World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

Check for updates

Beta-blockers and their impact on metabolic processes

Halida Mahmutbegović Poljaković [1,*], Mithat Tabaković [1], Eldina Halilović [1], Halid Mahmutbegović [2], Elvedin Osmanović [2] and Aldijana Mahmutović Milićević [3]

[1] *European University "Kallos"; XVIII Hrvatske brigade br. 8, 75000 Tuzla, Bosnia and Herzegovina.*
[2] *JZU „Dom zdravlja"Živinice, ul. Alije Izetbegovića br.17, 75270 Živinice, Bosnia and Herzegovina.*
[3] *Cantonal Administration for Inspection Affairs of Tuzla Canton, Rudarska 72, 75 000 Tuzla, Bosnia and Herzegovina.*

World Journal of Advanced Research and Reviews, 2024, 23(02), 1938–1947

Publication history: Received on 08 July 2024; revised on 19 August 2024; accepted on 21 August 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.23.2.2490

Abstract

The aim of the study is to determine the effect of beta-blockers on lipid status, triglycerides and Body Mass Index (BMI) in patients using beta-blockers in the treatment of arterial hypertension. Our study included 120 patients at the Public Health Institution "Dom zdravlja" Živinice. The participants were monitored over a period of 3 years. Measurements were made after 12, 24 and 36 months of treatment. Patients were divided into two groups. The experimental group included 60 patients, who used beta-blockers in the treatment of arterial hypertension. The control group included 60 patients who used other antihypertensives as their first choice medication in the treatment of arterial hypertension. By monitoring cholesterol and triglyceride levels in patients using beta-blockers and other antihypertensive medications, and comparing these values within the group, no statistically significant difference in cholesterol and triglyceride levels was found in patients who used beta-blockers after 12, 24, and 36 months of treatment. There was also no statistically significant effect of therapy on the change in cholesterol and triglyceride values at observed time intervals, nor was there a statistically significant difference between these values. BMI monitoring showed a statistically significant difference between patients using beta-blockers and other antihypertensive drugs, with patients using beta-blockers having a higher BMI after 36 months of treatment. There was no statistically significant difference in BMI between patients using bisoprolol and carvedilol and patients using other beta-blockers, but patients using bisoprolol and carvedilol had lower BMI values. In studies conducted in recent years, it has been noted that many beta-blockers cause dose-dependent adverse metabolic effects on glucose and lipid metabolism, with the most adverse metabolic effects observed in patients treated with conventional non-selective beta-blockers. On the other hand, more favorable metabolic profile have drugs with β1 selective activity, such as atenolol and metoprolol, especially those with intrinsic sympathomimetic activity such as pindolol. In fact, with these beta-blockers, the adverse metabolic effects appear to be less prominent. In conclusion, beta-blockers do not lead to an increase in cholesterol and triglycerides, but they do lead to an increase in BMI in patients with arterial hypertension

Keywords: BMI; Metabolism; Beta-blockers; Lipid status

1. Introduction

In clinical practice, the use of beta-blockers dates back to the early sixties after the unexpected discovery of their antihypertensive action. However, their use was limited by a number of side effects until the introduction of propranolol in 1964. Their role in the treatment of angina pectoris was discovered later, and in the early eighties their effect in reducing mortality by 20-30% after acute myocardial infarction was proven, primarily reducing malignant catecholamine-dependent arrhythmias. (1)

* Corresponding author: Halida Mahmutbegović Poljaković

Although conventional beta-blockers have been used to treat hypertension for many years, their use in the treatment of overweight hypertonics is a matter of debate. Beta-blockers can increase the level of triglycerides and reduce the level of HDL cholesterol, and in already proven dyslipidemia can lead to an additional increase in lipids. (2) They also slow down the heart rate, making it difficult for patients to exercise and putting them at risk of weight gain and obesity. The use of conventional beta-blockers raises concerns about adverse metabolic effects, and a negative impact on overall energy consumption, which again leads to weight gain. (3)

The advantage of third-generation beta-blockers is to improve insulin resistance, lower LDL cholesterol levels and increase serum HDL cholesterol levels, reduce the number of asthma attacks, alleviate coronary spasm, improve peripheral arterial blood flow, prevent erectile dysfunction and better cooperation with the patient. Beta-blockers reduce peripheral vascular resistance (PVR) and myocardial oxygen demand. (4)

Our aim was to determine the effect of beta-blockers on lipid status, triglycerides and BMI in patients using these drugs in the treatment of hypertension.

2. Methods

The sample included 120 patients at the Health Center ''Dom zdravlja'' Živinice. The research is in line with the legal and ethical norms of the research, as well as with the protocol of the Ethics Committee of the public Health Center ''Dom zdravlja'' Živinice

Patients were divided into two groups. The experimental group studied included 60 patients who used beta-blockers (monotherapy and polytherapy) in the treatment of hypertension. The control group included 60 patients who used other antihypertensives as their first choice medication in the treatment of arterial hypertension. The patients were followed for a period of three years and the measurements were made: after 12 months, 24 months and after 36 months.

In this paper, two way ANOVA was used as a statistical method of data processing, based on which we obtained the following information:

- Does the measured data, when considering both groups together, statistically significantly depend on the duration of treatment (12, 24, 36 months)?
- Do the values of repeated measurements statistically significantly depend on the applied therapy?
- Is there a statistically significant difference in the measured values among participants using different therapies?

If a statistically significant difference was determined, we further conducted comparisons in a post hoc analysis using the Bonferroni correction

3. Results

Table 1 Descriptive statistics. Body Mass Index by tested groups and lenght of treatment

Length of treatment	Group	Mean	SD	N
12 months	Control group	32.0	5.7	58
	Beta-blockers	33.2	5.2	58
	Total	32.6	5.5	116
24 months	Control group	32.1	5.9	58
	Beta-blockers	33.2	5.2	58
	Total	32.7	5.6	116
36 months	Control group	32.4	6.1	58
	Beta-blockers	33.5	5.4	58
	Total	33.0	5.8	116

A two-way repeated measures analysis of variance (ANOVA) revealed a statistically significant difference in BMI values after 12, 24, and 36 months of treatment (F(2.113) = 3.67, P = 0.029). Post hoc analysis using Bonferroni correction found that BMI after 36 months of treatment was statistically significantly higher than BMI after 12 months (t=-2.26, P=0.039) and after 24 months of treatment (t=-2.624, P= 0.015). There was no statistically significant effect of administered therapy on BMI change at observed time intervals (F (2.113)=0.072, P=0.931). In order to determine the presence of statistically significant differences among treatments, we compared their values over time. There was no statistically significant difference in BMI between the groups (t=1.096, P=0.275).

Table 2 Results of post hoc testing of statistical significance of the difference in BMI by groups individually. Bonferroni correction was applied

(I) Lenght of treatment	(J) Lenght of treatment	Difference (I-J)	t	P
12 months	24 months	-0.041	-0,353	0.500
	36 months	-0.348	-2,260	0.039
24 months	12 months	0.041	0,353	0.500
	36 months	-0,307*	-2,624	0.015
36 months	12 months	0.348	2.260	0.039
	24 months	0,307*	2.624	0.015

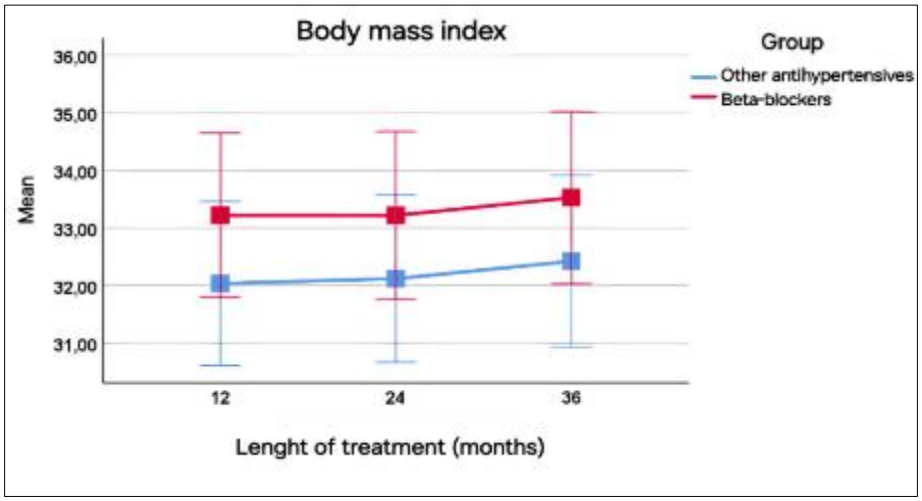

Figure 1 Mean values of BMI (kg/m^2). Vertical lines represent a 95% confidence interval (95% CI) of the mean

Table 3 Descriptive statistics. Cholesterol by groups and the lenght of treatment

Lenght of treatment	Group	Mean	SD	N
12 months	Control group	5.4	1.2	60
	Beta-blockers	5.5	1.2	59
	Total	5.5	1.2	119
24 months	Control group	5.4	1.2	60
	Beta-blockers	5.3	1.3	59
	Total	5.4	1.3	119
36 months	Control group	5.4	1.3	60
	Beta-blockers	5.1	1.4	59
	Total	5.3	1.4	119

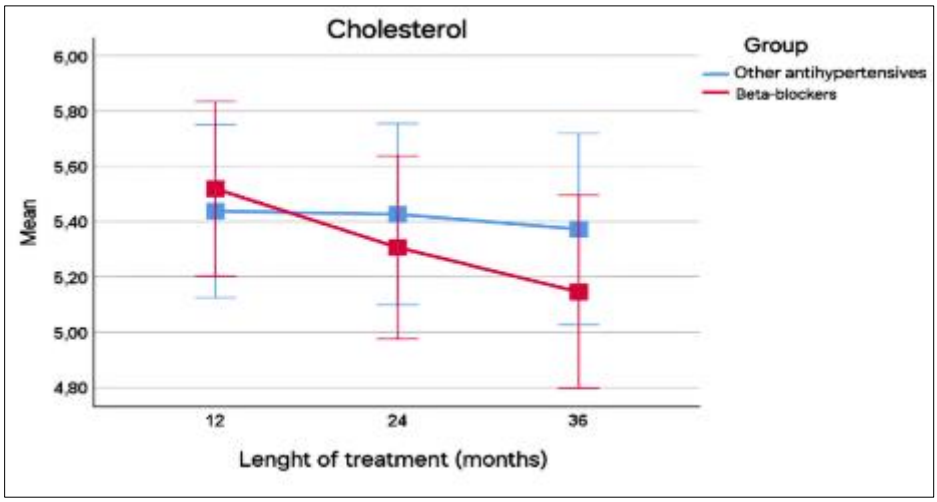

Figure 2 Mean values of cholesterol (mmol/L). Vertical lines represent a 95% confidence interval (95% CI) of the mean

There were no statistically significant differences in cholesterol values after 12, 24 and 36 months of treatment (F(2.116)=2.035, P=0.135). There was no statistically significant effect of administered therapy on BMI change at observed time intervals (F (2.113)=0.072, P=0.931). In order to determine the presence of statistically significant differences among treatments, we compared their values over time. No statistically significant difference in cholesterol levels among the groups was found (t = 0.44, P = 0.662).

Table 4 Descriptive statistics. Triglyceride values by tested groups and lenght of treatment

Lenght of treatment	**Group**	**Mean**	**SD**	**N**
12 months	Control group	5.4	1.2	60
	Beta-blockers	5.5	1.2	59
	Total	5.5	1.2	119
24 months	Control group	5.4	1.2	60
	Beta-blockers	5.3	1.3	59
	Total	5.4	1.3	119
36 months	Control group	5.4	1.3	60
	Beta-blockers	5.1	1.4	59
	Total	5.3	1.4	119

No statistically significant difference in triglyceride values was found after 12, 24, and 36 months of treatment (F(2,116) = 2.96, P = 0.056). Additionally, no statistically significant impact of the applied therapy on triglyceride values was observed during these time intervals (F(2,116) = 1.704, P = 0.186). In order to determine the presence of statistically significant differences among treatments, we compared their values over time. No statistically significant difference in triglyceride levels among the groups was found (t = 0.273, P = 0.539).

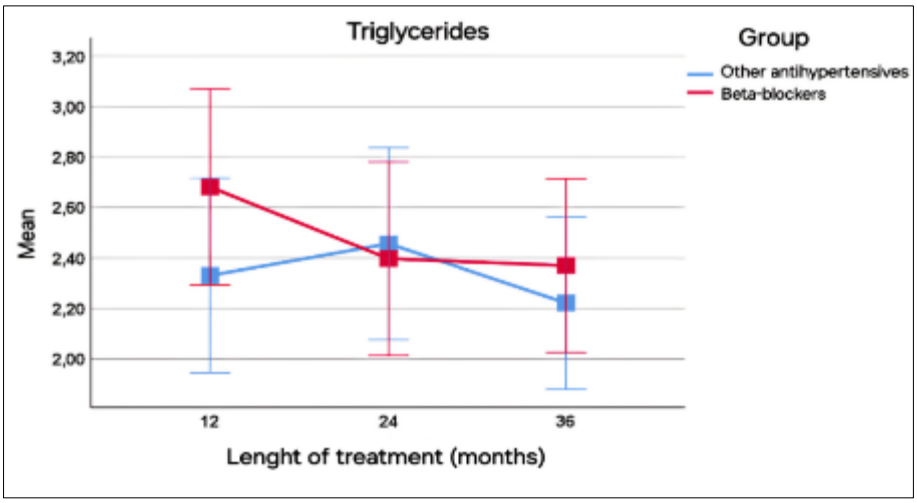

Figure 3 Mean values of triglycerides (mmol/L). Vertical lines represent a 95% confidence interval (95% CI) of the mean

Table 5 Body Mass Index by lenght of treatment and by tested groups

Lenght of treatment	Group	Mean	SD	N
12 months	Bisoprolol and Carvedilol	32.4	5.3	38
	Other BB	34.8	4.8	20
	Total	33.2	5.2	58
24 months	Bisoprolol and Carvedilol	32.4	5.3	38
	Other BB	34.8	4.9	20
	Total	33.2	5.2	58
36 months	Bisoprolol and Carvedilol	32.8	5.4	38
	Other BB	34.9	5.2	20
	Total	33.5	5.4	58

No statistically significant difference in BMI values was found after 12, 24, and 36 months of treatment ($F(2,55) = 0.869$, $P = 0.425$). Additionally, no statistically significant impact of the applied therapy on BMI values was observed during these time intervals ($F(2,55) = 0.566$, $P = 0.571$). In order to determine statistically significant differences among treatments, we compared their values over time. No statistically significant difference in BMI values among the groups was found ($t = 1.606$, $P = 0.114$).

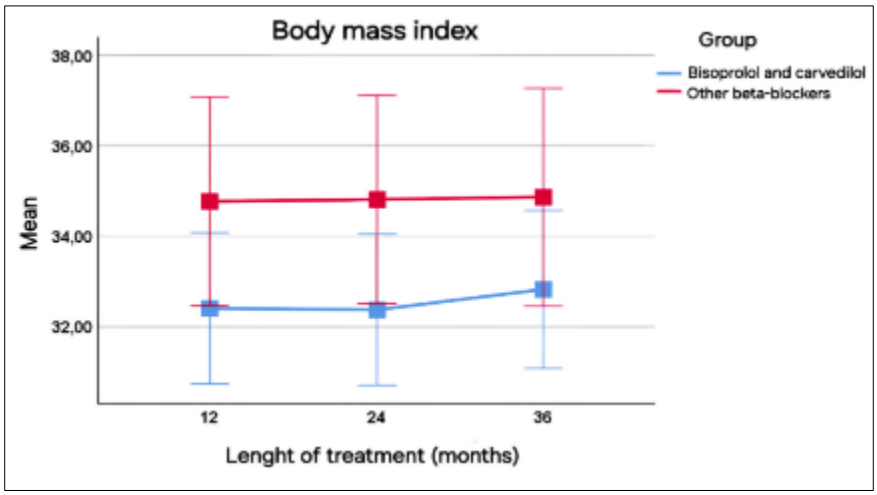

Figure 4 Mean values of BMI (kg/m^2). Vertical lines represent a 95% confidence interval (95% CI) of the mean

Table 6 Cholesterol by lenght of treatment and by tested groups

Lenght of treatment	Group	Mean	SD	N
12 months	Bisoprolol and Carvedilol	5.5	1.2	40
	Other BB	5.5	1.2	19
	Total	5.5	1.2	59
24 months	Bisoprolol and Carvedilol	5.3	1.4	40
	Other BB	5.2	1.3	19
	Total	5.3	1.3	59
36 months	Bisoprolol and Carvedilol	5.1	1.5	40
	Other BB	5.2	1.2	19
	Total	5.1	1.4	59

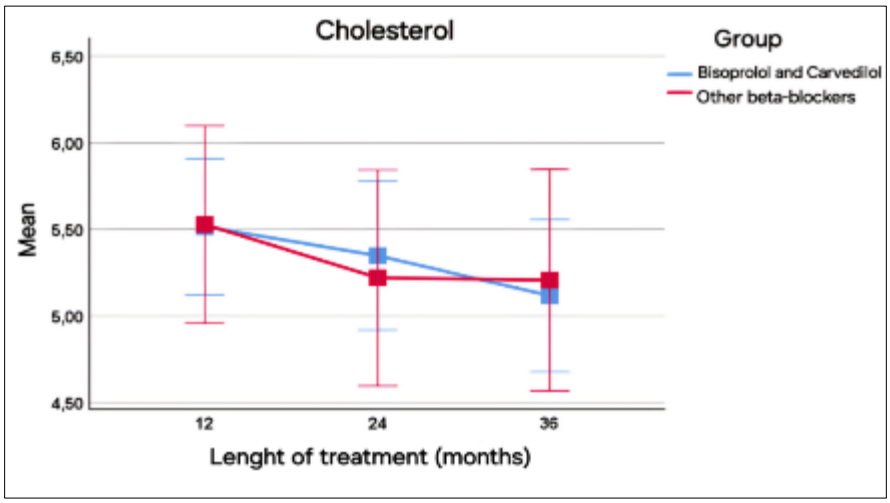

Figure 5 Mean values of cholesterol (mmol/L). Vertical lines represent a 95% confidence interval (95% CI) of the mean

No statistically significant difference in cholesterol values was found after 12, 24, and 36 months of treatment (F(2,56) = 0.2568, P = 0.086). Additionally, no statistically significant impact of the applied therapy on changes in cholesterol values was observed during these time intervals (F(2,56) = 0.119, P = 0.828). In order to determine the presence of statistically significant differences among treatments, we compared their values over time. No statistically significant difference in cholesterol levels was found among the groups (t = 0.025, P = 0.980).

Table 7 Triglycerides by lenght of treatment and by tested groups

Lenght of treatment	Group	Mean	SD	N
12 months	Bisoprolol and Carvedilol	2.6	1.5	40
	Other BB	2.7	1.8	19
	Total	2.7	1.6	59
24 months	Bisoprolol and Carvedilol	2.4	1.3	40
	Other BB	2.3	1.5	19
	Total	2.4	1.4	59
36 months	Bisoprolol and Carvedilol	2.4	1.5	40
	Other BB	2.2	1.2	19
	Total	2.4	1.4	59

No statistically significant difference in triglyceride values was found after 12, 24, and 36 months of treatment (F(2,56) = 2.510, P = 0.090). Additionally, no statistically significant impact of the applied therapy on triglyceride values was observed during these time intervals (F(2,56) = 0.407, P = 0.667). In order to determine the presence of statistically significant differences among treatments, we compared their values over time. No statistically significant difference in triglyceride levels was found among the groups (t = 0.181, P = 0.857).

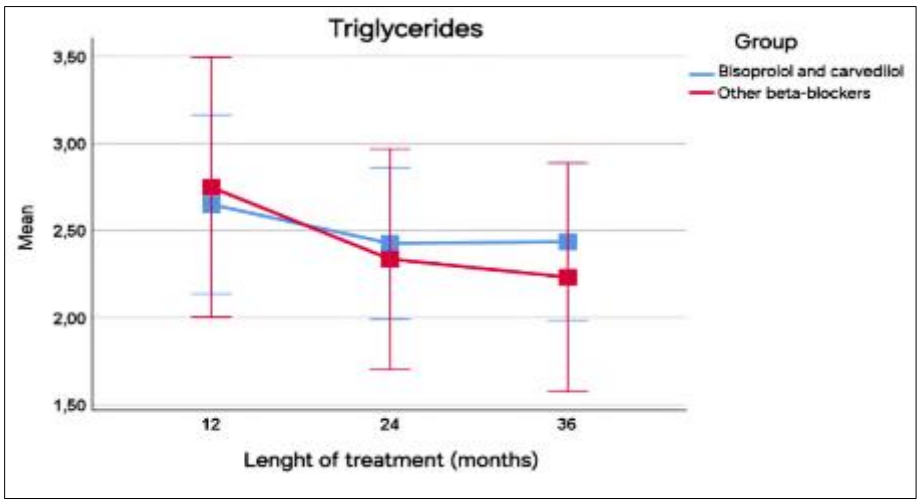

Figure 6 Mean values of triglycerides (mmol/L). Vertical lines represent a 95% confidence interval (95% CI) of the mean

4. Discussion

By monitoring cholesterol and triglyceride values in patients using beta-blockers and other groups of antihypertensive medications, and by comparing these values within the beta-blocker group, no statistically significant difference in cholesterol and triglyceride values was found after 12, 24, and 36 months of treatment. Also, there was no statistically significant effect of therapy on the change in cholesterol and triglyceride values at observed time intervals.

In order to determine the presence of statistically significant differences among treatments, we compared their values over time. There was no statistically significant difference between these groups.

By monitoring BMI values, a statistically significant difference was found between patients using beta-blockers and those using other antihypertensive medications, with patients using beta-blockers having a higher BMI after 36 months of therapy. There was no statistically significant difference in BMI between patients using bisoprolol and carvedilol and patients using other beta-blockers in the beta-blocker group, but patients using bisoprolol and carvedilol had lower BMI values.

In recent studies by other authors, it has been noted that many beta-blockers cause dose-dependent adverse metabolic effects on glucose and lipid metabolism, with the most significant adverse metabolic effects observed in patients treated with conventional non-selective beta-blockers. Non-selective beta-blockers without partial agonist activity increase triglyceride levels by 20-25% and decrease HDL cholesterol levels by 10-20%. On the other hand, β_1 selective drugs reduce HDL cholesterol by 7-10% and increase triglycerides by 10-20%. The exchange of triglycerides and cholesterol between VLDL and HDL leads to the enrichment of HDL with triglycerides and an increase in HDL cholesterol catabolism. (6) So, these antihypertensive agents are not considered to be first-line therapy in metabolic syndrome and they are recommended only in selected cases where beta-blocker treatment is essential or mandatory, such as heart failure, acute or previous myocardial infarction and ischemic heart disease.

The mechanism by which beta-blockers can cause adverse metabolic effects have not been well researched. Carbohydrate and lipid metabolism are also regulated by endogenous catecholamines, norepinephrine and epinephrine, via α and specifically β_2 adrenergic receptors, which are found on peripheral tissue such as skeletal muscle, liver, adipose tissue, pancreatic beta cells, and skeletal muscle cells.

Also, the activity of lipoprotein lipase, hormone-sensitive lipase and lecithin-cholesterol acetyltransferase and other enzyme systems involved in lipid and glucose metabolism is influenced by catecholamines. It has been suggested and partially demonstrated that blocking these adrenoreceptors with adrenergic antagonists may reverse the effects of catecholamines.

The main mechanism proposed to explain the adverse effects of insulin sensitivity observed during beta-blocker treatment is reduced blood flow in skeletal muscle where insulin resistance is prominent. Reduced blood flow, which interferes with the action of insulin on skeletal muscle cells, is a consequence of reduced cardiac volume and blockage of adrenergic β_2 receptors that mediate vasodilation in skeletal muscle. These data may at least partially explain the metabolic side effects of these antihypertensive drugs and the more favorable metabolic profile of β_1 selective activity, such as atenolol and metoprolol, and especially those with intrinsic sympathomimetic activity (ISA) such as pindolol. In fact, with the use of these beta-blockers, the adverse metabolic effects appear to be less prominent.

Clinical studies, including the largest ones with carvedilol (GEMINI study) and nebivolol (YESTONO study), showed no negative effects on lipids, carbohydrate metabolism and insulin sensitivity in hypertensive patients with type 2 diabetes. GEMINI (glycemic effects in diabetes mellitus: comparison of carvedilol-metoprolol in hypertensive patients) (7) is the largest study to evaluate the metabolic effects of carvedilol.

This is a randomized, double-blind parallel group study that compared the effects of carvedilol and metoprolol tartrate on glycaemic control in patients with hypertension and diabetes mellitus type 2. A total of 1,235 participants received an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker and were randomized to receive a dose of carvedilol of 6.25 to 25 mg (n = 498) or 50 to 200 mg of metoprolol tartrate (n = 737), each twice daily. Patients were followed for 35 weeks. Blood pressure was similarly controlled in both groups, but the use of carvedilol, in the presence of blockade of the renin-angiotensin system, did not affect glycemic control and improved some components of metabolic syndrome relative to metoprolol. In addition, metoprolol was associated with a significant increase in body weight ($p < 0.001$) and an increase in triglycerides ($p < 0.001$), while carvedilol had no such effect, although there was no difference in the treatment of low-density lipoprotein or high-density lipoprotein. Finally, progression to microalbuminuria was less common with carvedilol than metoprolol (6.4% vs. 10.3%; $p = 0.04$).

Nebivolol is a highly lipophilic selective β1-blocker that has additional nonadrenergic vasodilation activity, which is unique among beta-blockers currently available to clinicians. Clinical data on the effect of Nebivolol on hypertensive patients have shown that there are no adverse effects on metabolic parameters, on lipidemic profile, on plasma glucose levels and insulin sensitivity. The YESTONO study (Blood pressure-lowering effect of nebivolol in hypertensive patients with diabetes mellitus type 2) is the largest prospective study to date on the effects of nebivolol, that involved 2,838 hypertensive patients with concurrent diabetes mellitus type 2, with or without other conditions.

This is a three-month, open-label, multicentre study designed to collect data on the antihypertensive efficacy of Nebivolol 5 mg/day, either as monotherapy or as additional therapy with other antihypertensive drugs, as well as investigating the effects of this drug on metabolic parameters, microalbuminuria, and physical activity. In addition to effectively reduce blood pressure, this study showed a significant ($p < 0.001$) improvement in all metabolic parameters: mean values for both fasting glycemia and glycosylated hemoglobin decreased during the treatment period; mean body weight also decreased and similar results were found for plasma triglyceride, total and LDL cholesterol levels, while mean HDL cholesterol slightly increased. Also, microalbuminuria present in 10.1% of patients at baseline was found in only 6.8% of patients at the end of the study. (9)

The effects of beta-blockers on body weight can be largely explained by changes in energy metabolism. Van Baak (10) estimated that beta-blockers could reduce resting energy consumption by 3-4%. However, it should be noted that no significant effect of beta-blockade on overall energy consumption was found. However, Astrup et al (11) provided evidence that beta-blockers can reduce the thermic effect of food by 25% and oxygen consumption by 23%. Although the thermogenic effect of food (TEF) represents only a relatively small portion of daily energy consumption (3-10%), small differences in TEF over long periods of time can significantly contribute to the development and/or maintenance of obesity.

Beta-blockers also have a negative effect on exercise capacity, (12) which is a fact to consider when prescribing beta-blockers to physically active hypertensive patients without coronary artery disease.

Although these beta-blocker effects reduce total energy consumption by only 5 or 10% (corresponding to up to 100-200 kcal/d) it has been observed in clinical studies that this reduction can easily cause an average weight gain of 1.2 kg. A steady decrease in energy consumption will not be associated with a steady increase in weight. (13)

This result is consistent with the 2001 researcher's observation(14) that weight gain is evident at the start of beta-blocker treatment. Thus, patients achieve and maintain a new state of stability with higher body weight that suppresses the decrease in energy consumption attributed to beta-blockade. The ability to lose weight is obviously directly dependent on the ability to mobilize fat stores. However, beta-blockers are also capable to inhibit lipolysis in response to adrenergic stimulation.

Thus, systemic beta-blockade can promote weight gain at least partially by inhibiting beta-agonist-induced lipolysis. This effect would make it more difficult to lose weight to patients using beta-blockers. Mauriege et al (15) demonstrated that beta-blockers can selectively promote the accumulation of abdominal fat that is more sensitive to catecholamines than peripheral fat. So, a relatively small change in body weight may be associated with pronounced changes in belly fat deposits, thus contributing to abnormalities related to carbohydrate and lipid metabolism. (16).

5. Conclusion

The use of beta-blockers compared to other antihypertensive drugs does not lead to an increase in cholesterol and triglyceride values, but leads to an increase in BMI in patients with arterial hypertension. No differences in cholesterol, triglycerides and BMI values have been found within the group of beta-blockers, between the group of patients using bisoprolol and carvedilol and the group of patients using other beta-blockers. Beta-blockers are highly effective medications used in the treatment of arterial hypertension, and this practice should continue, with appropriate precautions that all mentioned parameters are regularly monitored to prevent potential adverse effects in a timely manner.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed and written consent was obtained from all individual participants included in the study.

References

[1] Knežević A, Beta-blokatori i njihova klinička primjena, Medicus; 19:2, 2010.

[2] Tabaković M, Salkić N, Baraković F, Trnačević S, Hypertension After Renal Transplantation, Current concepts in kidney transplantation, (ur.) Sandip Kapur, In Tech Open Access Publisher, USA, 2012.

[3] Marketou M, Gupta Y, Jain S, Vardas P, Differential Metabolic Effects of Beta-Blockers: an Updated Systematic Review of Nebivolol, Current Hypertens Rep.; 19:22, 2017.

[4] Zaninović-Jurjević T, i sar., Beta-blokatori: lijekovi koji produžuju preživljenje, Medicus; 25:2, 2016.

[5] Carella AM, Antonucci G, Conte M, et al., Antihypertensive Treatment with Beta-Blockers in the Metabolic Syndrome: A Review, Current Diabetes Reviews; 6:215-221, 2010.

[6] Prichard BN, Cruickshank JM, Graham BR: Beta-adrenergic blocking drugs in the treatment of hypertension. Blood Press.; 10:366–386, 2001.

[7] Messerli FH, Bell DS, Fonseca V i sar., GEMINI Investigators. Body weight changes with beta-blocker use: results from GEMINI. Am J Med.; 120:610–15, 2007.

[8] Schmidt AC, Graf C, Brixius K, et al. Blood pressure-lowering effect of nebivolol in hypertensive patients with type 2 diabetes mellitus: the YESTONO study. Clin Drug Investig.; 27(12):841-9, 2007.

[9] Carella AM, Antonucci G, Conte M, et al., Antihypertensive Treatment with Beta-Blockers in the Metabolic Syndrome: A Review, Current Diabetes Reviews; 6:215-221, 2010.

[10] Van Baak MA. Beta-adrenoceptor blockade and exercise. An update. Sports Med.; 5:209–225, 1988.

[11] Astrup A, Simonsen L, Bulow J, Madsen J, Christensen NJ. Epinephrine mediates facultative carbohydrate-induced thermogenesis in human skeletal muscle. Am J Physiol.; 257:340–345, 1989.

[12] Van Baak MA. Beta-adrenoceptor blockade and exercise. An update. Sports Med.; 5: 209–225, 1988.

[13] Jequier E, Tappy L. Regulation of body weight in humans. Physiol Rev.; 79:451–480, 1999.

[14] Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: Beta-adrenergic receptor blockers and weight gain: a systematic analysis. Hypertension; 37:250–254, 2001.

[15] Mauriege P, Brochu M, Prud'homme D, Tremblay A, Nadeau A, Lemieux S, Despres JP. Is visceral adiposity a significant correlate of subcutaneous adipose cell lipolysis in men? J Clin Endocrinol Metab.; 84:736–742, 1999.

[16] Pischon T, Sharma AM. Use of beta-blockers in obesity hypertension: potential role of weight gain. Obesity Reviews; 2(4):275-280, 2001.