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ORIGINAL ARTICLE

Effect of Metformin Glycinate on Glycated Hemoglobin A1c Concentration and Insulin Sensitivity in Drug-Naive Adult Patients with Type 2 Diabetes Mellitus

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Abstract

Aim: This study evaluated the effect of metformin glycinate on glycated hemoglobin A1c (A1C) concentration and insulin sensitivity in drug-naive adult patients with type 2 diabetes mellitus (T2DM).
Subjects and Methods: A randomized, double-blind, placebo-controlled clinical trial was carried out in 20 patients with drug-naive T2DM. Ten subjects received metformin glycinate (1,050.6 mg) once daily during the first month and force-titrated twice daily during the second month. Ten additional patients received placebo as the control group. Before and after the intervention, metabolic profile including A1C and insulin sensitivity (euglycemic-hyperinsulinemic clamp technique) was estimated.
Results: A1C concentrations decreased significantly with metformin glycinate administration ($8.0 \pm 0.7\%$ vs. $7.1 \pm 0.9\%$, $P = 0.008$) before and after the intervention, respectively. There were significant differences in changes from baseline of A1C between groups ($0.0 \pm 0.7\%$ vs. $-1.0 \pm 0.5\%$ for placebo and metformin glycinate groups, respectively; $P = 0.004$). A reduction of $\geq 1\%$ in A1C levels was reached in 60.0% of patients with metformin glycinate administration ($P = 0.02$). Insulin sensitivity was not modified by the intervention.
Conclusions: Administration of metformin glycinate during a 2-month period showed a greater decrease in A1C concentrations than placebo in a selected group of drug-naive adult patients with T2DM.

Introduction

In accordance with several algorithms for the medical treatment of patients with type 2 diabetes mellitus (T2DM), metformin hydrochloride along with lifestyle changes is the first line of treatment to achieve metabolic goals and, in combination with other oral agents or insulin, provides an efficacious therapeutic option.[1,2] Metformin is a biguanide that activates the 5′-AMP-activated protein kinase in several tissues, mainly liver, improving insulin sensitivity.[3,4] Pharmacological effects of metformin hydrochloride include significant beneficial changes in glucose control with moderate changes in body weight, insulin levels, and diastolic blood pressure.[5] Anti-atherosclerotic and cardioprotective effects of metformin hydrochloride have recently been confirmed in several studies and appear to be glucose independent. They may indeed be a direct consequence of its possible actions on the vascular endothelium, suppressing the effects on glycation, oxidative stress, and formation of adhesion molecules as well as stimulating fibrinolysis and improving the lipid profile.[6,7] Despite all the benefits obtained with metformin hydrochloride and its low risk of hypoglycemia, some patients experience gastrointestinal intolerance; others have a risk of serious adverse events, which should be considered if the contraindications are not observed.[8]

Metformin glycinate is a new, well-tolerated pharmaceutical preparation of metformin under investigation and has demonstrated a longer half-life than metformin hydrochloride.[9,10] Metformin glycinate exhibited a maximum concentration of $3{,}316 \pm 578$ ng/mL, a time to maximum

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concentration of 1.73 ± 0.97 h, a half-life of 2.6 h, and an area under the curve of 17,241 ± 3,411 ng/mL/h.[9] Equimolar doses of metformin hydrochloride (850 mg) and metformin glycinate (1,050.6 mg) in healthy volunteers showed that metformin glycinate has a rapid absorption with detectable levels of the drug within 7.8 min, without differences in side effects observed and with similar gastrointestinal tolerability between preparations.[10] Until now, clinical characteristics of metformin glycinate have not been completely studied, including insulin sensitivity and metabolic control.

The aim of this study was to evaluate the effect of metformin glycinate on glycated hemoglobin A1c (A1C) concentration and insulin sensitivity in drug-naive adult patients with T2DM.

Patients and Methods

A randomized, double-blind, placebo-controlled Phase 2A clinical trial, designed by the study authors, was carried out in 20 Mexican patients who were drug-naive from the time of diabetes diagnosis. Subjects were 30–60 years of age with recently diagnosed (< 5 years) T2DM and overweight or obesity (body mass index, 25.0–34.9 kg/m^2), fasting glucose levels between 7.1 and 11.0 mmol/L, and A1C levels between 7% and 9%. As part of their primary medical care, all subjects received medical nutritional therapy at least during the previous month by a registered dietitian in accordance with the guidelines of the American Diabetes Association.[11] Subjects were selected from the same residential area and socioeconomic status. Patients with excessive activity (considered as at least 1 h of physical activity/day) and those with excessively sedentary lifestyle (defined as <30 min of physical activity/day) were not included. All individuals were nonsmokers according to patient self-report. Their body weight had been stable for at least 3 months prior to the study. Blood pressure was <130/80 mm Hg. None of the subjects had a personal history of hepatic, renal, or coronary artery disease. Subjects had not taken any non-antidiabetes medications known to affect carbohydrate or lipid metabolism during the 6 months prior to the study. All subjects consumed an isocaloric diet containing >250 g of carbohydrate/day for 3 days prior to the study as confirmed by dietary history based on three 24-h dietary recall interviews.

Patients were evaluated before and after the 2-month study period as well as during the time they were still under the assigned treatment and prior to the time that the randomization code was broken. Tests were performed at 8:00 a.m. after a 10–12-h overnight fast. Blood pressure was measured after a 5-min rest period with the participant in sitting position. Measurements were taken with a standard mercury sphygmomanometer by the same investigator, and diastolic blood pressure was recorded at Korotkoff's phase 5. Height and weight were recorded with the individual wearing light clothing and without shoes. Height was measured and rounded off to the nearest centimeter with the subject standing. Body mass index was calculated as weight (in kg) divided by the height squared (m^2). Waist circumference was measured at the highest point of the iliac crest at minimal respiration to the nearest 0.1 cm. Venous blood was obtained with the subject lying supine in a quiet room. The blood was allowed to clot for 30 min at room temperature and then centrifuged at 1,500–2,000 *g* for 15 min. The resulting serum was placed into aliquots immediately used for measurement of serum creatinine, uric acid, glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and A1C.

To assess insulin sensitivity before and after pharmacological intervention, a euglycemic/hyperinsulinemic modified clamp technique was performed.[12] Two venous accesses were established. The first was placed in retrograde fashion in any hand vein through a 23-gauge catheter to obtain blood samples. The hand was wrapped with a thermal pillow until a temperature of >40°C was reached to arterialize the blood. The second venous access was established in the contralateral arm with a 20-gauge catheter for infusion. Insulin (Humulin® R, Eli Lilly Co., Mexico City, D.F., Mexico) was given as a primed continuous infusion targeted to produce plasma insulin levels of approximately 600 pmol/L. Afterward, the insulin infusion rate was fixed at 284 pmol/L/m^2/min. Blood glucose level was constant (approximately 5 mmol/L with a coefficient of variation of <5%) throughout the study (120 min) by infusing 10% glucose at various rates according to blood glucose measurements performed at 5-min intervals. At the end of the clamp technique, a 10% glucose infusion was maintained for an additional 30 min as a precaution to avoid hypoglycemia. Total glucose metabolism was used to evaluate insulin sensitivity.

Ethical considerations

The study protocol was reviewed and approved by the local ethics committee, and written informed consent was obtained from all volunteers prior to any medical procedure for screening.

Pharmacological administration

The allocation was concealed and done by simple randomization with closed envelopes that contained either a letter A or B. Investigators were unaware of the code of the pharmacological assignment during the study until the end of the statistical analyses. After randomization, metformin glycinate (1,050.6 mg) (Laboratorios Silanes, Mexico City) was administered once daily during the first month and force-titrated twice daily during the second month, or placebo was administered orally.

All adverse events were explored systematically during each visit throughout the study period including 28 calendar days after the last administration of the pharmacological intervention. Specifically, mild hypoglycemia was defined as follows: characteristic symptoms of hypoglycemia excluding neurological symptoms with or without home glucose monitoring measurement of <3.9 mmol/L or laboratory glucose value of <2.7 mmol/L with or without symptoms, excluding neurological symptoms. In both of the above-mentioned cases it was necessary for the patient to treat him- or herself with a collation meal.

All measurements were done in a certified clinical laboratory under appropriate quality-control conditions. Serum glucose was determined by the glucose oxidase colorimetric technique (Analox Instruments, Lunenburg, MA) with an intra- and inter-assay coefficient of variation of <1%. Serum creatinine, uric acid, total cholesterol, triglycerides, and high-density lipoprotein-cholesterol after selective precipitation of non–high-density lipoprotein fractions were assessed with enzymatic colorimetric techniques (Vitros®, Ortho-Clinical

Diagnostics, a Johnson & Johnson Co., Rochester, NY) with an intra- and interassay coefficient of variation of <2%. Insulin concentrations were measured with a microparticle enzymatic immunoassay method (Abbott Diagnostics Division, Japan Co., Ltd., Wiesbaden, Germany) with an intra- and interassay coefficient of variation of 3.3% and 3.8%, respectively. A1C levels were measured using an ion-exchange high-performance liquid chromatography technique (Bio-Rad Laboratories, Hercules, CA) with an intra- and interassay coefficient of variation of 0.4% and 1.6%, respectively.

Statistical analyses

Sample size was calculated by means of a formula for clinical trials[13] with a statistical confidence of 95%, statistical power of 80%, SD for A1C of 0.7%, and an expected difference of at least 1.0% of A1C between groups, obtaining a total of eight patients for each group. For insulin sensitivity, sample size calculation was higher, using a SD of total glucose metabolism of 1.2 mg/kg/min and an expected difference of at least 1.6 mg/kg/min of total glucose metabolism among groups, resulting in a total of nine patients for each group. Results were converted to SI units and are presented as mean ± SD values. Statistical analyses were done as intention to treat. Intra- and intergroup differences were tested by Wilcoxon's signed-ranks and Mann–Whitney U tests, respectively.

Results

Twenty volunteers were screened to participate in this study and fulfilled the selection criteria. No subject refused participation in the investigation. Nineteen subjects who were eligible after enrollment completed the 2-month pharmacological intervention. Written informed consent was withdrawn immediately after the first month of treatment in a patient from the metformin glycinate group. Statistical analyses were carried out as intention to treat. The placebo group consisted of seven women and three men, and the metformin glycinate group composed eight women and two men ($P=0.606$). There were no significant differences in the average age between groups (43.3 ± 6.4 vs. 47.7 ± 9.4 years for placebo and metformin glycinate groups, respectively; $P=0.190$). Body mass index was not modified by the intervention (30.3 ± 3.9 vs. 30.4 ± 4.3 kg/m^2 [$P=0.514$] and 30.7 ± 2.8 vs. 30.5 ± 3.0 kg/m^2 [$P=0.183$] for placebo and metformin glycinate groups, respectively). There were no significant differences in waist circumference due to the intervention (98 ± 8 vs. 98 ± 9 cm [$P=0.396$] and 101 ± 8 vs. 100 ± 7 cm [$P=0.674$] for placebo and metformin glycinate groups, respectively). Systolic blood pressure was not modified by the intervention (118 ± 14 vs. 118 ± 10 mm Hg [$P=0.953$] and 120 ± 6 vs. 116 ± 7 mm Hg [$P=0.270$] for placebo and metformin glycinate groups, respectively). Diastolic blood pressure was not modified by the intervention (79 ± 6 vs. 77 ± 5 mm Hg [$P=0.078$] and 77 ± 4 vs. 77 ± 6 mm Hg [$P=0.865$] for placebo and metformin glycinate groups, respectively).

There were no significant differences in laboratory measurements between groups at baseline. There were no significant differences after pharmacological interventions in each group with the exception of the A1C concentrations, which decreased significantly with the administration of metformin glycinate (Table 1). There were significant differences in changes from baseline of A1C between groups (0.0 ± 0.7% vs. −1.0 ± 0.5% for placebo and metformin glycinate groups, respectively; $P=0.004$). A reduction of ≥1% in A1C levels was reached in 60.0% of patients with the administration of metformin glycinate and in 10% of patients in placebo group ($P=0.02$).

Adverse events recorded throughout the study are shown in Table 2. A mild hypoglycemic episode was observed in one patient from the metformin glycinate group but did not require withdrawal of the patient from the study. There were no serious adverse events in any case.

Discussion

Pharmacological and clinical effects of metformin glycinate have not been previously tested in patients with T2DM. Therefore, it was decided to perform this study in recently diagnosed drug-naive patients, despite difficulties in locating volunteers with the mentioned characteristics. In Mexico, of patients with T2DM diagnosed slightly longer than 8 years, only 5.93% are being treated without medication.[14] Unfortunately, the mean duration in our population was not recorded. However, we were interested in evaluating the net effect of metformin glycinate compared with placebo when used as monotherapy and as a first line of therapy.

Table 1. Laboratory Measurements Before and After the Intervention in the Studied Groups

	Placebo			*Metformin glycinate*		
	Basal (n = *10*)	*2 months* (n = *10*)	P	*Basal* (n = *10*)	*2 months* (n = *9*)	P
Creatinine (μmol/L)	61.8 ± 8.8	53.0 ± 7.9	0.061	53.0 ± 7.9	53.0 ± 7.0	0.564
Uric acid (μmol/L)	321 ± 53	303 ± 47	0.153	303 ± 53	315 ± 89	0.859
TC (mmol/L)	5.5 ± 1.0	5.1 ± 0.7	0.074	4.8 ± 0.6	4.8 ± 0.6	0.514
TG (mmol/L)	2.4 ± 0.8	2.3 ± 0.6	0.721	2.2 ± 0.8	2.1 ± 1.1	0.953
HDL-c (mmol/L)	1.1 ± 0.2	1.1 ± 0.1	0.721	1.0 ± 1.3	1.2 ± 0.4	0.213
Glucose (mmol/L)	8.3 ± 1.2	8.4 ± 2.3	0.799	8.1 ± 1.2	7.2 ± 1.3	0.086
A1C (%)	7.6 ± 0.5	7.7 ± 0.6	0.959	8.0 ± 0.7	7.1 ± 0.9	0.008
Insulin (pmol/L)	80.4 ± 39.6	88.2 ± 45.0	0.333	72.6 ± 23.4	68.4 ± 21.6	0.441
M (mg/kg/min)	2.5 ± 2.0	2.2 ± 0.7	0.575	2.2 ± 0.6	2.3 ± 0.7	0.859

A1C, glycated hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; M, glucose metabolized; TC, total cholesterol; TG, triglycerides.

Table 2. Adverse Events Reported Throughout the Study

	Placebo (n = *10*)	*Metformin glycinate* (n = *10*)
Gastrointestinal infection	2	2
Headache	1	2
Decreased appetite	0	2
Flatulence	0	2
Abdominal distention	0	2
Diarrhea	2	0
Adynamia	2	0
Gastroesophageal reflux	1	1
Dental infection	0	1
Mild hypoglycemia	0	1
Edema	1	0
Genitalia itching	1	0
Upper respiratory tract infection	1	0

In our investigation, metabolic control at 2 months was evaluated by A1C concentrations. Metformin glycinate administration was demonstrated to decrease A1C by 1% after the intervention with a tendency to decrease basal glucose concentrations. It has been reported in the literature that the postprandial glucose level in patients with A1C levels close to normal value is more important than fasting glucose concentrations.[15] That may have been the case with these patients, but unfortunately postprandial glucose was not measured. In this study, peripheral insulin sensitivity was not modified, probably because biguanides improve mainly hepatic insulin sensitivity and the glucose-insulin clamp technique does not discriminate for the localization of insulin resistance. In some publications, however, this effect of improvement in insulin sensitivity due to metformin has been observed.[3,4,16] Of special interest to our investigation group was the proportion of patients who showed a decrease of ≥1% in A1C after the intervention. It is widely recognized that for every percentage point decrease in A1C, there is a 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality, and an 18% reduction in associated combined fatal and nonfatal myocardial infarction.[17] The above-mentioned goal was achieved by 60% of patients in the metformin glycinate group and in only one patient in the control group. In both cases, medical nutritional therapy during the month prior to the intervention may play a partial role in the results obtained. On the other hand, the known placebo effect[18] probably influenced the A1C decrease in the control group as demonstrated in other clinical trials with antidiabetes agents.[19]

Other metabolic benefits may be observed in a long-term study with a larger sample size. Additional limitations of the present study were lack of recording of dietary adherence and evaluation at the time of titration with laboratory measurements, which may provide important data in regard to the results.

The study was not designed to demonstrate safety with the administration of metformin glycinate; however, it was observed that the overall side effects were evenly distributed between groups. Those side effects usually associated with metformin (decreased appetite, flatulence, abdominal distention) were present as expected[20]; however, diarrhea was present in two of 10 patients receiving placebo. This fact may be explained by unproven gastrointestinal infections or simply due to the above-mentioned placebo effect[18] and observed in other studies.[20]

In conclusion, administration of metformin glycinate for a 2-month period was associated with a statistically significant greater decrease in A1C concentration than placebo in a selected group of drug-naive adult Mexican patients with type 2 DM.

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Author Disclosure Statement

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