Repaglinide Administration Improves Brachial Reactivity in Type 2 Diabetic Patients

DANIELA MANZELLA, MD
RODOLFO GRELLA, MD
ANGELA MARIE ABBATECOLA, MD
GIUSEPPE PAOLISSO, MD

OBJECTIVE — Several studies have demonstrated that endothelial dysfunction plays a central role in diabetic mortality and that the prooxidative effect of postprandial hyperglycemia may actively contribute to atherogenesis. Thus, we investigated the possible effect of short-acting (repaglinide) and long-acting (glibenclamide) insulin secretagogues on endothelial function in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — Sixteen type 2 diabetic patients undergoing diet treatment and with poor glucose control volunteered for the study. The study was designed as a 4-month, randomized, cross-over, parallel-group trial of repaglinide (1 mg twice a day) versus glibenclamide (5 mg twice a day). All patients underwent the following investigations: *1*) anthropometrics determinations, *2*) blood sampling for routine laboratory analyses and for assessment of oxidative stress indexes, and *3*) a brachial reactivity test to evaluate the endothelial function through the study of arterial diameter and flow changes with and without intraarterial infusion of N_G-monomethyl-L-arginine, an inhibitor of nitric oxide synthase and tetraethylammonium chloride (TEA), a Ca^{2+}-activated K^+ (K_{Ca}) channel blocker. All patients were randomly assigned to receive repaglinide or glibenclamide for a period of 4 weeks.

RESULTS — Repaglinide administration was associated with a significant reduction in 2-h plasma glucose levels ($P < 0.001$) and in plasma thiobarbituric acid–reactive substances (TBARS) concentrations ($P < 0.001$) and with a significant increase in plasma antioxidant power, assessed as Trolox equivalent antioxidant capacity (TEAC) ($P < 0.001$), effects not observed after glibenclamide administration. With regard to brachial reactivity parameters, repaglinide but not glibenclamide was associated with a significant improvement in brachial reactivity parameters ($P < 0.003$ for all parameters). In contrast, intra-arterial infusion of L-NMMA and TEA reduced the beneficial effect of repaglinide.

CONCLUSIONS — Repaglinide administration, through good control of postprandial glucose levels, improves brachial reactivity and declines oxidative stress indexes.

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Recent studies have suggested that plasma glucose fluctuations, such as those occurring in the absorptive state, may not only be an important determinant of overall glucose control and risk of diabetes complications, but they may also exert an independent negative effect on long-term outcomes of diabetes (1–4). In fact, acute elevations of plasma glucose concentrations trigger an array of tissue responses that may contribute to the development of vascular complications (5). Whether antihyperglycemic agents with different pharmacokinetic profiles may have diverse effects on endothelial function is still unknown. In fact, one cannot rule out that drugs having different pharmacokinetic profiles, through a reduced or a more profound effect on postprandial glucose levels, could exert a diverse impact on oxidative stress at the endothelial level.

Repaglinide and glibenclamide are two segretagogues with a strong difference in pharmacokinetic profile. Repaglinide is a short-acting drug mainly devoted to control for postprandial glucose excursions (6–7); glibenclamide has a smoothed effect on postprandial glucose excursions, but it has a more prolonged impact on glucose control (8).

To the best of our knowledge, no studies have addressed the possible influence of repaglinide and glibenclamide on both oxidative state and endothelial function. Thus, the present study was designed to examine the effects of repaglinide versus glibenclamide treatment on oxidative state and endothelial function in type 2 diabetic patients with poor glucose control.

RESEARCH DESIGN AND METHODS

— Sixteen type 2 diabetic patients undergoing diet treatment but with poor glucose control volunteered for the study. Exclusion criteria were type 1 diabetes, smoking habit, hepatic and renal diseases, cardiovascular diseases such as heart failure (New York Heart Association [NYHA] III, IV), unstable angina pectoris, recent myocardial infarction, and hypertension. Subjects who were taking any type of antihypertensive or lipid-lowering agents were excluded from the study.

Diet and lifestyle

All patients consumed a weight-stable diet (±1,500 kcal) made up of carbohydrate (~ 50%), fat (~25%), and protein (~25%). The polyunsaturated–to–saturated fatty acid ratio was 1.0. The

From the Department of Geriatric Medicine and Metabolic Diseases II, University of Naples, Naples, Italy.
Address correspondence and reprint requests to Giuseppe Paolisso, MD, Department of Geriatric Medicine and Metabolic Diseases VI, Internal Medicine, Piazza Miraglia 2 I-80138, Napoli, Italy. E-mail: giuseppe.paolisso@unina2.it.
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Abbreviations: FFA, free fatty acid; TBARS, thiobarbituric acid–reactive substances; TEA, tetraethylammonium chloride; TEAC, Trolox equivalent antioxidant capacity.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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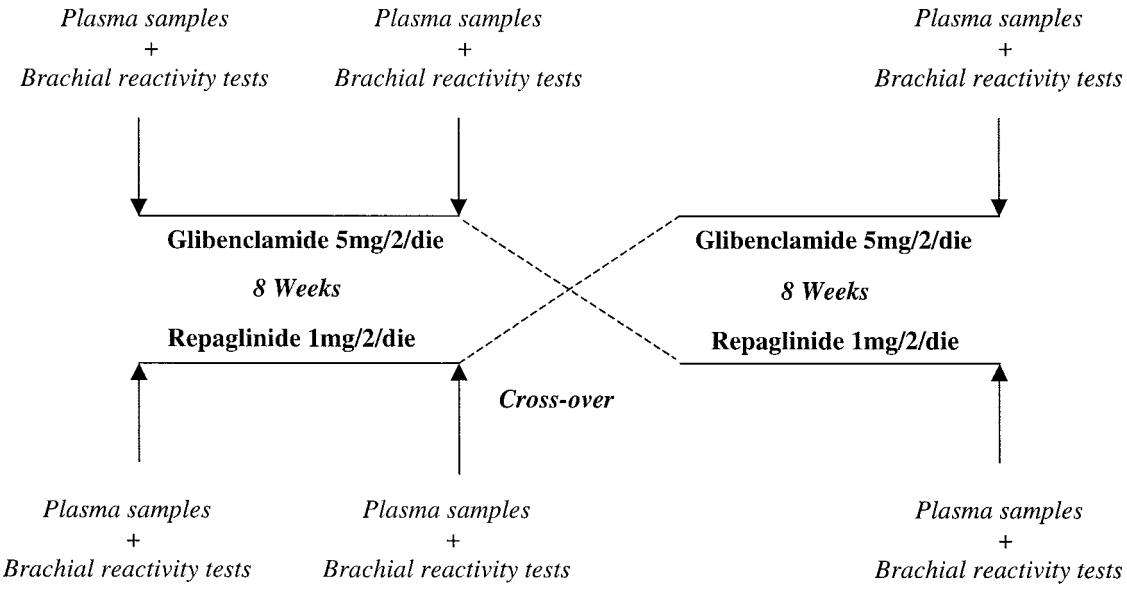

Figure 1—*Trial design.*

amount of fiber in the diet was ~10 g/day. The patients were encouraged to not eat additional foods. Furthermore, all patients were prompted to keep their lifestyle habits (encompassing frequency and degree of physical activity) through the duration of the study.

Study protocol

After a 1-week run-in period, all enrolled patients were invited to entry into the study, which was designed as a 4-month, randomized, cross-over, parallel-group trial of repaglinide (1 mg twice a day) versus glibenclamide (5 mg twice a day) (Fig. 1). At baseline, after an overnight fast (12 h at least), in a quiet, comfortable room with a temperature range between 22 and 24°C, all patients underwent the following investigations: *1*) anthropometrics determinations, *2*) blood sampling for routine laboratory analyses and for assessment of oxidative stress indexes, and *3*) a brachial reactivity test to evaluate the endothelial function through the study of arterial diameter and flow changes in presence or absence of an intra-arterial infusion of N_G- monomethyl-L-arginine, an inhibitor of nitric oxide (NO) synthase (Clinalfa) and tethraethylammonium chloride (TEA), a Ca^{2+}-activated K^+ (K_{Ca}) channel blocker (Sigma-Aldrich Italy). These tests were made in random order and in different days. Each patient was evaluated three times at baseline and at the end of each study treatment (Fig. 1).

After clear explanation of potential risks of the study, each volunteer gave written informed consent to participate in the study, which was approved by the Ethical Committee of the University of Naples.

Anthropometrics determinations

Weight and height were measured using a standard technique. BMI was calculated as body weight (in kilograms) divided by the square of height (in meters).

Endothelial function

Endothelial function was evaluated by a brachial reactivity study, as previously reported (9,10). Briefly, brachial reactivity was detected using a high-frequency ultrasound technique. All patients were kept at rest in a supine position in a temperature-controlled room (~22°C). The left arm was immobilized in the extended position to allow consistent brachial artery access for imaging. To assess the endothelium-dependent reactivity in the macrocirculation, the flow-mediated dilatation of the brachial artery was measured by using a high-resolution ultrasound with a 10-MHz linear array transducer ultrasound system (ATL5000HDI; Bothell). Reactive hyperemia is produced by inflating a pneumatic tourniquet distally to the brachial artery to 50 mmHg above the systolic pressure for 5 min and then deflating it. All images were recorded on videotape for subsequent offline analysis on the same instrument by the single observer blinded to the conditions under which the ultrasonic images were obtained.

To minimize any potential bias, the brachial reactivity test was performed by two independent investigators who were blinded to clinical and pharmacological treatment. Intraobserver variability for measuring brachial artery diameter and flow was assessed by comparing a minimum of three separate baseline measurements in each patient. These values were not dissimilar from those reported by other authors (11).

Analytical techniques

Plasma glucose concentration was determined by the glucose oxidative methods (glucose autoanalyzer; Beckman Coulter). Plasma insulin concentrations were determined by radioimmunoassay in which crossreactivity with proinsulin is <0.2% (Linco Research). Plasma fasting total and HDL cholesterol and triglyceride levels were determined by routine laboratory methods. Degree of serum oxidative stress was measured as the reaction products of malondialdehyde with thiobarbituric acid–reactive substances (TBARS) (12–14); the inter- and intra-assay coefficients of variation were 3.4 and 2.3%, respectively. The plasma total antioxidant capacity, assessed Trolox equivalent antioxidant capacity (TEAC), was estimated by the 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid radical cation decolorization assay, using Trolox as a standard,

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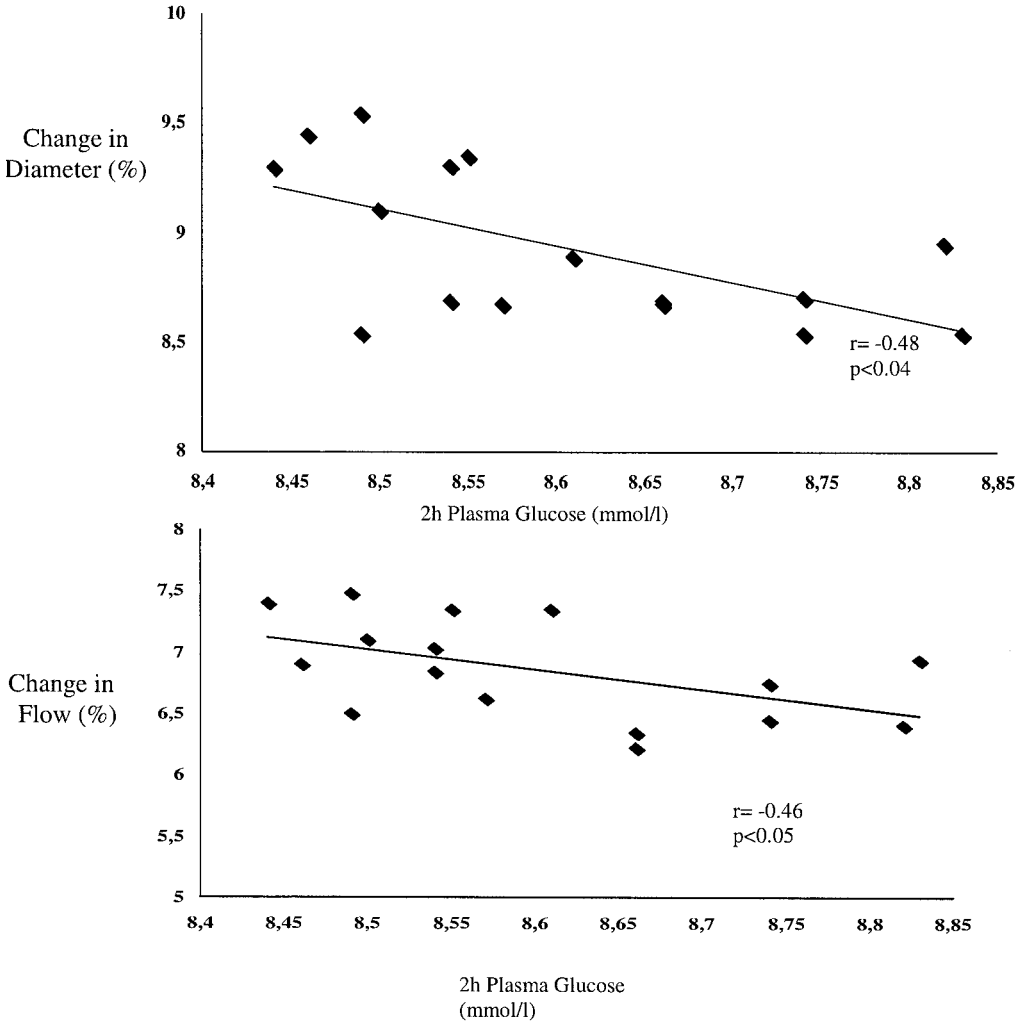

Figure 2—*Partial correlation between 2-h postprandial glucose and changes in diameter and in flow adjusted for metabolic control score, TEAC, and TBARS.*

according to the method of Pellegrini et al. (15); the inter- and intra-assay coefficients of variation were 5.2 and 3.8%, respectively.

Calculation and statistical analyses

All results are mean ± SD. The nQuery test was used to predict the adequacy of sample size. This test demonstrated that 16 subjects in each group were sufficient to obtain a significant difference in brachial reactivity parameters ($P < 0.001$). Non–normally distributed variables were log transformed (for all calculations) and then back transformed (for result presentation). The percent change was calculated with baseline values equal to 100%. Because we were interested in examining the effect of a risk factor cluster, we converted all risk factors associated with metabolic control (fasting plasma glucose, insulin, triglycerides and free fatty acids [FFAs], 2-h insulin level and HbA_{1c}, and systolic and diastolic blood pressure measurements) into the same unit, as the *z* score. Successively, the sum of the *z* score of all eight factors for each individual was calculated as a summary measure of the metabolic control score. The *z*-score sum gives equal weights to all factors and was shown to yield a measure of the metabolic control similar to one derived by a principal components analysis. It should be underscored that such an index is not a biological index but a surrogate variable made up by a mathematical calculation.

ANOVA allowed calculating the difference among parameters at all three different study times (baseline, after repaglinide, and after glibenclimide). Pearson's simple correlation allowed studying the association between the two variables. Partial correlation investigated the relationship between the two variables independently of covariates. All calculations were made on an IBM personal computer by SPSS 10.0.

RESULTS

Metabolic data

Patients were slightly overweight and had a poor metabolic control at recruitment. Repaglinide and glibenclamide administration were both associated with a significant decline in fasting plasma glucose, HbA_{1c}, triglycerides, and FFAs and with a significant increase in fasting plasma insulin, 2-h plasma insulin, and HDL cholesterol levels. In addition, repaglinide administration had a stronger reduction in 2-h plasma glucose levels compared with glibenclamide administration. With regard to the oxidative stress parameters, repaglinide but not glibenclamide showed a significant increase in plasma antioxidant power (TEAC), which paralleled the decline in plasma TBARS con-

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Table 1—*Clinical characteristics at baseline condition and after repaglinide and glibenclamide treatment*

	Baseline	*P*	Repaglinide	*P*	Glibenclamide
n	16		16		16
Age (years)	64.8 ± 7.9				
Sex (M/F)	9/7				
BMI (kg/m^2)	27 ± 0.8	NS	26.3 ± 0.9	NS	26.4 ± 0.8
Fasting plasma glucose (mmol/l)	9.6 ± 0.2*	0.001	6.9 ± 0.2	0.001	8.1 ± 0.3
2-h postprandial plasma glucose (mmol/l)	13.2 ± 0.4	0.001	8.7 ± 0.2	0.001	11.1 ± 0.9
HbA_{1c} (%)	8.3 ± 0.2*	0.001	7.1 ± 0.2	0.003	7.4 ± 0.2
Fasting plasma insulin (pmol/l)	69.2 ± 0.8*	0.001	78.7 ± 0.5	0.03	74.6 ± 0.6
2-h postprandial plasma insulin (pmol/l)	207 ± 61†	0.001	495 ± 68	0.008	388 ± 56
Fasting plasma total cholesterol (mmol/l)	5.3 ± 0.4	NS	5.1 ± 0.2	NS	5.2 ± 0.3
Fasting plasma HDL cholesterol (mmol/l)	1.22 ± 0.07†	0.001	1.31 ± 0.04	NS	1.28 ± 0.03
Fasting plasma triglycerides (mmol/l)	2.6 ± 0.2*	0.001	1.7 ± 0.1	0.001	2.1 ± 0.2
TEAC (mmol/l)	1.5 ± 0.2	0.001	2.7 ± 0.1	0.001	1.8 ± 0.3
TBARS (nmol MDA/ml plasma)	0.66 ± 0.06	0.001	0.36 ± 0.03	0.001	0.59 ± 0.02

Data are means ± SD. *$P < 0.001$ and †$P < 0.02$ vs. glibenclamide. MDA, malondialdehyde.

centrations. Only after repaglinide administration, changes in 2-h plasma glucose levels were significantly correlated with changes in plasma TEAC ($r = -0.57$, $P < 0.02$) and in plasma TBARS ($r = 0.55$, $P < 0.03$). Such correlations were independent of the metabolic control score ($r = -0.47$, $P < 0.05$ and $r = 0.46$, $P < 0.05$, respectively) (Table 1).

Cardiovascular data

At baseline all patients had arterial blood pressure within normal range. Repaglinide and glibenclamide administrations were not associated with any significant change in systolic and diastolic blood pressure. Repaglinide but not glibenclamide administration was associated with a significant improvement in brachial reactivity, as shown by the increase in changes in diameter and in flow. Assessment of changes in diameter and in flow after L-NMMA did not show any significant difference either between repaglinide and glibenclamide administration or between each drug versus the baseline values. In contrast, only TEA infusion, after repaglinide administration, was associated with slightly reduced beneficial effects on endothelial function (Table 2). After repaglinide administration, changes in 2-h plasma glucose levels were significantly correlated with the changes in diameter ($r = -0.58$, $P < 0.02$) and flow ($r = -0.56$, $P < 0.02$). Such correlations were independent of the metabolic control score ($r = -0.48$, $P < 0.04$ and $r = -0.46$, $P < 0.05$, respectively) (Fig. 2) but were lost after adjustment for the changes in plasma TBARS and TEAC ($r = 0.40$, $P < 0.1$ and $r = -0.38$, $P < 0.1$, respectively).

CONCLUSIONS — Our study confirms the beneficial effects of a strong control of postprandial glycemic excursion on endothelial function and demonstrates that repaglinide rather than glibenclamide administration is associated with a stronger decline in 2-h postprandial glucose, a better improvement in endothelial function, and a decline in oxidative stress.

Type 2 diabetes is associated with an enhanced risk of cardiovascular disease (16–18). This excess risk is still not fully explained. A prooxidative effect of postprandial hyperglycemia may actively contribute to the proatherogenic environment through an inappropriate regulation of vascular tone, permeability, coagulation, fibrinolysis, and cell adhesion and proliferation. In fact, it has been suggested that generation of reactive oxygen species (ROS) in endothelial cells exposed to hyperglycemia induces damage

Table 2—*Cardiovascular characteristics at baseline condition and after repaglinide and glibenclamide treatment*

	Baseline	*P*	Repaglinide	*P*	Glibenclamide
n	16		16		16
Systolic blood pressure (mmHg)	83 ± 2	NS	82 ± 3	NS	82 ± 3
Diastolic blood pressure (mmHg)	130 ± 5	NS	130 ± 4	NS	133 ± 6
Brachial artery diameter baseline (mm)	3.6 ± 0.7	NS	3.7 ± 0.1	NS	3.6 ± 0.5
Brachial artery diameter after cuff release (mm)	3.8 ± 0.3	0.001	4.1 ± 0.2	0.001	3.8 ± 0.2
Change in diameter (%)	6.4 ± 1	0.001	8.9 ± 0.4	0.001	6.8 ± 0.7
Change in flow (%)	5 ± 1	0.003	6.3 ± 1.1	0.003	5.1 ± 0.9
Change in diameter L-NMMA (%)	5.3 ± 1.4	NS	6.5 ± 1.1	NS	6.7 ± 1.1
Change in flow L-NMMA (%)	5.5 ± 1.1	NS	5.7 ± 1	NS	5.7 ± 1.2
Change in diameter TEA (%)	6.3 ± 1.2	0.03	7.8 ± 0.5	0.04	6.5 ± 1.3
Change in flow TEA (%)	4.8 ± 1	0.05	5.9 ± 0.5	0.05	5 ± 0.8

Data are ± SD.

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through reduction of endothelieal NO synthase (eNOS) activity (19). Moreover, hyperglycemia enhances glucose flux through glycolysis, leading to enhanced concentrations of NADH and pyruvate, thereby enhancing electron transport in mitochondrium (20), which in turn leads to the generation of ROS (20–21). In isolated mesenteric beds of Wistar rats with diabetes for 6 months, a reduction in endothelium-dependent relaxation was found (22). In addition, cultures of porcine aortic endothelial cells (PAECs) submitted to high-glucose concentrations showed an endothelial dysfunction mediated by hyperglycemia, which was revealed by reduced endothelial NO production or release (22–23), as well as severe changes in endothelial cell structure (24). More recently, several studies suggested plasma glucose fluctuations and glucose peaks, such as those occurring in the postabsorptive state, to provide a strong contribution to the development of endothelial dysfunction (25–27). According to such "in vitro" evidence, we can hypothesize that tight control in postprandial glucose excursions, such as that observed after repaglinide treatment, can improve endothelial function and decrease oxidative stress, thus contributing to a decline of cardiovascular disease risk in type 2 diabetic patients. Our data showing that repaglinide—but not glibenclamide—administration is associated with a significant improvement in 2-h postprandial glucose levels, the degree of oxidative stress, and brachial reactivity are in agreement with previous in vitro data (25–27). In addition, the relationship between changes in 2-h plasma-glucose levels and brachial reactivity is independent of the main metabolic parameters but is dependent on the TBARS and TEAC levels. The latter data, according to a previous study showing that endothelial dysfunction is present in the postprandial state in type 2 diabetic patients (28), support the hypothesis that 2-h plasma glucose levels are the main factor determining oxidative stress and endothelial dysfunction and that a tight control of postprandial glucose excursion—as those found after repaglinide—is a key point for preventing endothelial dysfunction and macroangiopathy. Furthermore, because the modulation of vascular tone is mediated by NO and endothelium-derived hyperpolarizing factor (EDHF), and because the role of EDHF in modulating vascular smooth muscle contraction is mediated by K_{Ca} channels on vascular smooth muscle (29–30), we have evaluated the effect of repaglinide and glibenclamide administration on both vasorelaxive factors. In fact, previous studies have demonstrated a different effect of glibenclamide and repaglinide on K_{Ca} channels on vascular smooth muscle (31–32). Our study demonstrated that both vasorelaxive factors are involved in mechanisms modulating vascular tone after repaglinide administration. Nevertheless, the main action of repaglinide seems mediated by NO. In fact, the beneficial effect of repaglinide administration on endothelial function is blocked after NO inhibitors (L-NMMA), whereas a K_{Ca} channel blocker (TEA) is able only to determine a slightly reduced inhibitory effect on endothelial function.

An unexpected finding of our study was the occurrence of lower fasting plasma glucose after repaglinide compared with glibenclamide. A possible explication could be found in body weight decline, which was slightly but not significantly greater after repaglinide. Indeed, a body weight change in patients treated by a weight-stable diet could seem paradoxical. Nevertheless, patients lost weight at the start of study, because they did not follow good diet control before entry into the study. Thus, after adhering to 1,500 kcal/day for 4 months, both groups were stable but had lost 2 kg by the end of the study. Because body weight change can affect metabolic control as well as endothelial function, partial correlation between postprandial glucose and endothelial function parameters were also adjusted for BMI.

A potential limitation of our study might be the lack of pharmacological washout. Indeed, ethical principle does not allow pharmacological washout between repaglinide and glibenclamide treatments. Nevertheless, this problem is alleviated by the experimental design, which examines the cross-over effect between repaglinide and glibenclamide treatments, and by adjustment of the results for metabolic control score.

In conclusion, our study demonstrates that repaglinide treatment, through good control of postprandial glucose levels, improves endothelial function and decreases oxidative stress in type 2 diabetic patients. Thus, our data might be useful for a preventive treatment of endothelial dysfunction in type 2 diabetic patients.

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