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Original Article

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Effects of Metformin Monotherapy on Metabolic Parameters in Japanese Patients With Type 2 Diabetes

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Abstract

Background: Although metformin is widely used as the foundation therapy for patients with type 2 diabetes, effects of metformin monotherapy on metabolic parameters have not been sufficiently elucidated.

Methods: We retrospectively picked up type 2 diabetic patients who had been treated by the first metformin monotherapy for more than 3 months, at National Center for Global Health and Medicine between January 2015 and October 2018.

Results: Twenty-two patients were eligible. Systolic blood pressure, plasma glucose, HbA1c, low-density lipoprotein-cholesterol (LDL-C), aspartate transaminase (AST), and alanine aminotransferase (ALT) were significantly reduced by the 3-month metformin monotherapy. Further, we divided subjects into two groups with body mass index (BMI) of 25 or more and less than 25, and compared changes in metabolic parameter due to metformin monotherapy between BMI $\geq$ 25 and BMI < 25 groups. HbA1c and LDL-C were significantly reduced in both groups. Body weight significantly decreased only in BMI $\geq$ 25 group, and systolic blood pressure, AST and ALT tended to decrease only in BMI $\geq$ 25 group.

Conclusions: The metformin monotherapy improved glycemic control regardless of the presence or absence of obesity. Interestingly, metformin improved body weight, blood pressure and liver function in only overweight patients with type 2 diabetes.

Keywords: Body weight; Gluconeogenesis; Metformin; Liver function; Low-density lipoprotein-cholesterol

Introduction

Although metformin is widely used as the optimal initial therapy for patients with type 2 diabetes and its main glucose-lowering mechanism is considered to be a reduction in hepatic glucose production, there still remains controversy regarding the drug's precise mechanism of its action. It is now recommended as first-line treatment in a consensus report by American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [1]. In addition to glycose-lowering effect, metformin has beneficial effects on serum lipids, inflammatory markers, and a reduction in cardiovascular events [2]. In recent randomized controlled trials (RCTs) using newer glucose-lowering drugs which showed cardioprotective effects, more than 70% of participants had been treated by metformin as "foundation therapy" in type 2 diabetes, however, there are no studies comparing metformin against newer glucose-lowering drugs [2-8]. Further, since metformin is an old and cheap drug, recent large-scale clinical trials using metformin were not performed.

Here, we studied effects of metformin monotherapy on metabolic parameters in Japanese patients with type 2 diabetes.

Materials and Methods

Study population

We retrospectively picked up type 2 diabetic patients who had been treated by the first metformin monotherapy for more than 3 months, at National Center for Global Health and Medicine Kohnodai Hospital, between January 2015 and October 2018. We obtained clinical and laboratory data by using electronic medical records and database after showing the opt-out. In the analysis of changes in serum lipids, patients who had taken anti-lipidemic drugs such as statin, fibrate and ezetimibe were excluded. In the analysis of changes in blood pressure, patients whose anti-hypertensive drugs had changed during observation period were excluded.

Statistical analysis

Statistical analyses were performed using SPSS version 23 (IBM Co., Ltd., Chicago, IL). All values are expressed as the mean ± standard deviation except for sex and family history of diabetes. We performed the paired *t*-test in the comparison between variables at baseline and those at 3 months after the start of metformin monotherapy. P values of < 0.05 and < 0.1 were

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considered to be statistically significant and have tendency, respectively.

Ethics statement

Because this study was a retrospective cross-sectional observational study, the opt-out method of obtaining informed consent was adopted. The patients were anonymized to protect their personal information. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-003119-00), and the study was performed in accordance with the Declaration of Helsinki.

Results

Twenty-two patients were eligible. Clinical and laboratory data of patients studied at baseline were shown in Table 1. Mean age and body mass index (BMI) were 51.4 years old and 27.8 kg/m^2, indicating that metformin was used in relatively young and obese patients. Mean estimate glomerular filtration rate (eGFR) was 87 mL/min/1.73m^2, meaning that patients studied had normal renal function. Mean daily dose of metformin was 568 mg.

Changes in clinical and laboratory data after the start of metformin monotherapy were shown in Table 2. Systolic blood pressure, plasma glucose, HbA1c, low-density lipoprotein-cholesterol (LDL-C), aspartate transaminase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γGTP) were significantly reduced by the 3-month metformin monotherapy. Diastolic blood pressure, total cholesterol and non-high-density lipoprotein-cholesterol (non-HDL-C) tended to decrease.

We compared the change in metabolic parameter due to metformin monotherapy by dividing all patients into two groups with BMI ≥ 25 and BMI < 25 (Table 3). HbA1c and LDL-C were significantly reduced in both groups. Serum γGTP significantly decreased in the BMI < 25 group, and tended to decrease in the BMI ≥ 25 group. Body weight significantly decreased only in BMI ≥ 25 group. Plasma glucose significantly decreased only in BMI < 25 group. Systolic blood pressure, AST and ALT tended to decrease only in BMI ≥ 25 group.

Table 1. Clinical and Laboratory Data of Patients Studied at Baseline (N = 22)

Data of Patients	Values
Clinical data	
Age (years old)	51.4 ± 13.1
Sex (male, n and %)	14 (64%)
Family history of diabetes (n (%))	12 (55%)
Body height (cm)	167 ± 10
Body weight (kg)	77.4 ± 14.3
Body mass index (kg/m^2)	27.8 ± 4.3
Waist circumference (cm)	98.2 ± 10.9
Systolic BP (mm Hg)	140 ± 15
Diastolic BP (mm Hg)	87 ± 14
Daily metformin dose (mg)	568 ± 172
Laboratory data	
AST (IU/L)	29 ± 15
ALT (IU/L)	39 ± 23
γGTP (IU/L)	65 ± 47
Plasma glucose (mg/dL)	177 ± 65
HbA1c (%)	8.2 ± 1.5
TC (mg/dL)	221 ± 34
TG (mg/dL)	199 ± 133
HDL-C (mg/dL)	40 ± 10
LDL-C (mg/dL)	146 ± 25
non-HDL-C (mg/dL)	168 ± 28
Creatinine (mg/dL)	0.73 ± 0.17
eGFR (mL/min/1.73m^2)	87 ± 26

ALT: alanine aminotransferase; AST: aspartate transaminase; BP: blood pressure; eGFR: estimate glomerular filtration rate; γGTP: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low- density lipoprotein-cholesterol; TC: total cholesterol; TG: triglyceride.

Discussion

Although metformin is widely used as the foundation therapy for patients with type 2 diabetes, effects of metformin monotherapy on metabolic parameters have not been sufficiently elucidated. Metformin is widely used as the optimal initial therapy for patients with type 2 diabetes; however, metformin should be carefully used in specific individuals such as aged people and patients with renal insufficiency. Although the potential lactic acidosis rarely happens with metformin treatment, it may still occur due to drug overdose or in patients with serious renal insufficiency and other contraindications [9]. Given that metformin is excreted by the kidney and not the liver [10], regularly monitoring the renal functions and strictly adhering to the manufacturer's recommendations and doctor's advice are necessary during metformin therapy. The Japan Diabetes Association also recommends that metformin should be carefully used in high risk patients such as patients with renal insufficiency and elderly patients. Our study showed that metformin was used in obese, young patients with normal eGFR, which may be due to that we prescribed metformin avoiding high-risk patients.

Metformin exerts its glucose-lowering effect primarily by decreasing hepatic glucose production through suppression of gluconeogenesis and enhancing insulin suppression of endogenous glucose production and, to a lesser extent, by reducing intestinal glucose absorption and possibly improving glucose uptake and utilization by peripheral tissues, such as skeletal muscle and adipose tissue [3, 9] Metformin may also improve glucose metabolism by interacting with the incretin axis through the action of glucagon-like peptide 1 (GLP-1) [3, 10]. In our study, metformin significantly reduced plasma glucose and HbA1c.

Table 2. Changes in Metabolic Parameters After the 3-Month Metformin Monotherapy

	n	Before metformin use	After 3 months	P values
Body weight (kg)	22	77.4 ± 14.3	75.5 ± 14.3	0.04
Systolic BP (mm Hg)	16	141 ± 16	129 ± 13	0.02
Diastolic BP (mm Hg)	16	87 ± 14	77 ± 9	0.08
AST (IU/L)	22	29 ± 15	24 ± 9	0.026
ALT (IU/L)	22	39 ± 23	30 ± 15	0.026
γGTP (IU/L)	17	60 ± 43	50 ± 47	0.002
Plasma glucose (mg/dL)	22	177 ± 65	142 ± 31	0.043
HbA1c (%)	22	8.2 ± 1.5	6.9 ± 0.8	< 0.001
TC (mg/dL)	11	208 ± 25	191 ± 33	0.061
TG (mg/dL)	14	167 ± 70	165 ± 86	0.845
HDL-C (mg/dL)	14	50 ± 12	49 ± 11	0.696
LDL-C (mg/dL)	5	152 ± 22	121 ± 27	0.001
non-HDL-C (mg/dL)	11	159 ± 22	143 ± 34	0.062
Creatinine (mg/dL)	22	0.73 ± 0.17	0.74 ± 0.18	0.112
eGFR (mL/min/1.73m^2)	22	87 ± 26	84 ± 26	0.14

ALT: alanine aminotransferase; AST: aspartate transaminase; BP: blood pressure; eGFR: estimate glomerular filtration rate; γGTP: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TC: total cholesterol; TG: triglyceride.

Metformin-mediated reduction of gluconeogenesis decreases glucose levels and secondarily reduces insulin levels. Several other molecular mechanisms directly targeting the cardiovascular system have been suggested, and a large part of these effects appears to be mediated by AMP kinase (AMPK) [11]. The activation of AMPK by metformin may improve an impairment of endothelium-dependent relaxation, decrease reactive oxygen species (ROS) production, and may increase

Table 3. Comparison in Changes in Metabolic Parameters After the 3-Month Metformin Monotherapy Between Patients With BMI ≥ 25 and BMI < 25

	BMI ≥ 25 (n = 14)			BMI < 25 (n = 8)		
	Before	After 3 months	P values	Before	After 3 months	P values
Body weight (kg)	83.5 ± 13.6	81.5 ± 13.7	0.044	66.6 ± 5.5	65.0 ± 7.8	0.411
Systolic BP (mm Hg)	139 ± 10	129 ± 14	0.079	142 ± 21	130 ± 10	0.163
Diastolic BP (mm Hg)	89 ± 17	78 ± 10	0.288	84 ± 8	76 ± 7	0.113
AST (IU/L)	32 ± 13	26 ± 9	0.07	24 ± 17	19 ± 7	0.246
ALT (IU/L)	44 ± 20	35 ± 14	0.08	29 ± 25	22 ± 13	0.203
γGTP (IU/L)	86 ± 52	64 ± 52	0.06	38 ± 18	28 ± 14	0.018
Plasma glucose (mg/dL)	178 ± 72	144 ± 38	0.19	178 ± 49	139 ± 25	0.043
HbA1c (%)	7.9 ± 1.4	6.9 ± 0.9	0.007	8.8 ± 1.5	7.0 ± 0.8	0.005
TC (mg/dL)	205 ± 29	193 ± 35	0.267	214 ± 8	183 ± 25	0.137
TG (mg/dL)	194 ± 49	189 ± 81	0.762	70 ± 47	77 ± 27	0.678
HDL-C (mg/dL)	47 ± 11	49 ± 12	0.37	59 ± 10	52 ± 5	0.172
LDL-C (mg/dL)	129 ± 12	93 ± 12	0.009	168 ± 10	140 ± 14	0.04
non-HDL-C (mg/dL)	120 ± 22	107 ± 29	0.203	141 ± 12	116 ± 25	0.206
Creatinine (mg/dL)	0.69 ± 0.15	0.68 ± 0.16	0.379	0.79 ± 0.18	0.84 ± 0.17	0.209
eGFR (mL/min/1.73m^2)	92 ± 30	90 ± 30	0.514	78 ± 16	72 ± 11	0.164

ALT: alanine aminotransferase; AST: aspartate transaminase; BMI: body mass index; BP: blood pressure; eGFR: estimate glomerular filtration rate; γGTP: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TC: total cholesterol; TG: triglyceride.

nitric oxide (NO) bioavailability [11]. Such vasculo-protective effects may induce reduction of blood pressure, which was observed in our study.

In present study, metformin significantly improved liver function. Non-alcoholic fatty liver disease (NAFLD) is commonly observed in patients with type 2 diabetes. Insulin-resistance plays a central role in the development and progression of NAFLD, and several studies have indicated that metformin, as an insulin sensitizer, effectively improves NAFLD and its related metabolic status [12]. Metformin-induced improvement of insulin resistance may be associated with amelioration of liver function in our patients.

Our study showed that metformin reduced LDL-C and non-HDL-C. It was recently reported that metformin exerts a beneficial effect on serum lipids by lowering TG, through a selective increase in very low-density lipoprotein (VLDL)-TG uptake and fatty acid oxidation in adipose tissue [13]. The metformin-induced reduction in tissue lipid storage is consistent with an increase in both fatty acid oxidation and inhibition of lipogenesis, presumably mediated by AMPK activation [13-15]. Such mechanisms may contribute to reduction of LDL-C and non-HDL-C in our study.

Our study demonstrated that metformin significantly reduced HbA1c in both patients with BMI < 25 and BMI ≥ 25 group. DeFronzo RA, et al reported that metformin suppressed hepatic gluconeogenesis regardless of the presence or absence of obesity [16], supporting our result. Interestingly, metformin improved body weight, blood pressure and liver function in only patients with BMI ≥ 25. Increased blood pressure and NAFLD are highly associated with insulin resistance, and insulin resistance may be more severe in patients with BMI ≥ 25 than in patients with BMI < 25. An amelioration of insulin resistance may decrease serum insulin levels which can induce weight loss, and may also improve blood pressure and liver function.

The present study has several limitations. First, food intakes and/or exercise levels may have an influence on the study results. Second, the number of studied subjects was small because of the limited availability. A more detailed prospective study is recommended to evaluate the effects of metformin monotherapy more validly.

Conclusions

The metformin monotherapy improved glycemic control regardless of presence or absence of obesity. Interestingly, metformin improved body weight, blood pressure and liver function in only overweight patients with type 2 diabetes.

Conflict Interest

The authors declare that they have no competing interests.

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