glucose levels in Type 2 diabetes patients. We have investigated whether it is possible to prevent pioglitazone-induced body weight gain with voglibose treatment.

A total of 31 randomly chosen Japanese Type 2 diabetic patients (14 men, 17 women) was recruited into this study. One group was treated for >3 months with diet alone (control group; $n = 17$, age 60.2 ± 2.5 years, duration of diabetes 11.7 ± 1.5 years); the other was treated with diet plus voglibose (0.9 mg daily) (voglibose group; $n = 14$, age 61.1 ± 3.6 years, duration of diabetes 9.6 ± 1.3 years). Pioglitazone treatment was given to each group at the dose of 15 mg for 3 months, and dosage was increased to 30 mg for the next 9 months. Diet therapy consisted of 104.6 kJ kg^{-1} of ideal body weight per day. All patients were instructed to maintain the same energy intake and physical activity as usual for the individual. There was no signifi-

cant difference in HbA_{1c} levels ($8.1 \pm 0.3\%$ for control group, 7.9 ± 0.3 for voglibose group) or body mass index (25.9 ± 1.5 for control group, 26.3 ± 1.2 for voglibose group) prior to the trial. Body weight was examined at the beginning and the end of the study. Four patients (one male and three female) dropped out of the trial due to the side-effects of pioglitazone (oedema).

There was no significant difference in body weight between the control and voglibose groups before starting the pioglitazone ($68.1 \pm 5.0 \text{ kg}$ for the control group, $72.7 \pm 4.7 \text{ kg}$ for the voglibose group: the body weight of the voglibose group prior to voglibose treatment was $72.6 \pm 4.5 \text{ kg}$). Body weight increased by $0.1 \pm 0.3 \text{ kg}$ (0.02%) in the voglibose group and $2.5 \pm 0.4 \text{ kg}$ (3.7%) in the control group ($P < 0.01$) after pioglitazone treatment (Fig. 1). This result suggests that voglibose treatment prevents the body weight gain induced by pioglitazone.

Clinically, it has been shown that TZDs specifically increase subcutaneous adipose tissue [5]. Body weight gain was significantly greater within 4 weeks; it increased on average by 3.88 kg (4.1%) and it did not reach a plateau even after 6 months [5, 6]. In our study, the body weight gain of 3.7% in the pioglitazone monotherapy control group was consistent with these clinical studies.

Voglibose is reported to cause side-effects on the small intestine, such as abdominal fullness or diarrhoea for the first several months. These side-effects usually disappear by intestinal adaptation within a couple of months. Since patients require several months to adapt to voglibose, it may be important to start voglibose therapy several months prior to pioglitazone therapy to achieve prevention of body weight gain by pioglitazone.

The precise mechanism whereby voglibose may prevent pioglitazone-induced body weight gain is unclear.

Figure 1

The effect of pioglitazone on body weight change with and without voglibose. * $P < 0.01$. Student's *t*-test was used for baseline comparison

AGIs have been reported to have no effects on body weight gain or intestinal mass when applied alone [7]. Indeed, in a separate study, we found that monotherapy of voglibose failed to reduce body weight in Type 2 diabetic patients (data not shown). There has been a report that body weight significantly decreased by the combination therapy of acarbose and sulphonylurea compared with sulphonylurea alone [8]. The subjects included in this study did not experience loss of appetite. Therefore, it is likely that the observed effects were independent of the appetite control or intestinal factors. AGIs are known to reduce insulin levels, and it is therefore likely that insulin level of subjects included in this study were reduced [9, 10]. Hyperinsulinaemia can cause body weight gain. We hypothesize that voglibose treatment prior to pioglitazone may have reduced the serum insulin levels, and thus pioglitazone was applied after the reduced insulin levels were established. Therefore, pioglitazone may have improved insulin resistance through this lack of increase in body weight of the patients. To confirm this hypothesis, further investigations are required.

In conclusion, we have found that voglibose treatment prevented the increase of body weight induced by pioglitazone in Type 2 diabetes patients. Thus, voglibose may be a potentially useful drug for increasing the benefit of pioglitazone treatment by controlling body weight.

Competing interest: None declared.

REFERENCES

- Smith S, De Jonge L, Volaufova J, Li Y, Xie H, Bray G. Effect of pioglitazone on body composition and energy expenditure: a randomized controlled trial. *Metabolism* 2005; 54: 24–32.

- Akazawa S, Sun F, Ito M, Kawasaki E, Eguchi K. Efficacy of troglitazone on body fat distribution in type 2 diabetes. *Diabetes Care* 2000; 23: 1067–71.
- Mori Y, Murakawa Y, Okada K, Horikoshi H, Yokoyama J, Tajima N, Ikeda Y. Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care* 1999; 22: 908–12.
- Kelly I, Han T, Walsh K, Lean M. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. *Diabetes Care* 1999; 22: 288–93.
- Neuschwander-Tetri B, Brunt E, Wehmeier K, Oliver D, Bacon B. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology* 2003; 38: 1008–17.
- Bajaj M, Suraamornkul S, Pratipanawatr T, Hardies L, Pratipanawatr W, Glass L, Cersosimo E, Miyazaki Y, DeFronzo R. Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. *Diabetes* 2003; 52: 1364–70.
- Casirola D, Ferraris R. alpha-Glucosidase inhibitors prevent diet-induced increases in intestinal sugar transport in diabetic mice. *Metabolism* 2006; 55: 832–41.
- Vannasaeng S, Ploybutr S, Nitiyanant W, Peerapatdit T, Vichayanrat A. Effects of alpha-glucosidase inhibitor (acarbose) combined with sulfonylurea or sulfonylurea and metformin in treatment of non-insulin-dependent diabetes mellitus. *J Med Assoc Thai* 1995; 78: 578–85.
- Sels J, Huijberts M, Wolffenbuttel B. Miglitol, a new alpha-glucosidase inhibitor. *Expert Opin Pharmacother* 1999; 1: 149–56.
- Clissold S, Edwards C. Acarbose. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs* 1988; 35: 214–43.

RECEIVED

28 February 2008

ACCEPTED

8 April 2008

PUBLISHED OnlineEarly

27 May 2008

CORRESPONDENCE

Dr Mayumi Negishi, MD, PhD, Heisei Hidaka Clinic, 807-1 Nakano-machi, Takasaki, Gunma 370-0001, Japan.
E-mail: mnegishi@med.gunma-u.ac.jp