Originales

Effect of metformin on cardiovascular risk factors in obese type 2 diabetic patients

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Background. Obese patients with type 2 diabetes mellitus often are in poor glycaemic control. Weight gain, hyperlipidemia and hypertension accompain insulin therapy in these patients.

Objective. The aim of our study was to evaluate the effect of metformin on these parameters in obese type 2 diabetic patients previously treated with other therapies.

Design. A group of 78 type 2 diabetic outpatients in poor glycaemic control (HbA_{1c} > 7.5%) and overweight (BMI > 25) were analyzed prospectively. All patients were treated with metformin during three months in a step up dosage schedule. Anti-hypertensive and anti-lipid therapy remained unchanged during the study. All patients remained with the same dietary intake (1.500 calories) and exercise.

Results. A decrease in basal glucose (24.8%) (173 ± 29.8 mg/dl vs 134.8 ± 21.4 mg/dl; p < 0.001) and HbA1c levels (15.4%) (8.5 ± 1.4% vs 7.2 ± 1.1%; p < 0.001) were achieved with a decrease in the number of hypoglycaemias, dose of insulin (39%) (0.39 ± 0.12 UI/kg/day vs 0.29 ± 0.08 UI/kg/day; p < 0.005) and dose of sulfonylurea (gliclazide) (46%) (107.5 ± 119 mg/day vs 57.5 ± 92 mg/day; p < 0.001). UP to 25.6% of the patients stopped the previous drug therapy achieving good control with metformin alone (HbA1c < 6.5%). Cardiovascular risk factors improved with a significant decrease in LDL (12.9%) (147.3 ± 33.7 mg/dl vs 128.8 ± 28.6 mg/dl; p < 0.05), total cholesterol (8.5%) (224.6 ± 126.9 mg/dl vs 205.3 ± 34.5 mg/dl; p < 0.01), triglycerides levels (13.7%) (139.8 ± 57 mg/dl vs 120.1 ± 42.7 mg/dl; p < 0.001) without changes in HDL. Blood pressure improved, with a significant decrease in systolic (5%) (137.9 ± 27 mmHg vs 130.7 ± 20; p < 0.01) and diastolic (9.4%) (85 ± 10 mmHg vs 79.3 ± 14 mmHg; p < 0.01) pressure. No patient dropped out the treatment due to side effects and the weight did not change.

Conclusions. In summary, the addition of metformin improved glycaemic, lipid and blood pressure control in obese diabetic type 2 patients in por glycemic control with a low incidence of side effects.

Key words: Metformin. Type 2 diabetes mellitus. Obesity.

EFECTO DE LA METFORMINA EN LOS FACTORES DE RIESGO CARDIOVASCULARES EN PACIENTES OBESOS CON DIABETES TIPO 2

Introducción. Los pacientes con diabetes mellitus tipo 2 y obesidad con frecuencia presentan un mal control glucémico. El exceso de peso, la hiperlipemia y la hipertensión a menudo acompañan a la terapia con insulina en estos pacientes.

Objetivo. El objetivo principal de nuestro estudio fue evaluar el efecto de la metformina en pacientes obesos con diabetes tipo 2 previamente tratados con otras terapias hipoglucemiantes.

Diseño. Se estudiaron de manera prospectiva un grupo de 78 diabéticos tipo 2 con mal control glucémico (hemoglobina glucosilada [HbA_{1c}] > 7,5%) y sobrepeso (índice de masa corporal [IMC] > 25). Todos los pacientes recibieron metformina durante 3 meses en un esquema ascendente. La terapia antihipertensiva e hipolipemiante permaneció invariable durante el estudio; asimismo, todos los pacientes recibieron una dieta de 1.500 calorías y realizaron su programa de ejercicios habitual.

Resultados. Se alcanzó un descenso en los valores de glucosa (24,8%) (173,1 ± 29,8 mg/dl frente a 134,8 ± 21,4 mg/dl; p < 0,001) y HbA_{1c} (15,4%) (8,5 ± 1,4% frente a 7,2 ± 1,1%; p < 0,001), con una disminución en el número de hipoglucemias y de la dosis recibida de insulina (39%) (0,39 ± 0,12 U/kg/día frente a 0,29 ± 0,08 U/kg/día; p < 0,005) y sulfonilurea (gliclazida) (46%) (107,5 ± 119 mg/día frente a 57,5 ± 92 mg/día; p < 0,01). A un 25,6% pacientes se les suspendió la medicación previa presentando un buen control glucémico sólo con metformina (HbA_{1c} < 6,5%). Los factores de riesgo cardiovascular mejoraron, con un descenso en los valores de lipoproteínas de baja densidad (LDL) (12,9%) (147,3 ± 33,7 mg/dl frente 128,8 ± 28,6 mg/dl; p < 0,05), colesterol total (8,5%) (224,6 ± 26,9 mg/dl frente a 205,3 ± 34,5 mg/dl; p < 0,01) y triglicéridos (13,7%) (139,8 ± 57 mg/dl frente a 120,1 ± 42,7 mg/dl; p < 0,001), sin cambios en los valores de lipoproteínas de alta densidad (HDL). La presión arterial mejoró, con un descenso significativo de la presión arterial sistólica (5%) (137,9 ± 27 mmHg frente a 130,7 ± 20 mmHg; p < 0,01) y diastólica (9,4%) (85 ± 10 mmHg frente a 79,3 ± 14 mmHg; p < 0,01). Durante el estudio, el peso no cambió y ningún paciente abandonó por efectos secundarios.

Conclusiones. La metformina mejora el control glucémico, lipídico y de presión arterial en pacientes obesos con diabetes tipo 2 y mal control metabólico, con una baja incidencia de efectos secundarios.

Palabras clave: Metformina. Diabetes mellitus tipo 2. Obesidad.

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Type 2 diabetes mellitus is more prevalent in obese patients or those will positive family history. Modification of dietary intake and weight loss improve glycaemic control. However, glycaemic goals are not achieved in some patients with dietary restriction alone. Sulfonylurea drugs have been the most popular drug therapy for obese type 2 diabetes patients[1]. Because, these patients are insulin resistant, high doses of sulfonylurea or insulin are required to achieve adequate glycaemic control. However, insulin therapy in these patients is associated with weight gain, which in turn, can worsen glycaemic and lipid control.

The approval of metformin for treating patients with type 2 diabetes provides an additional approach to obese diabetic patients[2-3]. The aim of our study was to evaluate the effect of metformin on glycaemic, lipid and blood pressure control in obese type 2 diabetic patients previously treated with other therapies.

MATERIAL AND METHODS

Study subjects

A group of 78 type 2 diabetic outpatients in poor glycaemic control ($HbA_{1c} > 7.5\%$) and overweight (BMI > 25) were prospectively studied. The following variables were specifically recorded: age, years of diabetes duration, pharmacological treatment of diabetes (dose and drug), smoking habit.

Procedure

All patients, previously receiving insulin and sulfonylurea (with a stabillization period 3 months before metformin treatment) were treated with metformin during three months in a step up dosage schedule: first week 425 mg b.i.d., second week 850 mg b.i.d., after the third week with 850 mg t.i.d. Weight, blood pressure, HbA_{1c}, number of ambulatory hypoglycaemic events, fasting glucose, albuminuria, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were measured initially and after three months of treatment with metformin. The decrease in previous drug therapy was assessed as well as the side effects appreciated during the study period. During the study and in the previous three months the patients had the same dietary intake (1,500 calories per day) and physical activity, information that was monrey monitored by a nurse. A decrease in drug dosage was recommended when pre-prandial blod glucose reached < 110 mg/dl. Antihypertensive (7.7% of patients) and anti-lipid therapy (10.3%) remained unchanged during the treatment.

Chronic diabetic complications assessment

Coronary heart disease was clinically assessed. The presence of any of the following was considered suggestive of coronary heart disease: T wave inversion, ST segment depression and Q waves. In patients with signs or symptoms of cerebrovascular a CNS computerized tomography was performed. Peripheral vascular disease was clinically defined by the presence of intermittent claudication, absent of weakened peripheral pulses, or both. Retinopathy was documented by standard fundus examination, and diagnosed on the observation of microaneurysmas, venous dilatation, cotton-wool, spots, neovascularization or hemorrhages. Clinical neuropathy was defined by an abnormal neurologic examination, consistent with the presence of peripheral sensorimotor neuropathy. Nephropathy was defined by the presence of urinary albumin excretion of 30 mg or more per 24 hours, and a rate of creatinine clearance below 70 ml per minute per 1.73 m².

Number of hypoglycaemic events (glucose level < 50 mg/dl with typical symptoms) was assessed from the blood glucose controls performed by the patients (nine controls per week per patient in average). The percentage of patients with one or more hypoglycaemic episode during the study (3 months) was assessed.

Assays

Fasting blood samples were drawn for measurement of glucose, cholesterol, triglyceride, lipid fractions and HbA_{1c}. 24-h urine collection was used to measure creatinine clearance and micro-albuminuria.

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y. USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfatemagnesium. LDL cholesterol was calculated using the Friedewald formula.

Hemoglobin A1c levels were measured by using highpressure liquid chromatography. Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, California).

Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged.

Statistical analysis

The results were expressed as mean ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, paired Student's-t test. Nonparametric variables were analyzed with the Friedman and Wilcoxon tests. Qualitative variables were analyzed with the chi-square test, with Yates correctin when necessary, and Fisher's test. A p-value under 0.05 was considered statistically significant.

RESULTS

Seventy-eight patients gave informed consent and were enrolled in the study. Mean age was 62.4 ± 12.6 years, mean diabetes duration 8.7 ± 8.4 years. And mean BMI 32.7 ± 6.5. Baseline characteristics (demographic data and chronic complications) are presented in table 1. All patients had normal liver function, and nephropathy, when present was in the form of microabluminuria, with normal serum creatinine. The mean dose of metformin was 1968,4 ± 570 mg per day, in a t.i.d. final schedule.

Table 2 shows changes from baseline in glycaemic control. A decrease in basal glucose (24.8%) and HbA_{1c}

TABLE 1. Clinical and epidemiological characteristics of the study subjects

Characteristics	Values
Age (years)	62.4 ± 12.6
Sex (male/female)	38/40
Diabetes duration (years)	8.7 ± 8.4
BMI (kg/m²)	32.7 ± 6.5
Smoking habit	51.3%
Insulin treatment	56.4%
Sulfonylurea treatment	43.6%
Coronary heart disease	2.6%
Cerebro-vascular disease	2.6%
Peripheral vascular disease	5.3%
Retinopathy	25.6%
Nephropathy	12.8%
Neuropathy	10.2%

TABLE 2. Changes in glycaemic control, weight and drug dosage

Factors	Initial	3 months
Fasting glucose (mg/dl)	173.1 ± 29.8	134.8 ± 21.4**
HbA1c (%)	8.5±1.4	7.2 ± 1.1**
Insulin dose (UI/day)	33.6 ±15	20.6 ± 18.4*
Sulfonylurea (mg/day)	107.5 ± 119	57.5 ± 92**
Hypoglycaemias (% of patients)	24.1%	0%**
Weight (kg)	85.4 ±12.5	84.7 ± 12.3

*(p < 0.05); **p < 0.001 (initial versus three months).
Hypoglycaemias (% of patients with an episode of symptomatic hypoglycaemia [< 50 mg/dl] in three months).

TABLE 3. Other cardiovascular risk factors

Factors	Initial	3 months
Total-cholesterol (mg/dl)	224.6 ± 26.9	205.3 ± 34.5*
HDL-cholesterol (mg/dl)	48.5 ± 26.1	45.8 ± 11.3
LDL-cholesterol (mg/dl)	147.3 ± 33.7	128.8 ± 28.6*
Triglycerides (mg/l)	139.8 ± 57	120.1 ± 42.7**
Systolic pressure (mmHg)	137.9 ± 27	130.7 ± 20*
Diastolic pressure (mmHg)	85 ± 10	79.3 ± 14*
Microalbuminuria (mg/day)	10.9 ± 17	10.7 ±16

*$p < 0.01$; **$p < 0.001$ (initial versus three months).

(15.4%) were achieved at the end of the study ($p < 0.05$). These improvements in diabetes control were accompanied with a decrease in the rate of hypoglycaemias (100%), dose of insulin (39%) and dose of sulfonylurea (gliclazide) (46%), a total of (25.6%) patients stopped the previous treatment achieving good glycemic control with metformin alone (HbA$_{1c}$ < 6.5%). Changes in microabluminuria were not detected during the study period.

Table 3 shows the improvement in the other cardiovascular risk factors with a significant decrease ($p < 0.05$) in LDL-cholesterol (12.9%), total cholesterol (8.5%) and triglycerides (13.7%) without changes in HDL. Blood pressure improved, with a significant decrease in systolic (5%) and diastolic (9.4%) pressure.

The same significant improvement in lipid and glycaemic control was detected in insulin and sulfonylurea subgroup.

The side effects of metformin were gastrointestinal (7.7%), one patient had nausea in the first week of treatment which dissappeared in the second week, and two patients had diarrhea with abdominal pain which disapeared with a dose decreased. No patient dropped out of the study.

DISCUSSION

A lot of reports have discussed the effects of metformin on peripheral insulin sensitivity and insulin action in patients with type 2 diabetes mellitus and obesity[4-8]. The use of metformin alone or in combination with sulfonylurea or insulin has been shown to improve glycaemic control in obese patients with type 2 diabetes mellitus[9-10]. Blood lipid abnormalities, hypertriglyceridemia and hypercholesterolemia, have also improved with metformin in obese diabetic patients[8-9]. Salt-induced hypertension has been attenuated with this drug in experimental animals[11].

Our study reinforced some data about the use of metformin, with the limitation, of non randomized controlled design. First, glycaemic control improved significantly in both sulfonylurea and insulin patients, with a decrease of previous dose, a decrease in HbA$_{1c}$ and fasting glucose levels. This reduction in HbA$_{1c}$ concentrations was smaller than that reported in other studies[6,10], who demonstrated a reduction of 1.84 and 2.5 points, whereas in our study the decrease was 1.3 points. Although HbA$_{1c}$ levels did not reach good levels (< 7%), metformin as an adjunct therapy seems to improve glycaemic control with less hypoglycaemic episodes than primary therapy (insulin and sulfonylurea). Other authors have reported a 25-25.4%[6,12], reduction in insulin dosage with the addition of metformin. We consider that the most reasonable cause for the inability to achieve good HbA$_{1c}$ concentrations is due to the short, our study was only 3 months.

The clinical benefits of adding metformin to an insulin or sulfonylurea therapy are related to the daily amount of primary therapy, to an improvement in glycaemic control, and the avoiding of weight gain[13,14].

An important secondary point is weight gain associated with improved glycaemic control in diabetic patients under intensified therapy. This effect has been reported both in DCCT[15] and UKPDS[13]. In our study, patients receiving metformin improved glydaemic control without increasing their weight, and this must be a main objective in intensive treatment.

Third, an improvement in additional cardiovascular risk factors was observed in our study. In other studies, metformin hase decreased low-density cholesterol[16-17], postprandial hyperlipemia[18], plasma free fatty acid oxidation[19] and plasma free fatty acids levels[20]. The magnitude of the decrease in plasma triglyceride concentrations is related to the fasting triglyceride levels and is independent of changes in the plasma glucose levels[16]. It also reduced triglyceride levels in nondiabetic patients with hypertriglyceridemia[21]. High-density cholesterol levels either did not change or increased slightly after metformin therapy[22]. Our data showed all these previous changes in lipoprotein levels. Blood pressure improved in our patients, and in experimental data, metformin improved arterial baroreflex function[23], decreased calcium influx[24], and showed a slightly decrease in diastolic pressure[25]. Our study is the first in the literature to show an improvement in blood pressure with this drug.

The side effects in our studies were only gastrointestinal. Nausea and diarrhea were trasient and occurred at the initiation of therapy. Other side effects refered in previous studies such as anorexia, hunger, bloating and abdominal pain did not appear. During the treatment metformin was well tolerated and the incidence of side effects was low[26], without any episode of lactic acidosis.

In summary, metformin was very effective in improving glycaemic, lipid and blood pressure control in obese diabetic type 2 patients, with a low incidence of side effects.

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