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Lispro Insulin and Metformin Versus Other Combination in the Diabetes Mellitus Type 2 Management after Secondary Oral Antidiabetic Drug Failure

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A B S T R A C T

The purpose of the study was to find out differences between treatments of diabetes type 2 after secondary oral antidiabetic drug failure. Three different methods of treatment were compared: lispro insulin in combination with metformin, glimepiride and metformin combination or two daily doses of biphasic insulin 30/70 together with bed -time NPH insulin. The study included 87 patients with diabetes mellitus type 2 randomly distributed into 3 different treatment groups. Fasting and postprandial glucose were analyzed by enzymatic colorimetric method and HbA_{1c} was measured by ion exchange chromatography. HbA1c significantly decreased in all three study groups. The decrease was mostly expressed among patients treated with lispro and metformin. When focused on postprandial glucose control, antihyperglycemic metformin and insulin lispro therapy has greater impact on the overall metabolic control (decrease in level of HbA_{1c}) in comparison with the above mentioned more traditional approaches.

Key words: *lispro insulin, metformin, NIDDM, antidiabetic drug*

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Introduction

Diabetes mellitus type 2 accounts for 85% of all diabetes cases worldwide. It affects approximately 5–7% of the population in developed countries. In those countries about 10% of the population above 70 suffer from diabetes[1,2]. Based on the United Kingdom Prospective Diabetes Study and the Kumamoto study, there is clear evidence that improved glycemic control through intensive diabetes management alleviates and significantly postpones the progression of microvascular complications in patients with diabetes mellitus type 2[3–8]. With the progression of diabetes type 2, there is progressive loss of pancreatic beta cell function and endogenous insulin secretion. At this point, most patients require exogenous insulin therapy to achieve optimal glucose control. About 30% of diabetic patients (type 2) above the age of 30 need insulin therapy. The effect of insulin treatment in diabetic patients (type 2) had been studied before[9]. Several studies have documented that intensive insulin therapy improves insulin sensitivity as measured by the glucose-insulin clamp method, besides it decreases glucose toxicity[10–13]. Prolonged hyperglycemia is known to cause impairment on the level of the pancreatic beta cells and on peripheral tissues such as skeletal muscle[3].

Three major pathophysiological abnormalities contribute to hyperglycemia in diabetes type 2. These include: excessive hepatic glucose production, impaired pancreatic insulin secretion and the effect of peripheral resistance to insulin occurring principally in liver and muscle tissue[13].

Our study estimates the outcome of different therapies in 87 type 2 diabetic patients with respect to their metabolic control and change in BMI during a three -month-period of treatment based on different mechanisms of efficiency for each pharmacological agent (secretion of insulin, decrease of gluconeogenesis, improvement of peripheral insulin resistance).

Patients and Methods

This study was carried out at the University Hospital »Split«, Split, Croatia, during three months. After secondary oral antidiabetic drug failure a total of 87 diabetic patients (type 2) were randomly included in 1 of 3 combination regimens. The patients were re-educated about diabetic diet and instructed to monitor their blood glucose level (fasting and postprandial) at least twice a day before paying their first visit. All patients who suffered from uncontrolled diabetes were included in the study. Uncontrolled diabetes is defined as an HbA_{1c} value >8.5%, fasting blood glucose values >8.9 mmol/1 in more then 20% of all recorded glucose values and/or glucose values >10 mol/l before meal after maximal doses of a sulphonylurea during a minimal period of three months before starting the study. The first group of patients were treated with glimepiride + metformin. The second group of patients was treated with two daily doses of biphasic insulin 30/70 with bedtime NPH insulin. The third group of patients was treated with a combination of three daily doses of lispro and metformin. The first group, treated with combination of glimepiride and meformin, at baseline, had BMI 32.3 ± 3.6 kg/m^2 and ages between 52 and 80 years with a mean age of 60.9 ± 6.5 years and were diabetics 9.3 ± 2.5 years. This group consisted of 16 women (55.2%) and 13 men (44.8%). The second group, treated with two daily doses of biphasic insulin 30/70 and bed-time NPH insulin, at baseline, had BMI 27.9 ± 3.9 kg/m^2 and ages between 62 and 82 years with a mean age of 63.6 ± 4.8 years and were in average 10.5 ± 3.2 years diabetics. This group consisted of 19 women (65.5%) and 10 men (34.5%). The last group, treated with combination of three

daily doses of lispro insulin analogue and metformin, at baseline, had BMI 30.2 ± 4.8 kg/m^2 and ages between 46 and 70 years with a mean age of 62.3 ± 7.2 years and were diabetics 9.5 ± 3.1 years. This group consisted of 17 women (58.6%) and 12 men (41.4%).

The collected data were: age, sex and body mass index. The glycemic profile, defined as fasting and postprandial glucose and HbA_{1c}, was collected at the beginning and after three months of treatment. The fasting and postprandial glucose were analyzed by the enzymatic colorimetric method (Glucose GOD PAP, Chronolab AG, Zürich, Switzerland, on Olympus, chemistry analyzer AU 400, Japan). HbA_{1c} was measured by the ion exchange chromatography method based on separating hemoglobin adducts according to their charge – (Chronolab AG, Zürich, Switzerland). The data was analyzed using SPSS for Windows, version 9.0.0 1998 ® SPSS Inc.

Results

The groups did not differ in their composition (Table 1). The baseline value of HbA_{1c} was significantly different among groups (χ^2=6.71, p=0.035). The third group had higher HbA_{1c} than the others (9.21% ± 1.72%; 9.21% ± 1.54%; 10.0% ± 1.73% in groups 1, 2 and 3, respectively) (p<0.05). Three months later the value of HbA_{1c} changed in all three groups (8.52% ± 1.70%; 8.03% ± 1.05%; 8.00% ± 0.63% in groups 1, 2 and 3, respectively) (p<0.05). At the endpoint HbA_{1c} decreased significantly by similar values in all groups, with no statistical significance (χ^2=0.82, p=0.66). The greatest fall of HbA_{1c} was noticed in the group treated with lispro + metformin: –1.96 % ± 1.72% (Figure 1) or in percentage terms 17.01% ± 17.30% (Figure 2).

We observed an improvement of fasting glucose in the first and third groups, but the most important improvement was noticed in the group treated with lispro +

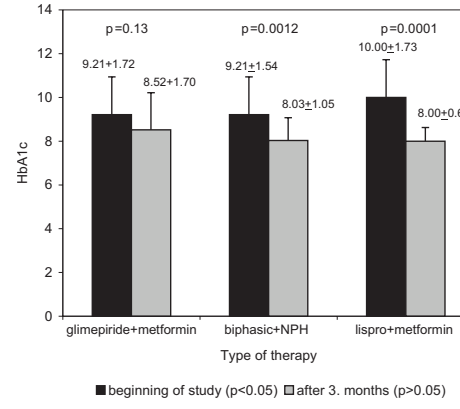

Fig. 1. Results of HbA_{1c} were assessed by Wilcoxon matched pair test at the beginning and after three months for each group.

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION

		Glimepiride + metformin N=29 (33.3%)	Biphasic + NPH insulin N=29 (33.3%)	Lispro + metformine N=29 (33.3%)	p
Sex	Female	16 (55.2%)	19 (65.5%)	17 (58.6%)	0.67
	Male	13 (44.8%)	10 (34.5%)	12 (41.4%)	
BMI		32.3 ± 3.6	27.9 ± 3.9	30.2 ± 4.8	0.075
Age		60.9 ± 6.5	63.6 ± 4.8	62.3 ± 7.2	0.55
Duration of DM		9.3 ± 2.5	10.5 ± 3.2	9.5 ± 3.1	0.45

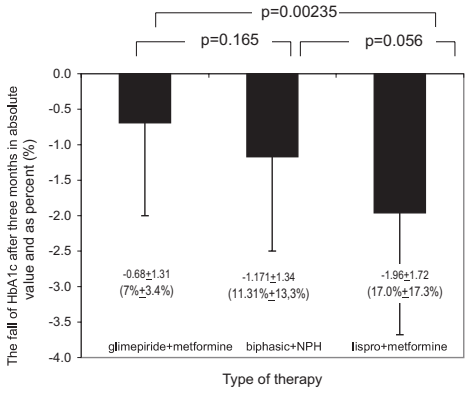

Fig. 2. The fall of HbA_{1c} expressed as percent after three months treatment tested by Mann -Whitney test for comparison between two different groups. The greatest decrease was observed in the group treated with lispro + metformin.

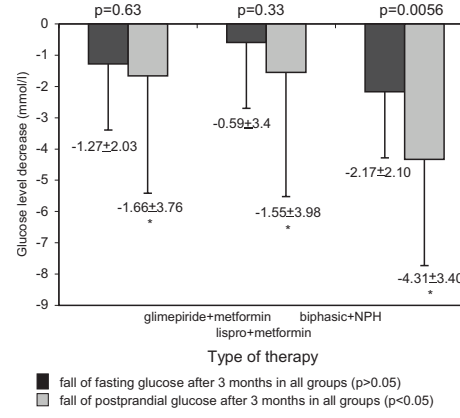

Fig. 3. The change of fasting and postprandial glucose expressed in mmol / l tested by Wilcoxon matched pairs test for comparison results at the beginning and after three months for each group separately.

metformin, but it was not significant. The fall of fasting glucose was in the first group –1.27 ± 2.03 mmol/l (–10.99% ± 17.17%); in the second group –0.59 ± 3.4 mmol/l (+5.93% ± 52.05%) and in the third group –2.17 ± 2.10 mmol/l (–16.19% ± 14.74%). The fall of postprandial glucose from the beginning to the end of the study was higher in the group treated with lispro + metformin –4.31 ± 3.4 mmol/l (–26.06% ± 22.05%) than in the group treated with biphasic insulin 30/70 + bedtime NPH 1.55 ± 3.9 mmol/l (–5.6% ± 34.7%) and in the group treated by glimepiride + metformin 1.66 ± 3.76 mmol/l (–9.72% ± 36.85%). The beneficial effects of various kinds of treatments was mostly reflected by postprandial glucose in the group treated with lispro + metformin (χ^2 =10.3, p=0.006) (Figure 3 and 4).

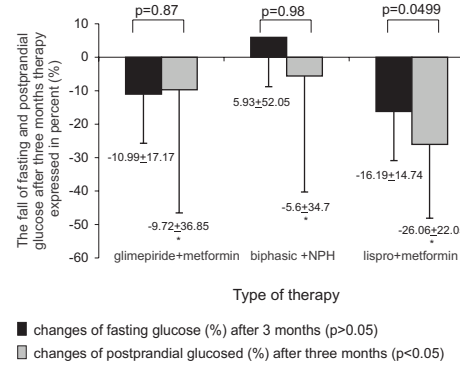

Fig. 4. The change of fasting and postprandial glucose expressed as a percentage tested by Wilcoxon matched pairs test for comparison results at the beginning and after three months for each group separately.

Discussion

The objective of the study was to analyze different ways of treatment of diabetic patients (type 2), using our clinical experience. There are several therapeutic schemes available and recommended, for the treatment of diabetic patients (type 2)[14–27]. The effect of peripheral resistance to insulin and impaired pancreatic beta cell secretion are early and primary abnormalities, whereas increased hepatic glucose production is a late and secondary manifestation. In the early phase of

disease, patients with diabetes type 2 compensate increased insulin resistance of peripheral tissue by increasing beta cell insulin secretion. When this compensation is no longer adequate to overcome the insulin resistance, blood glucose level begins to rise. Over the course of the disease, insulin levels slowly begin to decrease and most patients with diabetes type 2 are unable to achieve optimal glycemic control with oral agents[28–30]. To achieve optimal glycemic profile in patients with type 2 diabetes, multiple pharmacological agents, including sulfonylureas, meglitinides, metformin, alfa glucosidase inhibitors, thiazolidinediones and insulin, are available and can be used.

The first group of patients in the study was treated with a combination of metformin and glimepiride. We preferred glimepiride as a new sulphonylurea because of the more pronounced insulin secretion activity then glibenclamide and stronger extra pancreatic activity[29,30].

Hepatic glucose output is directly decreased by insulin and is indirectly inhibited by the ability of insulin to reduce adipose tissue lipolysis so we added bedtime NPH insulin to the most frequent insulin combination of two daily doses of biphasic insulin 30/70[31]. Due to mentioned, we have treated the second group of patients with a combination of two daily doses of biphasic insulin 30/70 and bedtime NPH.

Because of the rapid effect and shorter duration of efficacy of insulin lispro, compared to regular human insulin, the use of insulin lispro in many clinical trials was associated with improved control of postprandial hyperglycaemia[32–36]. Today, it is well known that postprandial hyperglycemia strongly co-relates with developing macro vascular complications[6,7,34]. This was the reason why we selected lispro insulin for the treatment of postprandial hyperglycemia. The danger of increasing body weight and hypoglycemic events are eliminated by the short and rapid effect 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 regimen. Metformin offers the advantage of not stimulating insulin secretion and exacerbating hyperinsulinemia. The beneficial effect of adjuvant metformin therapy has been demonstrated in a randomized, double blind, placebo-controlled study involving 43 obese patients with type 2 diabetes who were poorly controlled with insulin[36]. Therefore, combination of lispro insulin and metformin remains a treatment option in this patient population.

According to a literature search (1966 –2003) there have been no clinical trials similar to our study, which compares different ways of treatment diabetes type 2 based on lispro insulin and metformin administration.

There is one report about treatment improved by metformin and lispro insulin administration in one 19-year-old woman who suffered from late onset lipoatrophic diabetes, a syndrome of extreme insulin resistance due to acanthosis nigricans and polycystic ovary syndrome[37].

The optimal approach to glucose control at the time of sulfonylurea failure was speculative for many authors. So, there is examination of the impact of adding preprandial lispro or metformin or bedtime NPH insulin to glyburide[33].

Data from Bastyr's[27] study suggests that improved glycemic control can occur when a second antihyperglycemic agent is added, regardless of the regimen.

Conclusion

The greatest therapeutic challenge in diabetology is defining the right time when to include the adequate treatment for secondary beta cell failure in type 2 diabetes mellitus. The therapeutical combi-

nation of lispro and metformin provides a better improvement in daylong glycemia, which may account for the overall reduction in HbA_{1c}, than combinations of glimepiride and metformin and two daily doses of biphasic insulin30/70 with bedtime NPH insulin.

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LISPRO INZULIN I METFORMIN NASPRAM DRUGIH KOMBINACIJA U LIJEČENJU ŠEĆERNE BOLESTI TIPA 2 NAKON SEKUNDARNOG ZATAJENJA ORALNIH ANTIDIJABETIČKH LIJEKOVA

S A Ž E T A K

Cilj ovog rada je istaknuti različitosti u liječenju tipa 2 šećerne bolesti nakon sekundarnog zatajenja oralnih antidijabetika. U radu su ispitana tri oblika liječenja – lispro inzulin s metforminom, glimepirid s metforminom te dvije dnevne doze miješanog inzulina 30/70 uz NPH inzulin pred spavanje. Ispitano je 87 oboljelih od šećerne bolesti tipa 2 koji su randomizirani u 3 grupe. Glikemija natašte i postprandijalno je analizirana enzimatskom kolorimetrijskom metodom, a glikozilirani hemoglobin (HbA1c) kromatografski. Snižavanje HbA1c je bilo signifikantno u sve tri grupe, ali najviše kod bolesnika liječenih lispro inzulinom s metforminom. Antihiperglikemijsko liječenje kombinacijom lispro inzulina s metforminom, usmjereno na postprandijalne hiperglikemije utječe na metaboličku kontrolu (snižavanje HbA1c) te se pokazalo učinkovitijim od gore navedenih klasičnih kombinacija.