COMPARATIVE ASSESSMENT OF THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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Background: The objective of the study was to estimate the most successful way of treating patients with type 2 diabetes mellitus.

Patients and Methods: A total of 87 patients with type 2 diabetes mellitus were selected for a three-month study. The patients were divided into three groups comprising 29 patients in each group, based upon the treatment regimen. Group 1 (BMI 32.3±3.6 kg/m^2) was treated with glimepiride and metformin; group 2 (BMI 27.9±3.9) was treated with daily doses of insulin mixture 30/70 and bed-time NPH insulin; and group 3 (BMI 30.2±4.8) was treated with a combination of three daily doses of lispo and metformin. The groups did not differ significantly in terms of sex and age.

Results: Initially, there were significant statistical differences in HbA_{1c} (P=0.035) between the three groups (9,21%±1.72%; 9.21%±1.54%; and 10,0%±1.73%, respectively). After three months, there were no statistically significant differences in $HbA1_c$ (P=0.66) between the groups (8.52%±1.7%; 8.03%±1.05%; and 8.0%±0.63%, respectively). Decreases in HbA_{1c} were significant in all groups, but most pronounced in patients treated with lispro and metformin (17% on average).

Conclusion: The study results suggest the need for establishing guidelines on how to treat type 2 diabetics.

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Key words: Glycemic control, lispro, NPH, biphasic insulin, metformin, glimepiride.

Type 2 diabetes mellitus accounts for 85% of all the incidence of diabetes worldwide. It affects approximately 5%-7% of the Western population, where about 10% of the population above 70 years of age are diabetic.[1-3] Many studies have demonstrated the substantial cost of treating diabetes mellitus on countries' health budgets.[4-6] Good glycemic control delays and reduces diabetic complications not only in type 1,[7] but also in type 2 diabetes.[8] Glycosylated hemoglobin (HbA_{1c}) needs to be checked every three months as an indicator of glycemic control. Poor glycemic control cause macro- and micro-vascular complications, with increased morbidity and mortality in type 2 diabetic patients worldwide.[9] Insulin is needed for about 35% of type 2 diabetic patients above the age of 30.[10] The effect of insulin treatment in type 2 diabetic patients has been studied before.[11]

Our study shows the outcome of different treatments in 87 type 2 diabetic patients with respect to their metabolic control.

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Patients and Methods

This study was carried out at the Split Clinical Hospital in Croatia, between December 2000 and April 2001. A total of 87 type 2 diabetic patients were enrolled on a treatment program. The patients were given instructions on diabetic diet and asked to monitor their blood glucose level, both fasting and postprandial, a minimum of twice a day before their initial visit. Patients who suffered from uncontrolled diabetes were included. This was defined as an HbA_{1c} value of less than 8.5%, with less than 20% of all recorded fasting blood glucose levels of less than 8.9 mmol/L and/or pre-meal glucose levels of less than 10 mmol/L. The first group of patients was treated with glimepiride and metformin. The second group was treated with two daily doses of biphasic insulin with bed-time NPH insulin. The third was treated with a combination of three daily doses of lispo and metformin.

Data collected from the patients included age, sex and body-mass index. The glycemic profile, defined as fasting and postprandial glucose levels and HbA_{1c}, was collected at the start and after three months of treatment. Data was not collected on the patients' weight at the end of the study due to the short duration of the observation period. The fasting and postprandial glucose levels were analyzed by the enzymatic colorimetric method (Glucose GOD-PAP, Chronolab®). HbA_{1c} was measured by the spectrophotometric ion exchange method (Chronolab®). The normal values for fasting capillary blood glucose are 4.2-6.1 mmol/L (coefficient of variation 1.4%) and for

HbA_{1c} are 4.2%-6.2% (coefficient of variation <1.5%). The data was analyzed using SPSS for Windows (version 9.0., 1998 ® SPSS Inc.).

Results

The first group of patients which was treated with a combination of glimepiride and meformin, had a BMI of 32.3±3.6 kg/m^2 and ages between 52 and 80 years, with a mean age of 60.9±6.5 years. This group comprised 16 women (55.2%) and 13 men (44.8%). The second group which was treated with two daily doses of biphasic insulin and bed-time NPH insulin, had a BMI of 27.9±3.9 kg/m^2 and ages between 62 and 82 years, with a mean age of 63.6±4.8 years. This group consisted of 19 women (65.5%) and 10 men (34.5%). The last group, treated with a combination of three daily doses of lispro insulin analogue and metformin, had a BMI of 30.2±4.8 kg/m^2 and ages between 46 and 70 years, with a mean age of 62.3±7.2 years. This group consisted of 17 women (58.6%) and 12 men (41.4%).

There were no statistically significant differences between the groups when analyzed by sex (P=0.67) or age (P=0.55). Using Kruskal-Wallis variance analysis to test differences in BMI between the groups, no significant difference in BMI was noted among the group (P=0.075).

There was significant difference in the initial value of HbA_{1c} among the groups (χ^2=6.71, P=0.035). The third group had a higher HbA_{1c} than the other two (9.21%±1.72%, 9.21%±1.54%, and 10.0%±1.73%, respectively). Three months later, the value of HbA_{1c} had changed in all groups (8.52%±1.70%, 8.03%±1.05%, and 8.00%±0.63% , respectively). At the end of the study, HbA_{1c} was significantly decreased by similar values in all groups, with no statistical significance (χ^2=0.82, P=0.66). The biggest fall in HbA_{1c} was noticed in the group treated by lispro and metformin: –1.96%±1.72%, when expressed in percentage terms –17.01%±17.30%.

An improvement in fasting glucose levels was observed in the first and third groups. The biggest improvement was noticed in the group treated with lispro and metformin, but this was not considered significant. In the first group, the fall of fasting glucose was –1.27±2.03 mmol/L (–10.99%± 17.17%); in the second group, it was 0.59±3.4 mmol/L (+5.93% ± 52.05%); and in the third group, it was –2.17±2.10 mmol/L (–16.19%±14.74%). The fall of postprandial glucose measured from the beginning to the end of the study was higher in the group treated with lispro and metformin, which was –4.31±3.4 mmol/L (–26.06%±22.05%) than in the group treated by biphasic insulin and bedtime NPH, which was 1.55±3.9 mmol/L (–5.6%±34.7%) and the group treated by glimepiride and metformin at 1.66±3.76 mmol/L (–9.72%± 36.85%). The beneficial effect of the various kinds of treatment was mostly reflected by postprandial glucose in the group treated by lispro and metformin (χ2=10.3, P=0.006).

Discussion

The basic theme of the study was to determine the most efficient way of treating type 2 diabetic patients using the experience gained in our hospital at Split in Croatia. There are several therapeutic schemes recommended for the treatment of type 2 diabetic patients.[12-26] Both non-insulinotropic and insulinotropic drugs are valid options for the crucial treatment of those patients with various pathophysiological origins of type 2 diabetes.[27] Because some degree of insulin deficiency is always present in an individual with diabetes type 2, we included metformin which is an agent known to influence insulin sensitivity without affecting insulin secretion.

The first group of patients in the study were treated by a combination of metformin and glimepiride. Due to the high BMI of those patients, we preferred glimepiride as a new sulphonylurea because of the more pronounced insulin secretion activity than glibenclamide, and also its stronger extrapancreatic activity.[28,29] As sulphonylurea treatment failure is frequent in diabetic patients,[30] insulin is often required in order to achieve adequate metabolic control.

Many studies have emphasized different strategies for basal insulin supplementation required in combinations with biphasic insulin 30/70. As a result, we have treated many patients with a combination of two daily doses of biphasic insulin 30/70 and bed-time NPH.

Because of the rapid onset of action and shorter duration of efficacy of insulin lispro compared with regular human insulin, the use of insulin lispro in many clinical trials was associated with improved control of postprandial hyperglycemia.[27,31,32] Today, it is well known that postprandial hyperglycemia strongly co-relates with developing macrovascular complications.[7,8,33-37] This was the reason we selected lipro insulin for the treatment of postprandial hyperglycemia. The danger of increasing body weight and hypoglycemic events are eliminated by the short and rapid action of lispro insulin. Weight gain, which seems to be proportional to the number of insulin injections used, can be counteracted by the inclusion of metformin in the treatment program.[13-17]

A *Medline* search from 1966 to May 2001 did not show any previous similar clinical trial comparing different ways of treating type 2 diabetics based on the use of lispro insulin and metformin. The study by Bastry et al.[38] confirms previous reports that improved glycemic control can occur when a second antihyperglycemic agent is added, regardless of the program. Our observations are in accord with the conclusions achieved in that study, which shows that antihyperglycemic therapy with insulin lispro when focused on postprandial glucose control has a greater impact on overall metabolic control. Compared wth the more tradtional approaches of NPH insulin at bedtime, the

therapeutic combination of metformin should be considered for type 2 diabetes. We believe that decreased fasting glucose and postprandial hyperglycemia reflect an improvement in diabetic regulation.

The greatest therapeutic challenge recently in diabetology is finding the right time to include adequate treatment for secondary beta cell failure in type 2 diabetes mellitus. Our pathophysiological knowledge allowed many therapeutical combinations. There are different mechanisms of action for each drug (secretion of insulin, decreasing of gluconeogenesis, improvement of peripheral insulin resistance, etc). The therapeutical combination of lispro and metformin provides a significant improvement in daylong glycemia, which may account for the overall reduction in HbA_{1c}.

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