ACARBOSE IMPROVES INDIRECTLY BOTH INSULIN RESISTANCE AND SECRETION IN OBESE TYPE 2 DIABETIC PATIENTS

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SUMMARY - Background: Acarbose is an oral antidiabetic mainly acting on postprandial blood glucose, inhibiting alaphaglucosidase. Through this mechanism, it could improve the peripheral insulin sensitivity and/or increase the insulin secretion. The aim of the present study is to assess the therapeutic efficacy of Acarbose in obese type 2 diabetic patients on both insulin resistance and insulin secretion.

Methods: 17 obese non insulin-dependent diabetic patients, well controlled with diet alone were randomized into 2 groups: acarbose (2 × 50 mg) or placebo during 16 weeks. A glucagon test allowed to evaluate insulin secretion before and after treatment as well as a triple test (glucose-insulin-somatostatin) with indirect calorimetry allowed to evaluate insulin sensitivity.

Results: A significant improvement in post-prandial plasma glucose was detected only in the Acarbose group (8.0 ± 0.5 mmol/l before vs 6.5 ± 0.5 mmol/l after, p < 0.05). Basal C-peptide secretion was similar between groups and remained unchanged after treatment. However, stimulated insulin secretion was significantly increased by 30%, p < 0.05, in the Acarbose group while no change was detected in the placebo group. Interestingly, the group receiving Acarbose disclosed a 15% reduction in insulin resistance (15.0 ± 1.8 mmol/l before vs 12.8 ± 1.4 mmol/l after).

Conclusions: Our results show that a treatment with Acarbose is efficient even in diabetic patients presenting a good glucose control without any other associated treatment. By decreasing post-prandial blood glucose, acarbose improves both insulin sensitivity and secretion.

Key-words: acarbose, insulin resistance, insulin secretion.

RE´ SUM´E - L’Acarbose améliore indirectement l’insulino-résistance et la sécrétion d’insuline chez le diabétique de type 2 obèse.

Contexte : L’Acarbose est un antidiabétique oral agissant principalement sur les glycémies post-prandiales en inhibant les alphaglucosidases. Par ce mécanisme, il pourrait améliorer la sensibilité périphérique à l’insuline et/ou augmenter la réponse insulinique. Le but de cette étude est d’évaluer l’efficacité de l’Acarbose chez des patients obèses diabétiques sur la sécrétion insulinique et sur la résistance à l’insuline.

Méthodes : Nous avons étudié 17 patients diabétiques non insulinodépendants, obèses randomisés en deux groupes Acarbose (2x50 mg), ou placebo pendant 16 semaines. Un test au glucagon a permis d’évaluer, avant et après traitement, la sécrétion insulinique et un triple test (glucose-insuline-somatostatine) avec calorimétrie indirecte a permis d’évaluer la sensibilité à l’insuline.

Résultats : Après traitement d’Acarbose, les glycémies post-prandiales sont améliorées significativement (8,0 ± 0,5 mmol/l avant vs 6,5 ± 0,5 mmol/l après p < 0,05). La sécrétion basale de C-peptide est identique dans les deux groupes et ne change pas après traitement. Par contre, la sécrétion insulinaire stimulée augmente significativement de 30 % (p < 0,05) après traitement d’Acarbose alors qu’elle ne change pas dans le groupe placebo. De plus, le groupe traité par l’Acarbose montre également une amélioration de la sensibilité à l’insuline de 15 % (15,0 ± 1,8 mmol/l avant vs 12,8 ± 1,4 mmol/l après).

Conclusions : Nos résultats montrent qu’un traitement d’Acarbose est efficace même chez des patients diabétiques présentant un bon contrôle glycémique sans autre traitement associé. L’Acarbose en diminuant les glycémies post-prandiales améliore la sécrétion d’insuline et la sensibilité à l’insuline.

Mots-clés : acarbose, résistance à l’insuline, sécrétion d’insuline.

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Acarbose is commonly used in Type 2 Diabetes therapeutic arsenal. Several clinical studies have confirmed its efficacy either as monotherapy or in combination with other oral hypoglycemic agents [1-5]. Alpha-glucosidase(s) enzymatic inhibition slows down carbohydrate absorption which, as a consequence, reduces post-prandial glycemic peaks and insulin responses [6]. Additionally, Acarbose also improves fasting blood sugar levels [7-11]. The latter phenomenon might be due to an improvement in peripheral insulin sensitivity and/or optimization of pancreatic beta-cell responsiveness. Both mechanisms are probably interrelated and secondary to glucotoxicity disappearance once post-prandial hyperglycemic peaks are corrected and hyperinsulinism is reduced [12-13].

Moreover, Acarbose has been shown to reduce insulin-resistance in impaired glucose tolerant (IGT) patients through glycemia reductions [14]; nevertheless, Acarbose effects on poorly controlled type 2 diabetes metabolism are not easy to elucidate due to the vicious interplay between glucotoxicity, insulin-resistance and finally, impaired/reduced insulin secretion [15, 16].

The aim of the present study is to assess the therapeutic efficacy of Acarbose in obese type 2 diabetic patients on metabolic control and peripheral insulin-resistance and insulin secretion parameters.

**MATERIALS AND METHODS**

**Design-Intervention**

The study was designed to be a double-blind randomized (placebo/control (Acarbose) prospective clinical trial.

**Patients**

Seventeen (N = 17) type 2 diabetes obese patients were selected among those belonging to the outpatient pool followed in our Division on a regular basis.

Inclusion criteria were a diagnosis of type 2 diabetes according to the ADA 1997 criteria/WHO 1987 criteria for the 24 ± 6 previous months, a stable body weight as well as capillary blood glucose (CBG) readings for 2 months prior to enrolment in the study.

All the study participants had previously been given the benefit of a two-week-in-hospital therapeutic educational programme aimed at improving their diabetes management skills, dietary knowledge and weight stabilization strategies [17].

Exclusion criteria concerned those patients with either uncontrolled type 2 diabetes, presence of micro/macro-vascular complications, treatment with insulin and/or other oral hypoglycaemic agents, dyslipidemia, hypertension and any drug known to affect insulin resistance/secretion.

Patients were thoroughly informed of the aims, set up and procedures involved in the study. An informed consent form was signed by all patients. The study protocol was approved by the Ethical Committee of the University Hospital Geneva.

According to the study design, patients were blind randomized into two groups (Acarbose and placebo) and therefore followed for sixteen weeks. Hence, patients received a rather low daily dosage: either a pill containing 50 mg of Acarbose (1 tab/day) or placebo (1 tab/day) for two weeks then 100 mg of Acarbose (2 tabs/day) or placebo (2 tabs/day) for the following 14 weeks. Home blood glucose monitoring was done 4 times per day at 7h00, 11h00, 17h00, 22h00.

**METHODS**

Reaven’s triple test was employed to measure insulin sensitivity [18]. Briefly, patients were fasted for 12 hours after which a triple intravenous infusion containing somatostatin (35 mcg/hour), insulin (25 mU/min) and glucose (7 mg/Kg of lean body mass/min) was started and ran for 180 minutes. Blood draws were performed each 10 minutes during the last hour of infusion (min 120-180) in order to check blood glucose (BG) levels. The mean of these 7 BG readings is known as the steady state plasma glucose concentration (SSPG) and is commonly accepted as a reliable measurement of insulin sensitivity.

**Methodology for body composition analysis**

Subcutaneous fat deposition was determined by skinfold thickness. Basal metabolic rate (BMR) was measured using indirect calorimetry. Carbohydrate and fat oxidation were assessed for 45 minutes prior to the triple infusion procedure and during its last hour (min 120-180) [19].

Glucagon test was employed to assess insulin secretion – through C-peptide endogenous secretion – both fasting and 6 minutes after the injection of 1 mg of Glucagon intravenously. Stimulated insulin secretion was reported as delta C-peptide ([stimulated C-peptide] – [basal C-peptide]).

**Statistical analysis**

Data belonging to both groups of patients before and after treatment were analysed using a two-way analysis of variance (2 way ANOVA). Results are expressed as x ± SEM. p < 0.05 is considered statistically significant.
Results

Table I depicts the anthropometric characteristics of both groups of patients. As shown, both groups disclosed a similar and stable body weight and body composition analysis at entry and by the end of the sixteen-week-trial.

Table II discloses the biologic characteristics of our participants. As seen, the degree of metabolic control was similar between groups before and after treatment (HbA1c = 6.8 ± 0.5% -Acarbose- vs 7.5 ± 0.6% -placebo-; p = NS). On the contrary, a significant improvement in post-prandial CBG readings was detected only in the Acarbose group (8.0 ± 0.5 mmol/L before vs 6.5 ± 0.5 mmol/L after; p < 0.05, Table II). Neither group disclosed a significant change in fasting CBG readings at the end of the study.

The lipid profiles were similar in both groups and remained unchanged at the end of the study.

Table III illustrates glucagon test results in both groups before and after treatment. Basal C-peptide secretion was similar between groups (1.2 ± 0.1 mmol/l Acarbose vs 1.5 ± 0.2 mmol/l placebo), and remained unchanged after treatment (1.3 ± 0.1 mmol/l Acarbose and 1.4 ± 0.1 mmol/l in placebo group). Stimulated insulin secretion was significantly increased (p < 0.05) in the Acarbose group (1.8 ± 0.1 mmol/l before and 2.2 ± 0.2 mmol/l after treatment) while no change was detected in the placebo groups at the end of the study (2.0 ± 0.3 mmol/l before and 18 ± 0.2 mmol/l after placebo treatment). The Delta C-peptide between stimulated-C-peptide during the glucagon test and the basal C-peptide was significantly increased by 3% p < 0.05 (Fig. 1).

Table II depicts the insulin-resistance index (SSPG) and Fasting Insulin SSPI and Glucose concentrations. Baseline peripheral insulin resistance (SSPG) was similar in both groups before treatment. Interestingly, the group receiving Acarbose disclosed a 15% improvement in insulin resistance (SSPG).

Table I. Anthropometric characteristics.

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<thead>
<tr>
<th></th>
<th>Acarbose (N = 9)</th>
<th>Control (N = 8)</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>6/3</td>
<td>3/5</td>
</tr>
<tr>
<td>Body weight (Kg)</td>
<td>103.8 ± 2.9</td>
<td>104.6 ± 2.9</td>
</tr>
<tr>
<td>BMI (Kg.m2)</td>
<td>36.1 ± 1.5</td>
<td>36.3 ± 1.6</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>37.9 ± 1.3</td>
<td>37.2 ± 1.5</td>
</tr>
<tr>
<td>Fat mass (Kg)</td>
<td>39.4 ± 1.9</td>
<td>39.0 ± 2.2</td>
</tr>
<tr>
<td>Lean mass (Kg)</td>
<td>64.5 ± 2.0</td>
<td>65.5 ± 1.9</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>142 ± 3</td>
<td>135 ± 6</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>84 ± 3</td>
<td>84 ± 2</td>
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</tbody>
</table>

Table II. Biological characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Acarbose (N = 9)</th>
<th>Control (N = 8)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8 ± 0.5</td>
<td>6.7 ± 0.3</td>
</tr>
<tr>
<td>FCBG (mmol/L)</td>
<td>7.1 ± 0.5</td>
<td>6.5 ± 0.4</td>
</tr>
<tr>
<td>PPCBG (mmol/L)</td>
<td>8.0 ± 0.5</td>
<td>6.5 ± 0.5*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.2 ± 0.4</td>
<td>5.4 ± 0.3</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.0 ± 0.3</td>
<td>1.8 ± 0.2</td>
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</table>
reduction in SSPG (15.0 ± 1.8 mmol/L – before- vs 12.8 ± 1.4 mmol/L – after-; p = NS) while SSPG was not modified in the placebo group (15.4 ± 1.4 mmol/L – before- vs 14.9 ± 1.0 mmol/L – after-; p = NS). Baseline glucose and insulin concentrations were similar in both groups and remained so after treatment. Baseline SSPI concentrations were similar in both groups and remained so after treatment. Table III depicts also basal and Reaven’s triple infusion, carbohydrate oxidation and fat oxidation rates. Carbohydrate oxidation rates appear to be similarly stimulated during the triple test in both groups.

**Table III.** Insulin resistance, carbohydrate and fat oxidation measured by the Reaven’s triple infusion.

<table>
<thead>
<tr>
<th></th>
<th>Acarbose (N = 9)</th>
<th>Control (N = 8)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>7.8 ± 1.2</td>
<td>7.3 ± 0.7</td>
</tr>
<tr>
<td>Basal Insulin (ng/L)</td>
<td>0.85 ± 0.17</td>
<td>0.90 ± 0.12</td>
</tr>
<tr>
<td>SSPG (mmol/L)</td>
<td>15.0 ± 1.8</td>
<td>12.8 ± 1.4</td>
</tr>
<tr>
<td>SSPI (ng/L)</td>
<td>2.6 ± 0.3</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>Basal CHO oxidation (mg/Kg/min)</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Stimulated CHO oxidation (mg/Kg/min)</td>
<td>1.7 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Basal Fat oxidation (mg/Kg/min)</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Inhibited Fat oxidation (mg/Kg/min)</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
</tbody>
</table>

**Fig. 1.** Insulin secretion measured during the glucagon’s test.
before and after treatment. Accordingly, fat oxidation was similarly inhibited in both groups during the triple test before and after treatment.

Regarding secondary adverse effects, 7 out of 9 patients in the Acarbose group reported gastro-intestinal complaints such as abdominal bulging, flatulence and aerophagia once Acarbose doses reached 2 × 50 mg/day; nevertheless, these side-effects disappeared gradually between the 4th and 12th week of treatment. No drop out was recorded. Treatment compliance was monthly monitored by counting the remaining number of pills.

**Discussion**

Our results confirm a short-term (4 months) treatment with Acarbose allows a significant improvement in post-prandial glycemic peaks in otherwise well-controlled obese type 2 diabetes patients. This is in agreement with the UKPDS dataset [20] in which Acarbose efficacy was demonstrated in well controlled type 2 diabetes patients.

Our patients had indeed good glycemic control (HbA1c ranged between 6.2%-8.0%). The latter had been achieved through participation in a two-week-in-hospital therapeutic educational programme aimed at improving their diabetes management skills, dietary knowledge and weight stabilization strategies.

Acarbose benefits were not limited to the post-prandial phase. Hence, fasting CBG values did also improve in the Acarbose group although the observed differences did not reach statistical significance. Thus, 6 out of 9 patients in the Acarbose group disclosed fasting CBG values under 7 mmol/L.

The post-prandial glycemic improvement can be taken into account for the 30% significant improvement in stimulated C-peptide secretion (p < 0.05) in the Acarbose group. Hence, the observed improvement in insulin secretion is likely to be secondary to diminished glucotoxicity on pancreatic beta cells [14-16]. Chiasson et al. also studied the effect of Acarbose on insulin sensitivity using the same method. They demonstrated similar results in IGT patients with a significant improvement in insulin sensitivity.

Additionally no weight gain or increment in body fat composition was observed in the Acarbose group in our study. This finding in a shorter period of time is again in agreement with those of the UKPDS [20]. When compared to sulfonylureas at comparable hypoglycaemic efficacy, Acarbose does not carry along weight gain, which is almost invariably met in type 2 diabetes treated with sulfonylureas.

Some authors have described interesting effects of Acarbose on lipid profiles [1, 15]. Our study population did not disclose a particular benefit of Acarbose on them. Moreover, patients with significant dyslipidemia were excluded and the study design did not properly assess the issue of post-prandial hyperlipemia.

Taken into account the rapid onset of endothelial dysfunction in type 2 diabetes, the deleterious effect of post-prandial glucose excursions on macrovascular disease and the high prevalence of the latter in the diabetic population, Acarbose holds a key role with its combined properties in the type 2 diabetes therapeutic armamentarium.

Acarbose does significantly improve post-prandial glycaemic excursions (p < 0.05), lowers insulin resistance (SSPG) by 15% and significantly improves beta cell secretion by 30% (p < 0.05) without weight gain as previously demonstrated by Chiasson et al. [14].

Finally, our results disclose Acarbose’s efficacy as monotherapy in otherwise well controlled obese type 2 diabetes patients. Thus, Acarbose finds its multiple metabolic advantages in being prescribed early in the natural history of type 2 diabetes when only post-prandial BG values are elevated. Unfortunately, oral anti-diabetic agents are introduced well too late in clinical practice, once beta cell gluco-toxicity has paid its toll.

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