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INFLUENCE OF BETA-BLOCKERS ON INSULIN RESISTANCE IN PATIENTS WITH DIABETES MELLITUS TYPE 2

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The insulin resistance is present when the concentration of insulin is normal and biological response is decreased. The most frequent metabolic change that was detected during anti-hypertension therapy is a change in the insulin resistance.

Beta-blockers are generally accompanied by the deterioration of metabolic control in patients with diabetes. It is considered that using certain beta-blockers in hypertension therapy in patients with diabetes mellitus type 2 (DM type 2) can significantly influence the insulin resistance.

Taking into consideration the latest knowledge on pharmaco-dynamics of insulin analogues and beta -blockers, by observing the parameters of glycoregulation, it would be of great interest and practical significance to determine the following influence of beta - blockers and their selectivity on the insulin resistance in patients with DM type 2 and hypertension.

The research was conducted at the Endocrinology Clinic of the Clinical Centre Niš, and it included 60 patients with diagnosed diabetes mellitus type 2.

After collecting anamnesis data, clinical and laboratory research performance, all patients were divided into two therapy groups: first group, 30 patients that were administered the therapy based on insulin glargine and second group, 30 patients that were administered the therapy based on insulin glargine and blocker divided into two therapy subgroups: 15 patients that were administered the therapy based on insulin glargine and carvedilol and 15 patients that were administered the therapy based on insulin glargine and metoprolol.

Higher values of glycaemia and glycolised haemoglobin were found in patients receiving therapy based on beta–blocker ($p<0.05$). Therapy group treated with metoprolol had higher average values of glycaemia and HbA1C, compared to the group treated with carvedilol. The obtained difference was not statistically significant.

Is confirmed that the group of patients to which beta–blockers had been administered had statistically higher values of glycaemia and glycolised haemoglobin. This indicates that the application of beta – blockers deteriorates glycoregulation, thus increasing the possibility of early manifestation of complications caused by diabetes. *Acta Medica Medianae 2011;50(4):23-28.*

Key words: *beta-blockers, carvedilol, metoprolol, insulin glarine, insulin resistance*

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Introduction

Diabetes is a disease characterized by complex disorders of metabolism of carbo-hydrates, fats, proteins, electrolytic and acidobasal status, where hyperglycaemia and abnormalities in insulin secretion of periphery effect are primary characteristics (1).

In order to decelerate the occurrence of complications caused by diabetes, European Society of Cardiology has issued a reference for control of the patients blood pressure which must not be higher than 130/80 mmHg, or the patients with diabetes with increased urinary excretion of proteins with values under 120/80 mmHg (2).

Metabolic syndrome (MS) represents a group of metabolic disorders that increase the risk of the on-set of diabetes and cardiovascular diseases (3). The prevalence of MS significantly increases with the increase of insulin resistance (4). The insulin resistance is present when the concentration of insulin is normal and biological response is decreased. Besides this observation, it is possible to examine the insulin resistance by following the metabolic rout of insulin from its synthesis in beta-cell of endocrine pancreas, over its transport via circulation to its binding to target tissue receptors and the activating post-receptor mechanisms via which the insulin response is generated (5). Although the insulin resistance varies a lot even in healthy normoglycaemic

individuals, it has been suggested that the insulin resistance takes an important part in the on-set of a chain of diseases (6).

The most frequent metabolic change that was detected during anti-hypertension therapy is a change in the insulin resistance occurring as a result of various mechanisms including decrease of microcirculation in muscles and disorders in intracellular metabolism of glucoses. Decrease of microcirculation in muscles is a result of the effect of beta-blockers due to preponderance of alpha-receptor activity (7).

The antagonists of β-adrenergic receptors are a very important group of drugs found in 1958. The most significant are the effects on the cardio-vascular system and smooth bronchial muscles. The mechanism of action is common to all – basic therapy features are the result of blocking β1 receptors in the heart and chemo-dynamic changes that are caused by this. The anti-hypertension effect is moderate and is developed within 2-4 weeks (8). The anti-hypertension effect of the antagonists of β-adrenergic receptors is clinically very useful due to the preserved reflexive vasoconstriction (9).

Beta -blockers are generally accompanied by the deterioration of metabolic control in patients with diabetes. It is considered that using certain beta-blockers in hypertension therapy in patients with diabetes mellitus type 2 (DM type 2) can significantly influence the insulin resistance.

Aims

Taking into consideration the latest knowledge on pharmaco-dynamics of insulin analogues and beta -blockers, by observing the parameters of glycoregulation, it would be of great interest and practical significance to determine the following influence of beta - blockers and their selectivity on the insulin resistance in patients with DM type 2 and hypertension.

Patients and methodology

This study included a retrospective, comparative method of clinical research, applying an alternative therapy monitoring. The research was conducted at the Endocrinology Clinic of the Clinical Centre Niš, and it included 60 patients with diagnosed diabetes mellitus type 2.

The patients were administered insulin analogue therapy, insulin glargine, in therapeutic range from 16 i.u. to 32 i.u. The insulin doses were determined individually, depending on the glycaemia level and the values of glycolized haemoglibin A1C.

Normal values of Hb A 1C were considered the concentrations from 5.0 to 6.9%.

The patients with diagnosed hypertension were administered beta-blockers therapy: carvedilol in therapeutic range from 12.5 mg to 25 mg) and metoprolol in therapeutic range from 100 mg to 200 mg.

All patients were on the same hygienic-dietary regime.

After collecting anamnesis data, clinical and laboratory research performing, all patients were divided into two therapy groups:

- first group: 30 patients that were administered the therapy based on insulin glargine;
- second group: 30 patients that were administered the therapy based on insulin glargine and blocker where divided in the two subgroups;
- IIa subgroup: 15 patients that were administered the therapy based on insulin glargine and carvedilol;
- IIb subgroup: 15 patients that were administered the therapy based on insulin glargine and metoprolol;

The estimation of pharmaco-dynamic effect included therapy monitoring (determining and observing parameters of glycoregulation control-glycaemia and glycolised haemoglobin) in the morning blood sample.

Laboratory testing included glycaemia control and HbA1C determination.

The previously mentioned biochemical methods were determined via ready tests produced by Ellitech company, on the biochemical analysator BTS – 370 (Bio–system).

The statistical processing was performed in programmes Excel 7.0 and SPSS 11.0 in windows 98 environment, while the results were shown in tables.

Results

General characteristics and anthropometric indicators of the examined patients are presented in Table 1.

The performed statistic analysis did not show significant differences in the frequency of occurence between the genders. The average duration of diabetes mellitus and a patient's age did not significantly differ between male and female patients. Men were much taller and heavier than women ($p<0.01$), but the obesity rate expressed by BMI did not differ significantly between the genders.

The influence of beta–blockers on the insulin resistance, observing the parameters of glucoregulation (values of glycaemia and haemoglobin HbA1C), is presented in Table 2.

Statistically significantly higher values of glycaemia and glycolised haemoglobin were determined in patients receiving therapy based on beta–blocker ($p<0.05$).

Comparative values of glicemia and HbA1C in patients receiving therapy based on beta–blockers of different selectivity: carvedilol – non – selective and metroprolol – β1 selective beta–blocker was presented in the Table 3.

Table 1. General characteristics of the examined patients and anthropometric indicators

	Women	Men	Total
Number(%)	38 (63%)	22 (37%)	60 (100%)
Age	58.07±12.08	57.9±13.05	58.01±12.34
Duration of illness(months)	160.84±6.2	171.9±6.3**	164.9±8.2
Height (cm)	69.39±13.2	79±12.58**	72.91±13.7
Weight (kg)	26.7±4.9	26.31±3.1	26.56±4.33
BMI (kg/m2)	114.57±75.32	133.2±80	121.4±76.95

Table 2. The influence of applied beta–blockers (bb) on glucoregulation

Therapy group	Glycemic values (mmol/l)	HbA1c values (%)
with bb	7.33±1.08*	7.9±0.96*
with bb	6.94±1.05	7.42±0.8

Table 3. Comparative values of glycaemia and HbA1c in patients receiving therapy based on carvedilol and metoprolol

Therapy group	Glycemic values (mmol/l)	HbA1c values (%)
karvedilol	7.28±0.36	7.67±0.56
metoprolol	7.32±0. 78	7.72±0.83

Data analysis showed that the therapy group treated with metoprolol had higher average values of glycaemia and HbA1C, compared to the group treated with carvedilol. The obtained difference was not statistically significant.

Discussion

Controlled glucoregulation in patients with DM type 2 takes an important part in prevention and decelerating complications caused by diabetes. Due to the specific pharmacokinetics of insulin glargine, which is the closest to the physiological profile of basal insulinization, an optimal control of glucoregulation parameters is provided (10).

Beta – blockers can generally have metabolic side effects in patients with diabetes. The effects primarily refer to metabolism of glucose and lipids. The expected metabolic disorders are caused by using beta–blockers with higher affinity for β1 receptors, because lypolysis in adipocutes, muscle glucogenolysis and secretion of insulin and glucagon are intermediated by sympatic activation of β2 receptors (11).

The information announced by an epidemiology study of European Prospective Investigation into Cancer in Norfolk (EPIC – Norfolk) shows that HbA1c is a positive risk factor for cardiovascular mortality, even in normal limits 5.0 – 6.9%. This indicates that, included in the metabolic syndrome, disordered tolerance to glucose and DM type 2, there is a continuous RISK concerning the level of HbA1C (12).

In this research, the analysis of pharmacodynamic response of the applied insulin analogue, insulin glargine and β–blockers confirmed that the group of patients where beta–blockers had been applied had statistically higher values of glycaemia and glycolised haemoglobin. This indicates that the application of beta–blockers deteriorates glucoregulation, thus increasing the possibility of early manifestation of complications caused by diabetes.

According to their selectivity, beta–blockers are divided in: selective and non-selective. Metroprolol is a selective β1 blocker with the half–time of elimination of 3h. Carvedilol is a non–selective beta–blocker with vasodilatation effect. In "in vitro" experiments and examinations that involved patients with diabetes and hypertension, carvedilol increased endolateral vasodilatation, decreased inflammation and aggregation of thrombocytes and had a little effect on metabolism of glucose and insulin resistance, compared to the selective beta–blockers (13).

The data analysis showed that the therapy group treated with metoprolol had higher average values of glycaemia and HbA1C, compared to the group treated with carvedilol. There were insignificant differences between comparative values of glycaemia and HbA1C in the patients that received therapy based on carvedilol or metoprolol, and these values were not statistically significant.

In order to decrease the cardiovascular risk, a multilateral approach to diabetes is necessary and it is mainly directed to controlling glycaemia, dislypidaemia and hypertension (14).

Cardioprotective effect of beta–blockers is especially important in patients with diabetes due to high risk of the onset of coronary disease and coronary insufficiency. These patients are at risk of the onset of heart insufficiency, whereas beta – blockers show favorable effect (15).

The research did not show the difference between the values of glycaemia in the groups of patients treated with carvedilol or metoprolol, which was indicated by many studies. In the studies, the difference is explained by different effects of the applied β–blockers on the insulin sensitivity (7, 16).

Beta–blockers are efficient anti-hypertensive drugs, especially in prevention of ischemic heart disease, but some of them, e.g. β1 blockers, have numerous metabolic side–effects, especially in deterioration of insulin resistance and masking hypoglycaemia symptoms via adrenalin; beta–blockers as nebivolol can even improve the insulin sensitivity. In patients with diabetes it was detected that nonselective blockage prolonged the insulin-induced hypoglycaemia (10). That is why the application of beta–blockers is not absolutely counterindicated in diabetes, as it was suggested earlier, but during the application an individual balance should be provided, primarily taking care of the prevention of cardiovascular risk in patients with diabetes (17).

The Carvedilol or Metoprolol European Trial (COMET) confirms that carvedilol leads to significant and clinically relevant survival rate improvement, better living conditions, fewer newly detected cases of diabetes and significant decrease of vascular events as myocardial infarction (16).

The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GIMINI) indicates that metoprolol significantly deteriorates the insulin resistance, and this effect is not noticed during the application od carvedilol (7).

Application of beta-blockers in combination with alpha-blockers (Carvedilol) showed a neutral effect on the metabolism of glucosis and favorable effect on the lypide profile. The intracellular metabolism of glucoses was deteriorated with the decrease of the insulin secretion.

This could be a direct consequence of beta-blockage, due to decreased response of pancreas beta-cells (hypoglycemia) caused by the use of thiazide diuretics (7).

The choice of beta-blockers should be individual, taking into account the type of diabetes.

The selective beta-blockers have an advantage in patients with diabetes mellitus type 1, while the non-selective beta-blockers, as carvedilol, can be additionally beneficial in patients with the insulin resistance and peripheral artery disease (18).

Most studies indicate the systemic changes at the level on the insulin resistance, but the research performed by Queiborgh et al. indicates that the two beta-blockers, carvedilol and metoprolol have different effects on the vascular insulin sensitivity, whereas carvedilol is the first choice (19). Carvedilol does not have a negative effect on the control of glycaemia and glycoregulation and it improves certain components of the metabolic syndrome (which is not the case with metoprolol) in patients with diabetes and hypertension (20).

Conclusion

The application of beta-blockers is indisputable in the therapy concerning cardiovascular diseases accompanied by diabetes, although they increase the level of glycaemia and glycosides hemoglobin. It is necessary to make the right choice of a beta-blocker. The selectivity of beta-blockers is very important in choosing the therapy. In the case of choosing between carvedilol and metoprolol as beta-blockers in the therapy of cardiovascular diseases accompanied with diabetes, carvedilol is more favorable as a non-selective beta-blocker with vasodilatation effect.

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UTICAJ BETA BLOKATORA NA INSULINSKU REZISTENCIJU KOD BOLESNIKA SA DIJABETES MELITUSOM TIP 2

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Insulinska rezistencija postoji kada je uz normalnu koncentraciju insulina smanjen biološki odgovor. Najčešća metabolička promena koja se zapaža tokom antihipertenzivne terapije jeste promena insulinske rezistencije.

Beta blokatori su generalno udruženi sa pogoršanjem metaboličke kontrole kod bolesnika sa dijabetesom. Smatra se da primena pojedinih beta blokatora u terapiji hipertenzije kod bolesnika sa dijabetes melitusom tip 2 (DM tip 2) može značajno uticati na insulinsku rezistenciju.

Imajući u vidu najnovija saznanja o farmadinamici insulinskih analoga i beta blokatora, praćenjem parametara glikoregulacije, bilo bi od interesa i praktičnog značaja utvrditi uticaj beta blokatora i njihove selektivnosti na insulinsku rezistenciju kod bolesnika sa DM tip 2 i hipertenzijom.

Ispitivanje je obavljeno na Klinici za endokrinologiju Kliničkog centra u Nišu i obuhvatalo je 60 bolesnika sa dijagnostikovanim dijabetes melitusom tip 2.

Nakon anamnestičkih podataka, kliničkog i laboratorijskog ispitivanja, svi bolesnici su podeljeni u dve terapijske grupe: prva grupa, 30 bolesnika na terapiji insulinom glargine i druga grupa, 30 bolesnika na terapiji insulinom glargine i beta blokatorom koja je podeljena u dve terapijske podgrupe: 15 bolesnika na terapiji insulinom glargine i karvedilolom i 15 bolesnika na terapiji insulinom glargine i metoprololom.

Veće vrednosti glikemije i glikoziranog hemoglobina nađene su u grupi bolesnika na terapiji beta blokatorom ($p<0.05$). Terapijska grupa sa metoprololom imala je veće prosečne vrednosti glikemije i HbA1C, u odnosu na grupu sa karvedilolom. Pri tome, dobijena razlika nije bila statistička značajna.

Utvrđeno je da grupa bolesnika u kojoj je beta blokator primenjen ima statistički veće vrednosti glikemije i glikoziliranog hemoglobina. Ovo ukazuje da primena beta blokatora pogoršava glikoregulaciju, a time povećava mogućnost ranijeg ispoljavanja komplikacija dijabetesa. *Acta Medica Medianae 2011;50(4):23-28.*

Ključne reči: beta-blokatori, karvedilol, metoprolol, insulin glargine, insulinska rezistencija