The Effects of Combined Insulin and Metformin Therapy in Obese Patients with Diabetes Mellits Type 2 in the Early Stage of the Disease

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Abstract

Combination of insulin and metformin has been shown to improve glycaemic control in clinical trials, particularly in obese patients with diabetes type 2. Insulin therapy can improve function of pancreatic beta cells and periphery insulin activity in target cells in order to enhance glycaemic homeostasis (1, 2, 3). In our study we included obese patients with diabetes type 2 in the early stage of the disease. The study is partially retrospective and partially prospective. The study encompassed 40 patients split in two groups. The first group of 20 patients received insulin therapy combined with metformin, while the patients of the second group were treated with oral antidiabetic drugs, sulfonylureas and metformin. Three months later, the group treated with insulin and metformin showed improvement in the monitored parameters, namely significant reduction in HbA1c ($p = 0.003$), MFBG ($p = 0.0009$), PPG ($p = 0.028$). Insulin therapy administered together with metformin, in obese patients with diabetes type 2, in the early stage of the disease, resulted in well regulated fasting blood glycaemia, as well as post challenge glycaemia and HbA1c

KEY WORDS: insulin therapy, obese patients, diabetes mellitus type 2

Introduction

Diabetes mellitus type 2 is a progressive disease with a silent onset. Early diagnoses of the disease and maintaining an approximate normoglycaemia is crucial in control of progressive complications of the disease. Diabetes mellitus type 2 is characterised by long asymptomatic period during which micro and macrovascular complications may be developed (1, 2). Inclusion of insulin therapy combined with oral antihyperglycaemic agents is recommended for moderate form of diabetes mellitus type 2. However, many patients do not readily accept insulin therapy at early stages of the disease, or postpone it until the first complications appear, which results in severe disorders at the later stage of the disease. Insulin therapy can improve function of pancreatic beta cells and periphery insulin activity in the target cells in order to enhance glycaemic homeostasis (3). Insulin therapy can help in correction of the underlying pathogenetic mechanisms responsible for type 2 diabetes, insulin resistance and impaired insulin secretion. Based on studies of animal models and patients with diabetes, many researchers believe that glucose toxicity from hyperglycemia contributes to both insulin resistance and b cell impairment seen in type 2 diabetes (4). *In vitro* studies using human b cells showed that even mild, short-term hyperglycemia blunts the glucose-stimulated insulin response (5). Research has also shown that hyperglycemia increases insulin resistance and that better glycaemic control improves insulin sensitivity. Hyperglycemia is thought to stimulate insulin resistance by down-regulating the glucose transport system (6). Since monotherapy with oral agents has high secondary failure rate, multydrug therapy is necessary for most patients. Very often, these multydrug regimens are not effective enough in achieving and maintaining the target blood levels. It can be assumed that by early inclusion of the insulin therapy combined with metformin, in treatment of obese patients with diabetes mellitus type 2, a better regulation of the disease might be achieved and at the same time instigate a decrease and a delay of late complications of the disease. European Diabetes Policy Group established a set of objectives for control of glycaemia, where postprandial peak should not exceed 7.5 mmol/l in order to reduce cardiovascular risk. New studies (UKPDS, Heart Protection Study) suggest achieving a better control of the disease in order to reach fasting normoglycaemia, as well as better control of postprandial glycaemia with the main objective to reduce late complications of the disease (7, 8, 9). In view of the above, selection of the appropriate procedure for treatment of patients with diabetes mellitus type 2 is very important.

Aim

The aim of the study is to compare the effects of insulin therapy combined with metformin, with the oral antidiabetic agents therapy (sulfonylureas combined with metformin) by monitoring the values of clinical parameters in obese patients with diabetes mellitus type 2 in early stage of the disease.

Patients and Methods

The study is partially retrospective and partially prospective. It was conducted over six month period at the Clinic of Endocrinology, Diabetes and Metabolic Diseases. In the study we included patients with diabetes type 2 treated with 2550 mg of metformin in three daily doses for 3 months. We examined 40 patients with BMI > 25 kg/m2, values of fasting glycaemia higher than 8 mmol/l, postprandial glycaemia higher than 8.9 mmol/l and HbA1c above 7.7 % divided in two groups. 20 patients in the first group were treated with insulin combined with metformin, while the patients of the second group were treated with oral antidiabetic drugs, sulfonylureas and metformin. The age structure of the patients of both sexes was 45 – 65 years. We monitored the laboratory tests prior and after the study. In the first group of patients the insulin therapy was initiated with NPH insulin at bedtime which was adjusted where necessary (starting dose up to 0.5 units / kg) until the glycaemia FBG and postprandial glucose targets were achieved. After meals, patients were treated with 850 mg of metformin. The group treated with oral hyperglycaemics were taking metformin up to 2550 mg and glibenclamid up to 20 mg until better glycaemia control was achieved. The parameters monitored during the study: BMI, HbA1c, fasting blood glycaemia (mmol/l), postprandial glycaemia (mmol/l).

Results

Total of 40 patients with type 2 diabetes (21 men and 19 women), of average age 54.12 (S.D. = 5.51) were included in our study. Prior to the study the subjects received 850 mg of metformin three times a day after meal for three months and had mean BMI 29.025 kg/m^2 (S.D. = 2.2), HbA1c 9.7% (S.D. = 0.78), FBG 9.86 (S.D. = 1.03), PPG 11.78 (S.D. = 1.49). Patients were divided in two groups according to the treatment of diabetes. 20 patients began receiving insulin therapy (NPH before bedtime) with 850 mg of metformin three times a day while 20 patients continued with metformin 850 mg three times a day with the addition of sulfonylureas (dose adjusted from 5

PARAMETERS	REFERENT VALUES	PRIOR STUDY	AFTER STUDY
BMI kg/m^2	25.0	29.0	28.5
HbA1c %	6.0	9.7	6.19
MFBG mmol/l	6.1	9.8	6.5
MPPG mmol/l	7.5	11.7	8.0

TABLE 1. Group of patients treated with insulin and oral hyperglycaemic therapy

to 20 mg). Three months after change in treatment, the group of patients on insulin therapy had mean BMI 28.5 kg/m2 (S.D. = 14.46), HbA1c 6.19 % (S.D. = 3.15), FBG 6.52 (S.D. = 3.48), PPG 8.015 (S.D. = 4.08), while group on multioral hyperglycaemic drugs had mean BMI 28.05 kg/m^2 (S.D. = 14.27), HbA1c 8.57% (S.D. = 4.35), FBG 8.55 (S.D. = 4.34), PPG 9.7 (S.D. = 4.96). Group of patients treated with insulin and metformin had significantly reduced in HbA1c ($p = 0.003$), MFBG ($p = 0.0009$), PPG ($p = 0.028$). Combining insulin with oral antidiabetic drugs may help maintaining good glycaemia control in most patients with diabetes type 2. For statistical analyses we used Student t–test to test significance of differences between parameters prior and after the study ($p < 0.05$).

Discussion

Small doses of insulin are effective in the control of hyperglycemia in early stages of diabetes type 2. The combination of insulin and metformin is beneficial in obese patients with diabetes type 2. In a number of studies, insulin therapy greatly improved insulin secretion in patients with type 2 diabetes, presumably by reducing hyperglycemia. Certain studies also demonstrated an improvement in peripheral insulin sensitivity after insulin therapy in type 2 diabetes. It appears that even short-term insulin therapy results in long-term improvement in blood glucose control, especially when administered in the earliest stages of diabetes. Based on these observations, some diabetes experts advocated initiating intensive insulin therapy early in the course of type 2 diabetes, or immediately after a diet and exercise regimen failed, in an effort to preserve remaining b cell function and improve long-term glycaemia control (10, 11). The long-term complications of diabetes are a result of hyperglycemia effects (elevated blood glucose levels) on blood vessels. Two important studies, the Diabetes

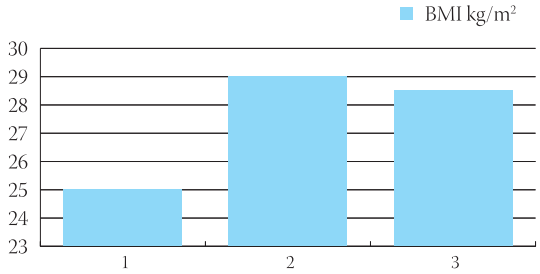

FIGURE 1. BMI prior and after the study

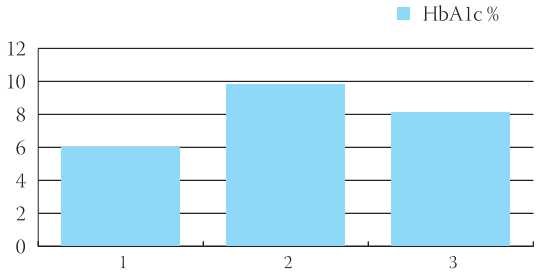

FIGURE 2. HbA1c prior and after the study

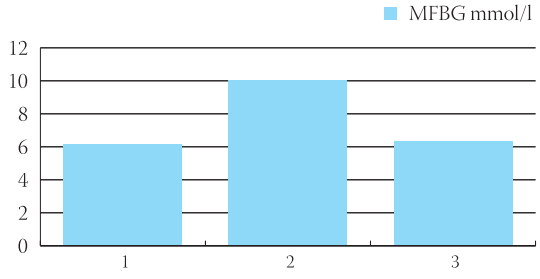

FIGURE 3. MFBG prior and after the study

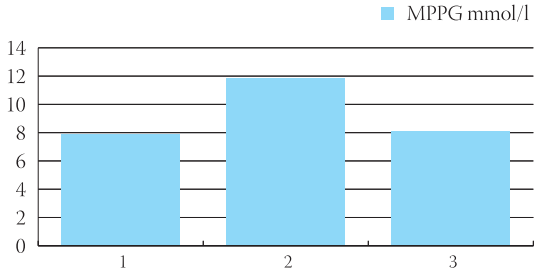

FIGURE 4. MPPG prior and after the study

PARAMETERS	REFERENT VALUES	PRIOR STUDY	AFTER STUDY
BMI kg/m^2	25.0	29.0	28.0
HbA1c %	6.0	9.7	8.6
MFBG mmol/l	6.1	9.8	8.5
MPPG mmol/l	7.5	11.7	9.7

TABLE 2: Group of patients treated with oral hyperglycemic therapy

Control and Complications Trial (DCCT), in patients with type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), in patients with type 2 diabetes, found that patients with lower blood glucose values had fewer complications than those with higher values (12). Keeping blood sugar level as close as possible to normal can go a long way towards preventing the long-term complications of diabetes mellitus. However, some risks are associated with such "tight control," particularly an increased risk of hypoglycemia (low blood sugar) (13, 14). That risk may be prevented by close cooperation of patients and health care professionals and appropriately balanced diet. During the treatment of our patients we noticed that many patients had poor glycaemia control. **The patients were at the early stage of diabetes and were treated with combined oral antidiabetic therapy. We decided to include insulin along with metformin therapy in the early stage of the** disease in one group of patients in order to improve poor glycaemia control. In this study, treatment with insulin along with metformin resulted in better glycaemia control with lower level of fasting blood glycaemia, postprandial glycaemia and HbA1c (6.19 % vs. 8.57%), when compared with the group of patient treated with combination of glibenclamid and metformin.

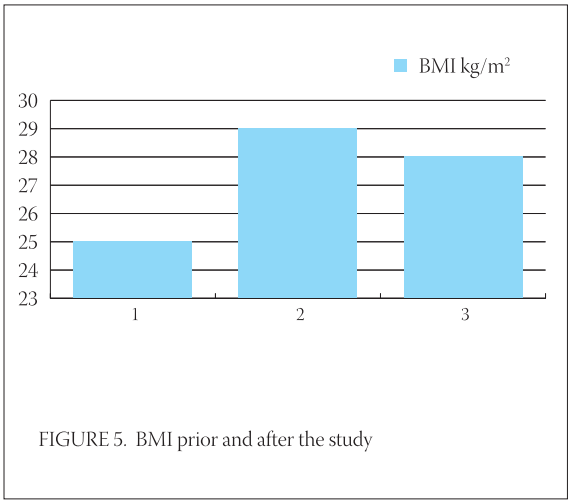

FIGURE 5. BMI prior and after the study

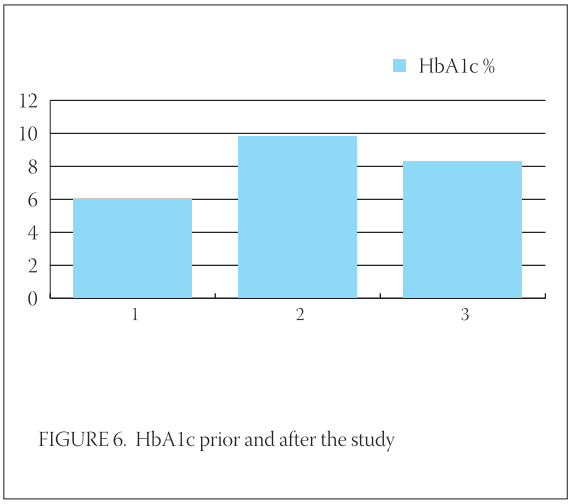

FIGURE 6. HbA1c prior and after the study

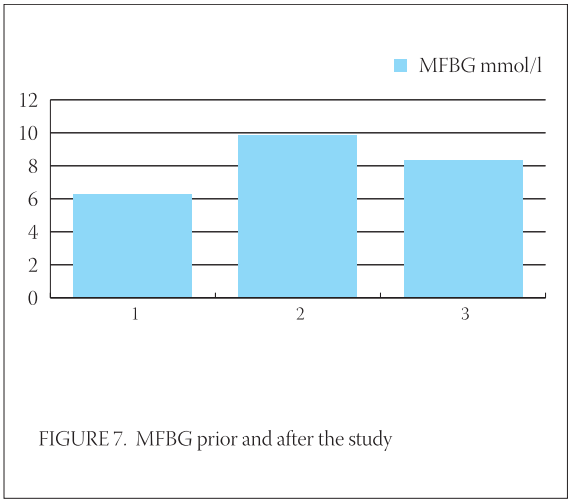

FIGURE 7. MFBG prior and after the study

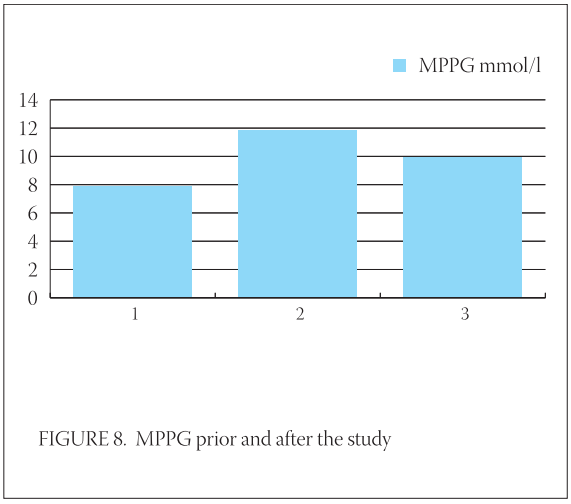

FIGURE 8. MPPG prior and after the study

Conclusion

In obese patients with diabetes type 2, insulin therapy administered in combination with metformin at the early stage of the disease, resulted in well regulated fasting blood glycaemia, as well as post challenge glycaemia and HbA1c, which will enable decrease and delay of the appearance of micro and macro vascular complications that accompany diabetes mellitus type 2.

ABBREVIATIONS:
BMI - Body Mass Index;
MFBG - Mean fasting blood glycaemia
MPPG - Mean postchallenge glycaemia
HbA1c - Hemoglobin A 1c

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