Effect of metformin on hepatic glucose production in Japanese patients with type 2 diabetes mellitus

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Abstract. We investigated the effect of metformin on hepatic glucose production and peripheral glucose uptake in Asian patients with type 2 diabetes mellitus. We recruited ten Japanese patients whose fasting glucose levels remained poorly controlled under meal-time injection of short-acting insulin. Metformin was added to their insulin therapy, and both hepatic glucose production and peripheral glucose uptake were assessed before and one week after metformin treatment, with the use of stable isotope [6,6-²H₂] glucose. Metformin was titrated to a maximum dose of 500 mg. As a result, fasting glucose levels and hepatic glucose production were significantly improved after the metformin treatment (p < 0.01 and 0.02), whereas their peripheral glucose uptake was not significantly changed (p = 0.63). Furthermore, the change of fasting glucose levels was significantly correlated with that of hepatic glucose production, whose coefficient ρ was 0.76 (p = 0.01). On the other hand, there was no significant correlation between the change of fasting glucose levels and that of peripheral glucose uptake (p = 0.43). In conclusion, low dose of metformin significantly reduced hepatic glucose production in Japanese patients with type 2 diabetes mellitus. The efficacy of metformin on correcting fasting hyperglycemia was strongly associated with reduced hepatic glucose production, rather than ameliorated peripheral glucose uptake.

Key words: Metformin, Hepatic glucose production, Stable isotope

METFORMIN is now regarded as the first-line medication for type 2 diabetes mellitus in many clinical guidelines [1], because of its hypoglycemic effectiveness as well as low price, although its mechanism of action is not fully understood. The mechanisms so far revealed are suppression of hepatic glucose production (HGP) and improvement of peripheral glucose uptake (PGU) [2], and the former is recognized as the main contributor to lowering fasting glucose levels in Caucasian patients, especially who are obese and therefore expected to have hepatic insulin resistance. However, no data are available about whether the efficacy of metformin can be similarly explained by HGP suppression in Asians, who are less obese but are reported to be more peripherally insulin resistant perhaps because of different fat distribution [3]. We therefore investigated the effect of metformin on HGP in Japanese patients with type 2 diabetes mellitus.

Patients and Methods

We recruited ten Japanese patients with type 2 diabetes mellitus, whose fasting glucose levels remained poorly controlled under meal-time injection of short-acting insulin. Their fasting glucose levels remained higher than bedtime glucose levels, even after insulin was titrated enough to keep their bedtime glucose levels below 7.8 mmol/L. Metformin was then added to their insulin therapy, and was titrated to a maximum dose of 500 mg. The medication was taken once a day, at bedtime. We assessed HGP and PGU, as well as their fasting glucose levels, before and one week after metformin treatment. HGP and PGU were evaluated with the use of [6,6-²H₂] glucose. In brief, [6,6-²H₂] glucose was infused for 120 minutes (a bolus infusion at 0.3 mg/kg/min for 10 minutes and a subsequent steady infusion at 0.05 mg/kg/min for 110 minutes), and blood samples were obtained. Its enrichment in plasma was analyzed by gas chromatography/mass spectrometry, after trifluoroacetylation of glucose [4]. We performed
the current study in accordance with the declaration of Helsinki, and it was approved by the ethics committee of Osaka University. We obtained written informed consent from all the recruited patients. Statistical analyses were performed using IBM SPSS Statistics Version 19 (SPSS Inc., IL, USA). Data are presented as medians and quartiles. A $p$ value was assessed with nonparametric procedures because of the small sample size and the uncertainty about data distribution.

### Results

Six patients were male and four were female. They were 56 (52, 60) years old, and their body mass index was 26.7 (22.8, 30.9) kg/m$^2$ (medians and quartiles). Their waist circumference was 101 (92, 108) cm; eight of ten had an increased waist circumference, defined as $\geq 85$ cm in males and $\geq 90$ cm in females. The baseline fasting glucose level were 8.3 (7.1, 9.0) mmol/L under multiple short-acting insulin injection. Triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol levels were 1.7 (1.4, 2.0) mmol/L, 1.3 (1.0, 1.5) mmol/L, and 3.4 (3.0, 4.1) mmol/L, respectively.

Fasting glucose levels and HGP were significantly improved after the metformin treatment ($p < 0.01$ and 0.02), whereas their PGU was not significantly changed ($p = 0.63$) (Table 1). Furthermore, the change of fasting glucose levels was significantly correlated with that of HGP, whose coefficient $\rho$ was 0.76 ($p = 0.01$). On the other hand, there was no significant correlation between the change of fasting glucose levels and that of PGU ($p = 0.43$). Neither was body mass index significantly associated with the change of fasting glucose levels, HGP or PGU ($p = 0.24, 0.33, \text{and} 0.61$, respectively).

### Discussion

It was long pointed out that metformin was effective in Asian patients, even in a low dose [5], but its mechanism remained unknown. Our current study revealed that efficacy of metformin on correcting fasting hyperglycemia was strongly associated with reduced HGP, rather than ameliorated PGU, in Japanese patients, as observed in Caucasians. Given that an impaired HGP suppression was observed in lean Japanese patients and was significantly associated with fasting hyperglycemia [4], these findings would support the validity of metformin therapy in Japanese patients to target at their underlying pathogeneses. In conclusion, low dose of metformin significantly reduced hepatic glucose production in Japanese patients with type 2 diabetes mellitus. The efficacy of metformin on correcting fasting hyperglycemia was strongly associated with reduced hepatic glucose production, rather than ameliorated peripheral glucose uptake.

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### References


