Effect of Diacerein on Insulin Secretion and Metabolic Control in Drug-Naïve Patients With Type 2 Diabetes

A randomized clinical trial

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OBJECTIVE—To assess the effect of diacerein on insulin secretion and metabolic control in drug-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—A randomized, double-blind, placebo-controlled clinical trial was carried out in 40 drug-naïve adult patients with type 2 diabetes. A metabolic profile including interleukin (IL)-1β, tumor necrosis factor-α, IL-6, and fasting insulin levels was carried out before the intervention and 2 months afterward. A hyperglycemic-hyperinsulinemic clamp technique was performed to assess the phases of insulin secretion and insulin sensitivity. After randomization, 20 patients received diacerein (50 mg once daily) for the first 15 days and twice daily for 45 additional days. The remaining patients received placebo. Intra- and intergroup differences were calculated by Wilcoxon signed rank and Mann-Whitney *U* tests.

RESULTS—There were significant increases in first (102 ± 63 vs. 130 ± 75 pmol/L; $P < 0.01$), late (219 ± 111 vs. 280 ± 135 pmol/L; $P < 0.01$), and total insulin (178 ± 91 vs. 216 ± 99 pmol/L; $P < 0.01$) secretions without changes in insulin sensitivity after diacerein administration. There were significant decreases in fasting glucose (7.9 ± 1.4 vs. 6.8 ± 1.0 mmol/L; $P < 0.01$) and in A1C levels (8.3 ± 1.0 vs. 7.0 ± 0.8%; $P < 0.001$) after diacerein administration. There were no significant changes after placebo administration in the above-mentioned evaluations.

CONCLUSIONS—Insulin secretion increased and metabolic control improved after diacerein administration in drug-naïve patients with type 2 diabetes.

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It has been suggested that several epigenetic factors are involved in the pathogenesis of type 2 diabetes; however, its development is at least partially a direct consequence of obesity (1,2). Obesity is associated with a low-grade chronic inflammatory state, which to a large extent emanates from adipose tissue. With its secretion of bioactive molecules, this may have an effect on insulin sensitivity in the liver and peripheral tissues as well as on insulin secretion, with a negative impact on the cardiovascular system (3,4). Some cytokines, in particular, tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β, are involved in apoptosis of β-cells, decreasing insulin secretion with the consequent hyperglycemia (4,5).

Diacerein is a medication used frequently in the treatment of some articular diseases as a result of its effect on the inflammatory process (6,7). Diacerein decreases cytokine concentrations, in particular, TNF-α and IL-1β, with an unknown mechanism of action (7,8). Therefore, if diacerein is prescribed for obese patients with type 2 diabetes, it may decrease cytokines, increase insulin secretion and probably insulin action, and thereby improve glucose control.

The aim of this study was to assess the effect of diacerein on insulin secretion and metabolic control in drug-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A randomized, double-blind, placebo-controlled clinical trial was carried out in 40 drug-naïve adults (40–60 years of age) with type 2 diabetes with <6 months since diagnosis. They were overweight or obese (BMI 25.0–34.9 kg/m^2), had fasting glucose levels between 7.0 and 11.1 mmol/L, and had A1C levels between 7 and 9%. The study protocol was reviewed and approved by the hospital-based ethics committee, and written informed consent was obtained from all volunteers. Subjects were selected from the same residential area and socioeconomic status. No participant was excessively sedentary or participated in heavy physical activity. All individuals were nonsmokers. Their body weight was stable for at least 3 months before the study. Blood pressure was <130/80 mmHg. None of the subjects had a personal history of hepatic, renal, or coronary artery disease. Subjects denied use of any medications known to affect metabolism during the previous 6 months.

All patients received general recommendations about their medical nutritional therapy and were instructed to not modify their usual forms of exercise. Before testing, an isocaloric diet of at least 250 g of carbohydrates per day was given for 3 days. Women were in the first phase of their menstrual cycle (3–8 days).

Tests, before and 2 months after the pharmacological intervention, were performed at 8:00 A.M. after a 10- to 12-h overnight fast. Weight and height were recorded with the subjects wearing light clothing and without shoes. Height was measured and rounded off to the nearest centimeter with the subjects standing. BMI was calculated as weight (kg) divided by height (m^2). Waist circumference was

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taken at the midline between the highest point of the iliac crest and the lowest rib in the midaxillary line. Blood pressure was evaluated by the investigator after a 5-min resting period with the individual sitting in a chair and determined using a standard mercury sphygmomanometer. Systolic and diastolic blood pressures were based on Korotkoff phases I and V, respectively. Venous blood was obtained with the subject supine in a quiet room. Blood was allowed to clot for 30 min at room temperature and then centrifuged. The resulting serum was placed into two aliquots. The first one was immediately used for the measurement of serum glucose, A1C, total cholesterol (TC), HDL cholesterol (HDL-C), and triglycerides (TGs). The second aliquot was frozen at −20°C for measurement of IL-1β, TNF-α, IL-6, and fasting insulin levels within the following 30 days. A hyperglycemic-hyperinsulinemic clamp technique was performed to assess the phases of insulin secretion and insulin sensitivity (9,10). Briefly, two venous accesses were installed: the first one retrograde over some of the veins of the hand through a 19-gauge butterfly catheter for taking samples during the test. The hand was wrapped in a thermal pillow to achieve a local temperature >40°C to arterialize the blood. The second access was installed on the contralateral arm with a 19-gauge catheter. A 20% dextrose infusion was initiated: a priming dose for 14 min equivalent to 240 mg/kg body wt followed by a maintenance dose based on body weight, basal glucose, and the glucose required throughout the test (6.9 mmol/L above basal value). At 2, 4, 6, 8, and 10 min, 5 mL of blood was taken and after that, at every 10 min until 120 min for insulin determination. At 5-min intervals, we took an additional 1.5-mL blood sample for glucose determination to calculate the estimate of glucose metabolism and to be able to adjust the rate of dextrose infusion. At the end of the test (120 min), dextrose infusion was maintained for 30 min as a precaution to avoid hypoglycemia. With the above-mentioned results and using a calculator program, first (0–10 min) and late (10–120 min) phases of insulin secretion as well as total insulin concentration (0–120 min) were calculated, and total glucose metabolism was used to evaluate insulin sensitivity.

The allocation was concealed and done by simple randomization with a closed envelope that contained a letter *A* or *B*. After randomization, 20 patients received diacerein (Representaciones e Investigaciones Médicas, SA de CV, Mexico City, Mexico) (50 mg once daily during the first 15 days and twice daily for 45 additional days). The other 20 subjects received placebo in the same pharmacological presentation for 60 days.

Serum glucose was determined by the glucose-oxidase technique (Analox Instruments Ltd., London, U.K.) with an intra- and interassay coefficient of variation <1%. A1C levels were measured using 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. Serum lipid levels (TC, HDL-C, and TG) were measured enzymatically. In particular, HDL-C was assessed after selective precipitation of non-HDL-C fractions. Determinations were performed with commercially available equipment (Ortho-Clinical Diagnostics, Rochester, NY) with an intra- and interassay coefficient of variation <3%. If TG levels were <4.4 mmol/L, LDL cholesterol (LDL-C) was estimated by the Friedewald formula (LDL-C = TC − HDL-C − TG/5) and VLDL cholesterol (VLDL-C) by TG/5. ELISA was used to measure IL-1β, TNF-α, and IL-6 concentrations (Bender MedSystems, Burlingame, CA) with an intra- and interassay coefficient of variation for all (<3.5 and <6.7%, respectively). Insulin concentrations were measured with 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.

Statistical analyses

Sample size was calculated by means of a formula for clinical trials (11) with a statistical confidence of 95%, statistical power of 80%, SD for A1C of 1.5%, and an expected difference of at least 1.5% of A1C between groups, obtaining a total of 20 patients for each group that included 20% of expected loss. With insulin secretion, the calculation of sample size was smaller. Values were converted to Système International units and presented as mean ± SD. Primary end points were considered first, late, and total insulin secretion phases after the intervention, as well as fasting glucose and A1C levels. Intra- and intergroup differences were calculated by Wilcoxon signed rank and Mann-Whitney *U* tests, respectively; $P \leq 0.05$ was considered significant.

RESULTS—All patients who were eligible after enrollment completed the 60 days of the pharmacological intervention, including 12 women and 8 men in the placebo group and 9 women and 11 men in the diacerein group ($P = 0.342$). There was no significant difference in age between groups (47.8 ± 5.2 vs. 47.5 ± 5.3 years, placebo and diacerein, respectively; $P = 0.820$). BMI at baseline was similar between groups (30.8 ± 2.4 vs. 30.6 ± 2.6 kg/m^2, placebo and diacerein, respectively; $P = 0.968$). There was no significant difference at baseline in waist circumference between groups in women (97 ± 9 vs. 101 ± 7 cm, placebo and diacerein, respectively; $P = 0.850$) and in men (112 ± 12 vs. 106 ± 9 cm, placebo and diacerein, respectively; $P = 0.310$). There were no significant differences at baseline in systolic (120 ± 7 vs. 117 ± 10 mmHg, placebo and diacerein, respectively; $P = 0.209$) and diastolic (78 ± 6 vs. 77 ± 7 mmHg, placebo and diacerein, respectively; $P = 0.892$) blood pressures between groups. There were no significant changes after pharmacological intervention in the above-mentioned evaluations. No patient had TG levels >4.4 mmol/L.

Table 1 shows laboratory measurements at baseline and after pharmacological intervention in both groups. Significant decreases in fasting glucose, A1C, TNF-α, and IL-1β concentrations with a tendency ($P = 0.064$) in VLDL-C, as well as significant increases in first, late, and total insulin secretions after diacerein administration, were observed.

There were significant changes from baseline to the end of the study in fasting glucose (0.6 vs. −1.1 mmol/L, placebo and diacerein, respectively; $P = 0.005$), A1C (0.1 vs. −1.3%, placebo and diacerein, respectively; $P < 0.001$), TGs (0.1 vs. −0.3 mmol/L, placebo and diacerein, respectively; $P = 0.015$), VLDL-C (0.0 vs. −0.1 mmol/L, placebo and diacerein, respectively; $P = 0.007$), TNF-α (−0.3 vs. −4.5 pg/mL, placebo and diacerein, respectively; $P < 0.001$), and IL-1β (−0.8 vs. −7.5 pg/mL, placebo and diacerein, respectively; $P = 0.003$), as well as significant increases in first (6 vs. 31 pmol/L, placebo and diacerein, respectively; $P < 0.001$), late (−9 vs. 60 pmol/L, placebo and diacerein, respectively; $P = 0.001$), and total (−4 vs. 37 pmol/L, placebo and diacerein, respectively; $P = 0.008$) insulin secretions.

Gastrointestinal symptoms (9 vs. 13 patients, placebo and diacerein groups, respectively; $P = 0.204$) and headache

Table 1—*Laboratory measurements at baseline and after the pharmacological intervention*

	Placebo		Diacerein	
	Baseline	60 Days	Baseline	60 Days
Fasting glucose (mmol/L)	7.8 ± 1.0	7.8 ± 0.9	7.9 ± 1.4	6.8 ± 1.0†
A1C (%)	7.9 ± 0.6	8.1 ± 0.8	8.3 ± 1.0	7.0 ± 0.8†
Total cholesterol (mmol/L)	4.3 ± 0.6	4.5 ± 0.5	4.7 ± 1.0	4.5 ± 0.8
HDL cholesterol (mmol/L)				
Male	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Female	1.2 ± 0.2	1.2 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
LDL cholesterol (mmol/L)	2.4 ± 0.5	2.6 ± 0.4	2.6 ± 0.9	2.6 ± 0.5
TGs (mmol/L)	1.8 ± 0.6	1.8 ± 0.3	2.2 ± 0.8	1.9 ± 0.8
VLDL cholesterol (mmol/L)	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.3 ± 0.1
TNF-α (pg/mL)	16.5 ± 4.1	16.2 ± 2.5	18.2 ± 3.9	13.8 ± 2.7*
IL-1β (pg/mL)	21.6 ± 4.7	21.2 ± 3.2	26.4 ± 6.6	17.9 ± 2.7*
IL-6 (pg/mL)	4.0 ± 0.7	4.0 ± 0.7	3.6 ± 0.7	3.4 ± 0.8
M (mg/kg/min)	3.4 ± 0.8	3.3 ± 0.5	3.6 ± 0.8	3.7 ± 0.8
Fasting insulin (pmol/L)	85 ± 43	72 ± 21	86 ± 40	89 ± 40
First phase IS (pmol/L)	91 ± 48	90 ± 36	102 ± 63	130 ± 75*
Late phase IS (pmol/L)	215 ± 152	175 ± 79	219 ± 111	280 ± 135*
Total IS (pmol/L)	165 ± 118	138 ± 61	178 ± 91	216 ± 99*

Data are mean ± SD. M, glucose metabolized (calculated with the clamp technique); IS, insulin secretion (calculated with the clamp technique). †$P < 0.001$ between baseline and 60 day evaluation. *$P < 0.01$.

(6 vs. 5 patients, placebo and diacerein groups, respectively; $P = 0.723$) were the most common adverse events after the pharmacological intervention. Patients reported no infection during the study period.

CONCLUSIONS—A low-grade chronic inflammatory state is present in obesity and diabetes (3). This fact may be a result of the participation of cytokines in defects of insulin secretion and insulin sensitivity observed in those patients (4,5).

As expected, IL-1β and TNF-α levels decreased after diacerein administration, resulting in increases in first, late, and total insulin secretions with the consequent improvement of glycemic control in this group of patients.

Both cytokines IL-1β and TNF-α are involved in β-cell apoptosis and in failure of insulin secretion (4,5). In accordance with most, but not all, publications in the medical literature due to differences in study characteristics, the decrease of cytokines with several pharmacological interventions such as anakinra (12,13), etanercept (14,15), nonsteroidal anti-inflammatory drugs (16,17), or thiazolidinediones (18,19) is related to improvement in β-cell function and insulin secretion.

With our study design, insulin sensitivity was not improved and IL-6 concentrations were not decreased with diacerein administration; however, we cannot exclude the fact that a longer intervention time could modify them. A transient dose-dependent effect of diacerein on local IL-6 production has been found (7). Postprandial glucose was not measured, and this measurement is, in general, considered a component of glycemic control; therefore, it may represent another limitation of the investigation.

Minimal reductions of TG and VLDL-C levels observed in our patients may be due to changes in glucose control.

Symptomatic hypoglycemia was not reported by any of our study patients, and none of the subjects interrupted treatment as a result of any adverse event. Concern about the inhibition of innate immunity and the increase of infections appears not to be justified because no significant increase in the incidence of infectious diseases with diacerein has been reported (20). In our study, this adverse event was not observed, despite the fact that the study was not designed for such purpose.

Our results suggest that diacerein administration may have a potential usefulness in the treatment of type 2 diabetes as a possible result of inhibition of IL-1β and TNF-α. Further studies are needed to test long-term administration, as well as to explore its use in combination with other pharmacological options and in patients with other characteristics.

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M.G.R.-Z. researched data and contributed to discussion. M.G.-O. designed the study, researched data, contributed to discussion, and wrote the manuscript. E.M.-A. researched data, contributed to discussion, and reviewed and edited the manuscript. J.A.R.-C. researched data and contributed to discussion. R.G.-L. and N.J.S.-H. researched data.

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