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Metformin plus low glimepiride doses, improve significantly HOMA(ir) and HOMA(¿cell) without hyperinsulinemia in patients with type 2 diabetes

Revista Latinoamericana de Hipertensión, vol. 1, núm. 4, octubre-diciembre, 2006, pp. 147-152

Sociedad Latinoamericana de Hipertensión
Caracas, Organismo Internacional

Available in: http://www.redalyc.org/articulo.oa?id=170217084004
Type 2 Diabetes mellitus is characterized by insulin resistance and defects in insulin secretion. These variables have been studied by the euglycemic/hyperinsulinemic clamp and MinMod, which difficult the HOMA IR and HOMA β cell failure study in clinical practice. The aim of this study was to evaluate three different anti-diabetic therapeutic options using a mathematical model (Homeostasis model assessment, HOMA). Seventy type 2 diabetic patients were randomly assigned one of the next therapeutic options: A) Metformin + ADA Diet + Physical activity (Walk, 60 minutes/day). B) Metformin + Glimepiride + ADA Diet + Physical activity. C) Only ADA diet + Physical activity.

A blood sample was taken before and after the treatment to determine basal and post-prandial blood glucose, basal insulin and HbA1c and to calculate HOMA IR and HOMA β cell. Before treatment basal and post-prandial levels of glucose, HbA1c, basal insulin and HOMA IR and HOMA β cell were significantly different when compared to after treatment levels for each group (p<0.01). Significant differences were also found when comparing basal blood glucose reduction (51.8 %; p<0.01), post-prandial blood glucose (55.0%; p<0.05), and HOMA IR (65.3%; p<0.01) of group B (Metformin + low glimepiride dose) with the other therapeutic options. We conclude that metformin plus glimepiride at a low dose is a more effective treatment for type 2 diabetes than other therapeutic options. HOMA IR and HOMA β cell are inexpensive and reliable methods to study HOMA IR and HOMA β cell function in DM2.

Key words: Type 2 diabetes, HOMA, Glimepiride, Metformin, insulinresistance.
the Hiperinsulinemic - Euglycemic clamp\textsuperscript{13}. Likewise, a recent study clearly demonstrated that HOMA\textsubscript{IR} correlates significantly with clamp studies before and after treatment with sulfonylureas in type 2 diabetic patients\textsuperscript{14-17}. However, the utility of HOMA\textsubscript{IR} and even HOMA\textsubscript{bet} to study the pharmacological approach of type 2 diabetes has not been deeply evaluated neither concerning about oral combination therapy nor isolated nutritional and physical activity approaches.

The aim of the present study was to evaluate HOMA\textsubscript{IR} and HOMA\textsubscript{bet} behavior in Type 2 diabetic patients under different treatment options, such as metformin plus glimepiride at a low dose.

**Methods**

**Subject selection**

A prospective study was carried out in 70 patients with type 2 diabetes, diagnosed according to the ADA criteria\textsuperscript{18}, which attended the Centro de Investigaciones Endocrinología Metabólica “Dr. Félix Gómez” (School of Medicine, University of Zulia, Maracaibo, Venezuela). Informed consent was obtained from all subjects before the beginning of the study and all of them were randomly assigned to three different groups for therapeutic intervention considering the following selection criteria:

- a) Age range: between 40 and 60 years; b) Diabetes Mellitus evolution (since diagnosis) no longer than 10 years. c) Altered metabolic control profile (HbA\textsubscript{1c} > 8%, fasting glycemia >126 mg/dl, post-prandial glycemia >140 mg/dl); and d) Only patients with previous monotherapy with sulfonylureas or subjects that, although diagnosed with diabetes mellitus, had not been under pharmacological or nutritional therapy.

**Pharmacological intervention groups**

Patients treated previously with sulfonylureas were randomly distributed to receive one of the following options: metformin 500 mg/three times daily or metformin 500 mg three times daily + glimepiride 0.5 mg/once a day. Those subjects without previous pharmacological therapy were directly assigned to the diet and exercise intervention group (Table 1). All patients were underwent to receive one of that therapeutical approaches during 10 weeks.

**Results**

**Metabolic variables follow-up**

Three fasting venous blood samples, with a 5 minute interval, were drawn from all subjects included in the study, in order to determine pre-treatment basal glycemia and basal insulin. An average of the three blood samples was used to determine the mean fasting glycemia and insulin levels by which HOMA\textsubscript{IR} and HOMA\textsubscript{bet} were calculated. Post-prandial (2 hours after breakfast ingestion) glycemia and glycosylated hemoglobin (HbA\textsubscript{1c}) were also determined previous therapeutic intervention. After this step, the patients were randomly distributed to each group according to the inclusion criteria described above.

Each patient was followed-up weekly by determining basal glycemia and all metabolic parameters previously mentioned, (post-prandial and fasting glycemia, fasting insulin, and HbA\textsubscript{1c}), were measured again ten weeks later.

Serum glucose levels were performed by a colorimetric enzymatic method (Glucose Oxidase; HUMAN, Germany). Serum insulin was quantified using a solid phase radioimmunoassay (DPC, USA) and HbA\textsubscript{1c} was measured by interchange resin separation method (SIGMA, USA).

**Insulin resistance and β cell function calculation**

Insulin resistance and β cell function calculation was accomplished through the application of the Homeostasis Model Assessment (HOMA) formulas published previously\textsuperscript{18,12} before and after treatment intervention.

**Statistical analysis**

All data were stored in a Pentium IV personal computer and processed using the SPSS program version 10.0 for Windows. Variables that did not fulfill variance normality and homogeneity, required logarithmic transformation in order to improve the curtosis; still, data are shown in their original form in figures and tables (no modification). The differences between means were established using either one way ANOVA or multifactorial ANOVA (Tukey’s post-hoc test) as required. The results were expressed as mean ± standard error or percentages according to the case and differences were considered statistically significant at p<0.05.

**Table 1**

**General Characteristics of the Groups Studied**

From the 70 patients’ original sample, eleven did not finish the study. Therefore, the final number consisted in sixty-one subjects: 28 women (45.31%) and 34 men (54.68%). The patient distribution according treatment was as follows: Group A (Metformin, diet and exercise): n = 29 (11 women, 18 men); Group B (Metformin, glimepiride, diet and exercise): n = 21 (14 women, 7 men); and Group C (Metformin, metformin, diet and exercise): n = 11 (3 women, 8 men).
men); Group C (Diet and exercise): n = 9 (4 women, 5 men). There were not statistically significant differences between groups when comparing age and diabetes evolution time since diagnosis. Table 1.

**Fasting and post-prandial blood glucose levels**

**Fasting Glycemia:** a statistically significant reduction was observed when comparing each group individually before and after the treatment (Group A: 10.6 ± 0.4 mmol/l vs. 6.1 ± 0.1 mmol/l; p<0.01; Group B: 13.5 mmol/l ± 0.7 vs. 6.0 mmol/l ± 0.1; p<0.01; Group C: 9.5 mmol/l ± 0.6 vs. 6.1 mmol/l ± 0.2; p<0.01). Likewise, a statistically significant difference was found when compared basal glycemia levels before and after treatment among the three groups. Thus, group B registered a significantly blood glucose level reduction of 51.8 % in basal glycemia vs. a smaller reduction of 40.5 % in group A and 33.7 % in group C (p<0.01). (Table 2, Figure 1).

**Post-prandial Glycemia:** there was a statistically significant reduction before and after treatment. (Group A: 12.9 mmol/l ± 0.6 vs. 7.1 mmol/l ± 0.3; p<0.01; Group B: 17.4 mmol/l ± 0.8 vs. 7.5 mmol/l ± 0.4; p<0.01; Group C: 10.9 mmol/l ± 0.9 vs. 6.4 mmol/l ± 0.5; p<0.01). Inter-group comparisons showed statistically significant differences with a 55.0 % in post-prandial blood glucose reduction in group B vs. only 42.9 % reduction in group A and 39.8 % reduction in Group C; p<0.05. (Table 2, Figure 1).

**Basal insulin behavior**

Statistically significant differences were observed only in intra-group comparisons, before and after treatment (Group A: 16.3 µU/ml ± 0.8 vs. 12.7 µU/ml ± 0.6; p<0.01; Group B: 18.7 µU/ml ± 1.2 vs. 12.6 µU/ml ± 0.5; p<0.01; Group C: 14.8 µU/ml ± 1.2 vs. 11.6 µU/ml ± 0.8; p<0.01), and not in inter-group comparisons. However, it can be noticed that serum insulin values were always found within normal levels (Table 2, Figure 1).

**HbA1c behavior**

A statistically significant reduction was observed in HbA1c when comparing each group before and after treatment (Group A: 10.1 ± 0.3% vs. 6.8 ± 0.2 %; p<0.01. Group B: 11.5 ± 0.6% vs. 6.9 ± 0.3%; p<0.01. Group C: 9.6 ± 0.5% vs. 6.0 ± 0.3%; p<0.01). No difference was found in inter-group comparisons. (Table 2, Figure 2).

**HOMA-IR**

A statistically significant reduction was observed when comparing each group before and after treatment (Group A: 7.8 ± 0.5 vs. 3.5 ± 0.2; p<0.01; Group B: 11.7 ± 1.3 vs. 3.4 ± 0.1; p<0.01; Group C: 6.4 ± 0.8 vs. 3.2 ± 0.2; p<0.01).

When performing inter-group comparisons, a statistically significant difference was also observed: 65.3% in group B vs. only a 52.4% reduction in group A and 46.9% reduction in group C; p<0.01. (Table 2, Figure 2)
HOMA\(_{\beta}\)Cell

When performing inter-group comparisons (before and after treatment), a statistically significant increases were observed in \(\beta\) cell function (Group A: 49.4 ± 3.5% to 103.2% ± 6.5%; p<0.01, Group B: 40.0 ± 3.1% to 105.8 ± 8.5%; p<0.01, Group C: 52.1 ± 5.0% to 97.9 ± 15.2%; p<0.01). No differences were observed in inter-group comparisons. (Table 2, Figure 2).

A key point in the pharmacological management of DM2 is to consider the natural evolution of the disease for each patient in order to develop a rational therapeutic approach. Furthermore, evaluation of the broad metabolic changes as seen in type 2 diabetes cannot be accomplished on the basis of isolated qualitative or quantitative data, like basal glycemia, as it is commonly done in our daily clinical practice. It is clear that classic parameters like HbA\(_1c\), post-prandial glycemia, and new parameters like HOMA\(_{\beta}\) and HOMA\(_{\beta}\) should be considered as routine element in type 2 diabetes evaluations.3,13,14,15,16

A number of longitudinal and cross-sectional studies have documented conclusively that the progression from normal to impaired glucose tolerance is associated with the development of severe insulin resistance10,25 whereas plasma insulin concentration, both in the fasting state and in response to glucose load, are markedly increased. Randle and others26,27,28 have explain this phenomena by enhanced free fatty acid oxidation that depletes NAD+ stores (increase of NADH/NAD+ ratio), leading to an inhibition of the Krebs cycle and a resultant increase in intracellular citrate and acetyl-CoA concentration. Accumulation of acetyl-CoA and Citrate leads to the inhibition of pyruvate dehydrogenase and phosphofructokinase-1, respectively. Build-up of glucose-6-P inhibits the hexokinase, leading to an inhibition of glucose transport into the cell via hexosamines pathway. Decreased glucose transport, plus the inhibitory effect of Acyl-CoA on glycogen synthase, results in diminished glycogen formation. More recently, Roden, Shulman and others29,30,31 have changed the biochemical basis of Randle cycle using the euglycemic clamp study, indirect calorimetry and NMR spectroscopy. They demonstrated that free fatty acid infusion in normal subjects inhibited both glycogen synthesis and glucose oxidation. However, muscle G-6-P concentrations (measured by 31P-NMR spectroscopy) declined, and that decrease preceded the FFA-mediated inhibition of glycogen synthesis. This led the investigator to postulate that the primary effect of an elevation in plasma FFA is to inhibit glucose transport and phosphorylation, which, in combination with the decrease in G-6-P (allosteric activator of glycogen synthase), leads to a reduction in glycogen synthesis 31,32.

These observations provide convincing evidence that insulin resistance, not impaired insulin secretion, initiates the process of type 2 diabetes in most ethnic populations. Thus, rationality of HOMA\(_{\beta}\) and HOMA\(_{\beta}\) usefulness lies on the individual variability in insulin sensitivity among human beings (healthy and diabetic) as well as the heterogeneous plasma insulin response to oral glucose stimuli that cause different therapeutic responses between patients.33,34,35 As a matter of fact, “normal” blood glucose levels are a consequence of a complex endocrine system in which the occurring or final variables are basal and post-prandial glycemia and consequently, HbA1c that depend on other variables do not evaluated in DM2 patients36.

From a pathophysiological point of view, HOMA\(_\beta\) and HOMA\(_{\beta}\) function can be considered as “incoming” variables because they interact with our biological system prior to the registration of occurring variables (blood glucose level and HbA\(_1c\)). Thus, in the management of patients with DM2, the quantization of these variables at diagnosis could characterize accurately the disease within its natural evolution and therefore a better pharmacological choice may be taken.

To date, the evaluation of the effectiveness of different therapeutic strategies in type 2 diabetes mellitus is carried out only through the determination of the previously mentioned occurring variables; i.e., measuring the effects and not quantifying the magnitude of the causes like Insulin resistance and \(\beta\) cell failure6,7,8,14,17,36.

From all of the above, many questions arise: What benefits could be obtained from measuring incoming metabolic variables in glycemia regulation systems, at the time of diagnosis and during follow-up? What would happen if these variables were considered at the time of establishing a therapeutic conduct in type 2 diabetic patients?

If the natural evolution of the disease is deeply analyzed, it cannot be shown that metabolic alterations related to type 2 diabetes mellitus begin a decade (or more) before the development of clinically evident diabetes, with the arising of progressive insulin resistance as a result of a sustained increase in body mass index, frequent alimentary transgressions and indeterminate genetic factors or a combination of all of them. Apparently, an increase in long chain fatty acid bioavailability generates the initial changes responsible for the decrease in peripheral insulin sensitivity and the hyperinsulinemnic response to insulin resistance20,31.

When plasma insulin concentration increases, a down-regulation of insulin receptors occurs in many tissues, especially muscle, adipose tissue, brain, liver, and others, which aggravates the functional metabolic conditions. Muscle tissue response to insulin diminishes which leads to evident fasting and post-prandial hyperglycemia, the characteristic markers of diabetes mellitus and later, become continuous stimulating elements.
of insulin secretion. This process determines an increase in insulin release until β-cell function declines due to the effect of hyperglycemia on insulin secretion. Hyperglycemia and high plasmatic free fatty acid lead to β-cell apoptosis via ceramides metabolism and Fas receptor up regulation and finally irreversible drop in insulin secretory function.

In this study, it is important to recall that fasting blood glucose reduction in Group B (metformin + gliclazide + exercise) was significantly lower than Groups C and B (p<0.01) However, it is more notable that post-prandial glycaemia percentage reduction was significantly higher again in Group B than the others intervention groups, a fact that clearly supports the advantages of combining a sulfonylurea and insulin-sensitizing agents.

Moreover, this study show, as it has been previously published that most diabetic patients at the time of diagnosis have some failure in global β-cell function, fact quantified only in small group studies through hyperinsulinemic clamp and MinMod. This phenomenon has been confirmed through the HOMA mathematical model in this research. Although fasting and post-prandial insulin levels in diabetics were normal, β-cell global function was altered (drop of 40-52% in function capacity for all groups). Therefore, this model is capable to sense global changes in β-cell function, beyond the two hours post-prandial period, and abnormal insulin secretion patterns.

Another interesting finding was the minimal dose of the oral hypoglycemic agent Gliclazide (0.5 mg/day) to reach a β-cell function around 100%; furthermore, it is noticeable that the group receiving exclusively Metformin also recovered β-cell function to 103 %. This clearly shows that, at least at this moment in the disease evolution, insulin production and secretion can be perfectly recovered, even with exercise and diet only. This finding must be analyzed along with insulin resistance, because the theoretical main target of these drugs is K+/ATP sensitive channels blockade in β-cells and a quite modest peripheral sensitizing effect. We postulate that normal to high sulfonylurea doses produce more hyperinsulinemia and consequent insulin-receptor down-regulation with more insulin resistance. Thus, we propose that Metformin, used as a tissue sensitizing agent, notably decreases the hyperglycemic and lipotoxic stress suffered by the β-cell, allowing it to rapidly recover its function, as shown in the HOMA determination before and after the treatment. If low sulfonylurea doses are used, like Gliclazide in this study, no β-cell hyperfunction is produced (and no hyperinsulinemia) as shown through HOMAβ-cell determination (105.8 ± 8.5 %).

It can be concluded that all of these patients had a moderate insulin resistance degree at the beginning of this study (HOMAIR = 6.4 – 11.7) that improved substantially with all treatment options. However, it must be recognized that with pharmacological intervention the percentage of IR decrease was higher with combined Metformin + Gliclazide therapy. That represents an interesting finding, because Metformin was the only sensitizing drug used in the study. This effect may result from a remarkable peripheral sensitizing effect of sulfonylurea at low dose causing a “down-regulation escape of the insulin receptors”, that is not usually observed because the amount of the standard sulfonylureas doses rank around 100-400 % higher (Gliclazide = 1-4mg/day). We assume that if the sulfonylurea daily dose had been increased, pancreatic function percentage would have been higher (HOMAIRpost = over 100 %) as expected from these drugs. Therefore, it can be implied that the majority of individuals treated exclusively with this type of drug group could end up with one of two unwanted effects: an unrestrained hyperinsulinemia and insulin receptor down regulation or a β-cell function failure. Taking all this evidence together early pharmacological intervention with drug combinations may improve metabolic variables as well as the overall control of the disease. More studies should be carried out to determine if early pharmacological oral drug combination improves β-cell function preventing long-term β-cell failure, which might avoid insulin use in diabetic patients with a long disease history.

Unfortunately, there was no significant difference between HbA1c values when comparing different treatment groups. This probably occurred because the study was designed to evaluate each patient after 10 weeks treatment, which could be considered a limited period to observe larger differences in HbA1c in any therapeutic modality. All patients that took part in this study are currently under control and will be reevaluated after a one-year period since the beginning of the treatment in order to answer these questions.

In conclusion, the HOMApost and HOMAIR mathematical models are reliable and practical methods, applicable in daily clinical practice in order to follow-up the effectiveness in the management of type 2 diabetic patients. The different therapeutic strategies used in this study, are effective in achieving a good metabolic control in type 2 diabetic patients. Nevertheless, the combined (Metformin + Gliclazide at low dose) pharmacological treatment, turned out to be significantly superior in the management of the metabolic variables, especially insulin resistance and β-cell secretion capacity study through HOMA. The β-cell secretion function fatigue is a reversible alteration, at least during the first years of the disease’s evolution. The use of mathematical models for the strict control of IR and β-cell function is highly recommended in daily clinical practice, at the time of diagnosis as well as during the follow-up of type 2 diabetic patients.

References


