EFFECTS OF BASAL INSULIN ANALOG AND METFORMIN ON GLYCAEMIA CONTROL AND WEIGHT AS RISK FACTORS FOR ENDOTHELIAL DYSFUNCTION

Belma Aščić – Buturović[1*], Mirsad Kacila[2]

[1] Clinic of Endocrinology, Diabetes Mellitus and Metabolic Diseases, University of Sarajevo Clinics Centre, Bolnička 25, 71 000 Sarajevo, Bosnia and Herzegovina

[2] Center for Heart Diseases, University of Sarajevo Clinics Centre, Bolnička 25, 71 000 Sarajevo, Bosnia and Herzegovina

[*] Corresponding author

Abstract

Obese patients with type 2 diabetes and impaired glucose tolerance are at increased risk of development of cardiovascular diseases. Endothelial dysfunction may be a reason for development of atherosclerosis and cardiovascular diseases. Lifestyle modification, increased physical activity, weight reduction, energy restricted diet and good glycaemia control can be useful for the endothelial function improvement and may decrease the risk of cardiovascular diseases. The aim of this study was to evaluate the effects of basal insulin analog and metformin on glycaemia control and weight as risk factors of endothelial dysfunction. Total of 15 patients (9 male and 6 female) with type 2 diabetes were studied. The patients were monitored over six months period. Glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body mass index (BMI) were observed. Mean age of the subjects was 53,4 ± 6,27 years. Mean diabetes duration was 3,71 ± 1,89 years. At the end of the study mean body mass index decreased from 27,5 ± 1,45 kg/m^2 to 25,7 ±1,22 kg/m^2. In this study we included diabetic patients with fasting glycaemia over 7 mmol/dm^3, postmeal glycaemia over 7,8 mmol/dm^3 and glycated hemoglobin over 7%. Prior to the study, the patients were treated with premix insulin divided in two daily doses and metformin after the lunch, which did not result in sufficient regulation of glycaemia. We started treatment with one daily insulin basal analog and three daily doses of metformin and monitored the above mentioned parameters. We advised patients to change their lifestyle, to practice energy restricted diet and to increase their daily physical activity. Insulin doses were titrated separately for each patient (0,7-1 IU/kg). Weight reduction was recorded after the study. Mean fasting glycaemia decreased from 8,6±0,49 mmol/dm^3 to 7,04±0,19 mmol/dm^3 ($p < 0,05$). Mean postmeal glycaemia decreased from 9,74 ± 0,79 mmol/dm^3 to 7,6 ± 0,43 mmol/dm^3 ($p<0,05$). Mean HbA1c decreased from 8,80 ± 0,59 % to 7,11 ± 0,22 % ($p<0,05$).

Treatment with one daily doses of basal insulin analog and three daily doses of metformin with lifestyle modification and weight reduction, in obese patients with type 2 diabetes can be useful for the endothelial function improvement and may decrease the risk of cardiovascular diseases.

KEY WORDS: diabetes type 2, weight reduction, endothelial dysfunction

Introduction

Hyperglycemia and insulin resistance are responsible for the vascular endothelial dysfunction in diabetic patients. Hyperinsulinemia and insulin resistance affect the atherogenic action caused by insulin. Obese diabetes type 2 patients, with impaired glucose tolerance, patients with metabolic syndrome, first degree relatives of patients with type 2 diabetes and women with pervious gestational diabetes are at high risk of atherosclerosis development, endothelial dysfunction and cardiovascular diseases. Therapeutic approach that can improve insulin sensitivity and glycaemia control will prevent cardiovascular complications of diabetes. Endothelial dysfunction is connected with decreased nitric oxide production in obese, hypertensive and diabetes type 2 patients. Elevated free fatty acid levels increase vascular tone in insulin resistant persons, which is associated with vascular dysfunction.

High level of blood glucose, increased blood pressure, dyslipidemia, obesity, physical inactivity, high energy diet, are identified as main risk factors of endothelial dysfunction. Good management of the above mentioned risk factors may improve endothelial function. It is well documented that good glycaemia control enables improvement in dyslipidemia, insulin resistance and blood pressure. Many contemporary studies indicate that regular exercise and weight loss can improve insulin resistance and endothelial function. Hyperglycemia is a risk factor of both micro and macrovascular disease (1).

Objective

The aim of this study was to evaluate the effects of basal insulin analog and metformin on glycaemia control and weight as risk factors for endothelial dysfunction.

Material and Methods

Total of 15 patients (9 male and 6 female) with type 2 diabetes were studied. The patients were observed over six months period. Glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose PPG), and body mass index (BMI), were monitored. Mean age of the subjects was 53,4 ± 6,27 years. Mean diabetes duration was 3,71 ± 1,89 years. Mean body mass index decreased from 27,5 ± 1,45 kg/m^2 to 25,7 ±1,22 kg/m^2 after the study. In this study we included diabetic patients with fasting glycaemia over 7 mmol/ dm^3, post-meal glycaemia over 7,8 mmol/dm^3 and glycated hemoglobin over 7%. Prior to the study, patients were treated with premix insulin divided into two daily doses + metformin 850 mg after the lunch, which did not result in sufficient regulation of glycaemia. We initiated treatment with one daily dose of basal insulin analog and three daily doses of metformin (2550 mg/day) and monitored the above mentioned parameters. Patients were advised to start with lifestyle modification, increase physical activity, reduce weight and practice energy restricted diet. Doses of insulin were titrated separately for each patient (0,7- 1 IU/kg).

Results

After six months of treatment with one daily dose of basal insulin analog and three daily doses of metformin, significant decrease was observed in fasting glucose, postmeal glucose level and glycosylated hemoglobin. Weight reduction was recorded after the study.

Mean fasting glycaemia decreased from 8,6±0,49 mmol/ dm^3 (Table 1., Figure 2.) to 7,04 ± 0,19 mmol/ dm^3 ($p < 0,05$) (Table 2., Figure 5.). Mean postmeal glycaemia decreased from 9,74±0,79 mmol/ dm^3 (Table 1., Figure 3.) to 7,6 ± 0,43 mmol/ dm^3 ($p<0,05$) (Table 2., Figure 6.). Mean HbA1c decreased from 8,80 ± 0,59 % (Table 1., Figure 1.) to 7,11 ± 0,22 % ($p<0,05$) (Table 2., Figure 4.).

Parameters	Reference Values	Prior to the Study
HbA1c %	7,0	8,8
MFBG mmol/ dm^3	6,1	8,6
MPPG mmol/ dm^3	7,8	9,3

TABLE 1. The group of patients treated with two daily doses of NPH + metformin

Parameters	Reference Values	Prior to the Study	After the Study
HbA1c %	7,0	8,8	7,1
MFBG mmol/ dm^3	6,1	8,6	7,04
MPPG mmol/ dm^3	7,8	9,3	7,78

TABLE 2. Group of patients treated with one daily dose of basal insulin analog and metformin

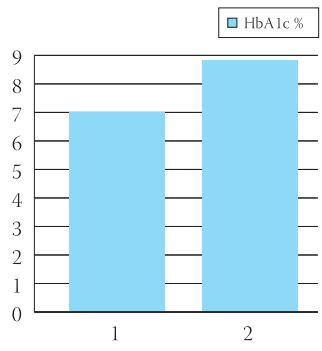

FIGURE 1. HbA1c prior to the study

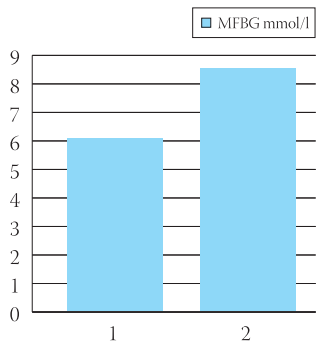

FIGURE 2. MFBG prior to the study

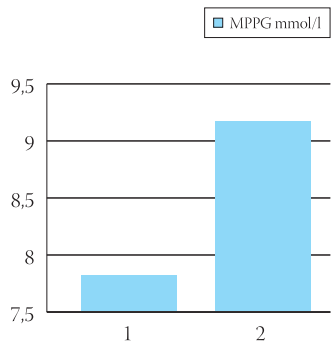

FIGURE 3. MPPG prior to the study

Discussion

Life style modification, with increased physical activity and weight loss has beneficial impact on endothelial function. Weight loss of 5-10% can improve insulin sensitivity and reduce hyperglycemia in obese diabetic persons (2). Weight reduction is effective in preventing type 2 diabetes. The US Diabetes Prevention Program included 3200 overweight persons at high risk for diabetes. In a group of persons with body weight loss of 5 - 7%, 58% reduction in diabetes was recorded (3). The impact of weight reduction on vessels wall with or without exercising has been studied in obese men. Mean BMI decreased from 32,3 kg/m² to 27,6 kg/m² and mean BP decreased by 6 % after three months of energy–restricted diet. Weight reduction positively effected an increase in carotid artery distensibility. Weight loss programs are useful for the treatment and prevention of diabetes and they can improve endothelial function, which can decrease the risk of atherosclerosis and cardiovascular disease in obese subject with or without diabetes (4). Twenty-four obese patients, BMI 36,7 kg/m² were studied and followed throughout the period of 6 months. Weight reduction of 6,6 % and significant improvement in insulin sensitivity were recorded after 6 months of diet therapy. The endothelial dependent vasodilatation was associated with percentage of weight reduction (5). Weight reduction and increased physical activity resulted in improvement of insulin resistance, serum glucose levels and lipid profiles (6). Over the past few decades several trails were conducted, and it is well established that weight reduction and diet therapy have good effects on endothelial function.

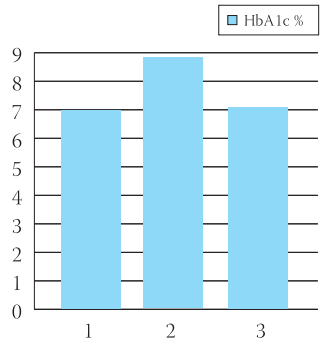

FIGURE 4. HbA1c prior to and after the study

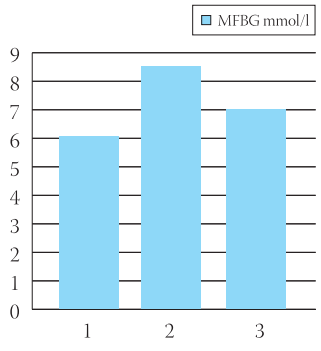

FIGURE 5. MFBG prior to and after the study

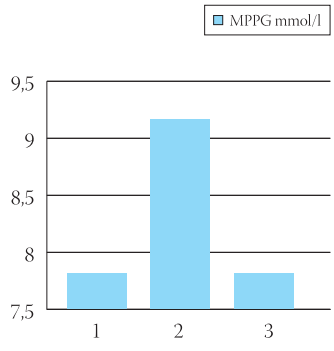

FIGURE 6. MPPG prior to and after the study

Conclusion

Treatment with one daily doses of basal insulin analog and three daily doses of metformin with lifestyle modification and weight reduction in obese patients with type 2 diabetes could be useful for the endothelial function improvement and may decrease the risk for cardiovascular diseases.

List of Abbreviations

HbA1c - glycated hemoglobin
BMI - body mass index
MFBG - mean fasting blood glycaemia
MPPG - mean postprandial blood glycaemia

References

(1) Intensive blood – glucose control with Sulfonylureas or INS compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS) UK Prospective Diabetes Study Group, Lancet 1998; 352(9131): 837 – 853.

(2) Watts N. B., Spanheimer R.G., DiGirolamo M., et al. Prediction of glucose response to weight loss in patients with non insulin dependent diabetes mellitus. Arch. Intern. Med. 1990; 150: 803-806.

(3) Knowler W. C., Barrett – Connor E., Fowler S. E., et al. Reduction in the incidence of type 2 diabetes with life style intervention or metformin. N. Engl. J. Med. 2002; 346: 393 – 403.

(4) Balkestein E. J., van Aggel-Leijssen D. P., van Baak M. A., Struijker – Boudier H. A., Van Bortel L. M. The effect of weight loss with or without exercise training on large artery compliance in healthy obese men. J. Hypertens. 1999; 17: 1831 – 1835.

(5) Hamdy O., Ledbury S., Mullooly C., et al. Lifestyle modification improves endothelial function in obese subject with the insulin resistance syndrome. Diabetes Care 2003; 26: 2119 – 2125.

(6) Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults – The Evidence Report, National Institutes of Health. Obes. Res. 1998; 6 (Suppl 2): 51 S - 209 S.