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Research Article

Effect Of Antihypertensive Therapy On The Level Of Fatty Tissue Hormones, Endothelium Dysfunction And Metabolic Indicators In Patients Of Arterial Hypertension With Metabolic Syndrome

Uzbekova Nelli Rafikovna[a], Vakhabov Bahrom Mo'minjanovich[b], Usmanova Dilorom Nematjonovna[c]

[a] DSc, Professor of the Department of Faculty Therapy, Andijan State Medical Institute, Andijan, Uzbekistan
[b,c] PhD, Associate Professor of Faculty Therapy Andijan State Medical Institute, Andijan, Uzbekistan

Abstract

This articlepresents the effect of combined antihypertensive therapy on target blood pressure (BP), insulin sensitivity, carbohydrate and lipid metabolism, adipose tissue hormones and endothelial dysfunction of arterial hypertension (AH) with stage II with metabolic syndrome (MS).

In 95.5 % of patients achieved the target level of the BP. As a result of 12 weeks of therapy there was a decrease in body weight, increase the glycemic index, improved lipid profile, reduced leptin and increase adiponectin, improvement in endothelial function.

In patients with MS and AH along with hypotensive activity combined antihypertensive therapy has a positive effect on insulin sensitivity, lipid metabolism, adipose tissue hormones and endothelial function.

Keywords: *Antihypertensive Therapy, Fatty Tissue Hormones, Endothelium Dysfunction, Metabolic Syndrome, Metabolic Indicators, Arterial Hypertension*

Introduction

Metabolic syndrome is associated with a high risk of coronary artery disease and cardiovascular mortality. The key mechanism in the pathogenesis of metabolic syndrome (MS) is insulin resistance (IR) and the accompanying hyperinsulinemia (GI), which trigger the development of both metabolic and cardiovascular disorders [5,7]. IR and compensatory GI lead to vascular endothelial (DE) dysfunction, increased activity of the sympathetic nervous system (SNS), disorders in the hypothalamic-pituitary-adrenal system, activation of the renin-aldosterone system (RAS) and the development of arterial hypertension (AH) [4,5,7].

Pathogenetic therapy of MS includes, among other things, the treatment of arterial hypertension. One of the important conditions for antihypertensive therapy in MS is the

achievement of target blood pressure levels – 130/80 mm Hg and less, since it is under the condition of achieving normotonia that the least number of vascular complications is observed [3,4]. The advantage should be given to drugs that have a neutral effect on metabolic processes and reduce IR and indicators of carbohydrate and lipid metabolism, endothelial dysfunction and adipose tissue function [2,3,4]. These drugs are combined antihypertensive therapy (AHT) [7,9].According to European recommendations [4], combination therapy is indicated for all patients starting from stage II of hypertension, that is, at a BP level of 160/100 mm Hg and more, and is also allowed as an alternative to monotherapy in the form of low-dose combinations in the early stages of hypertension.

The Purpose of the Study

The study of the effect of combined antihypertensive therapy on the target blood pressure, hormones of adipose tissue, indicators of carbohydrate and lipid metabolism and endothelial function in patients with metabolic syndrome and stage II arterial hypertension.

Material and Methods

The study involved 70 patients with MS (34 men and 36 women) aged 36-59 years (average 48.22±5.1 years), the duration of hypertension in MS was on average 9.2±2.14 years.

Metabolic syndrome was diagnosed according to the criteria proposed by the Experts of the US National Cholesterol Education Program (2005). The criteria for MS were considered to be a waist circumference of more than 94 cm in men and more than 80 cm in women; BP is higher than 130/80 mm Hg. fasting plasma glucose more than 5.6 mmol/L. Body mass index (BMI) was calculated using the formula BMI = body weight (kg)/height (m^2).

Glucose-insulin homeostasis was determined by the level of fasting blood glucose (GN), the level of immune-reactive insulin in the blood (IRI) on an empty stomach by the enzyme immunoassay in the radioimmunoassay laboratory of the Republican Center of Endocrinology (Tashkent), using kits from Beckman Coulter (Czech Republic). The HOMA index was calculated (fasting insulin μU/mL x fasting blood glucose mmol/L :22.5). With an insulin level on an empty stomach above 12.5 μU/mL, hyperinsulinemia was diagnosed. With a HOMA index above 2.77, patients were considered insulin resistant. To assess the effect of insulin, the glycemic index was calculated as the ratio of the fasting blood glucose concentration to the fasting IRI level. The index value less than 0.33 was considered as an indirect sign of the presence of IR.

Lipid metabolism parameters – total cholesterol (TC), high density lipoproteins cholesterol (HDL Ch), triglycerides (TG) were determined using a Reflotron plus express analyzer from Roshe (Germany) with Biocon (Germany) reagent kits. The content of low density lipoproteins cholesterol (LDL Ch) was calculated using the W. Friedwald formula.

The levels of leptin and adiponectin were determined from the hormones of adipose tissue using a competitive variant of the enzyme immunoassay using the Human Leptin ELISA and Human Adiponectin ELISA kits "Bio Vender-Laboratorni medicina ES" (Czech Republic), in the "Immunogen-test" laboratory of the Institute of Immunology of the Academy of Sciences of Uzbekistan.

Determination of the level of endothelin-1 (E-1) was carried out by enzyme immunoassay using reagents of the Endothelin kit (Germany). The level of circulating desquamated endothelium (CDE) was assessed by the method of G. Hiadovec.

Clinical systolic and diastolic blood pressure (SBP and DBP) was initially 170.4±2.9 and 101.6±1.9 mm Hg in the group of patients with MS. respectively.

All patients took combined antihypertensive therapy consisting of: angiotensin II receptor blockers (ARB II) – valsartan (valsacor) at a dose of 160 mg per day and imidazoline receptor agonists – moxonidine (physiotens) at a dose of 0.4 mg per day. The study was carried out before and 12 weeks after taking AGT.

Statistical data processing was carried out by the method of variation statistics using Student's t-tests. The results were processed using the Statistica-6 software package. The significance of differences was assessed using the Wilcoxon test. Differences were considered significant at $p<0.05$.

Results and Discussion

The results of the study showed that the use of AHT gave positive results in a number of clinical and metabolic parameters. So, according to office measurements, the target blood pressure level (130/80 mm Hg and less) was achieved in 95.5% of patients. At the same time, the heart rate did not change.

There was a positive dynamics in relation to body weight. So, after 12 weeks from the start of treatment, there was a significant decrease in BMI (from 38.36±4.1 to 35.01±3.45 kg/m^2; $p<0.05$), and total body weight (from 104.81±18.99 to 97.17±13.87 kg; $p<0.05$) (Fig. 1).

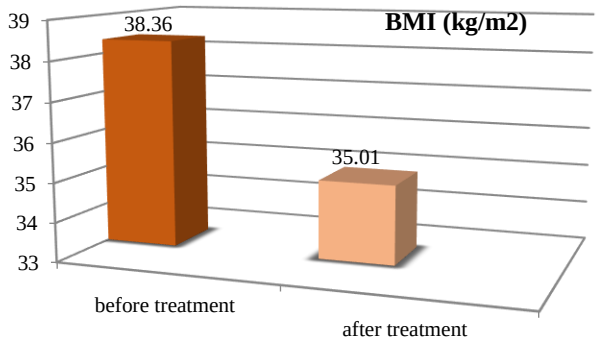

Fig. 1. Dynamics of BMI in AH patients with MS on the background of combined antihypertensive therapy

Has undergone changes and carbohydrate metabolism. Thus, the fasting blood glucose level changed insignificantly, amounting to 6.51±1.1 and 6.65±1.08 mmol/L, respectively ($p>0.05$). The fasting insulin level significantly changed (22.56±15.81 and 17.02±10.81 μU/mL; $p<0.01$). Against the background of AHT, the level of glycated hemoglobin changed insignificantly (6.61±0.62 and 6.40±0.55%, respectively; $p>0.05$). However, the glycemic index, which indirectly characterizes the sensitivity of tissues to insulin, significantly increased from 0.29±0.03 to 0.40±0.08 ($p<0.05$) (Fig. 2).

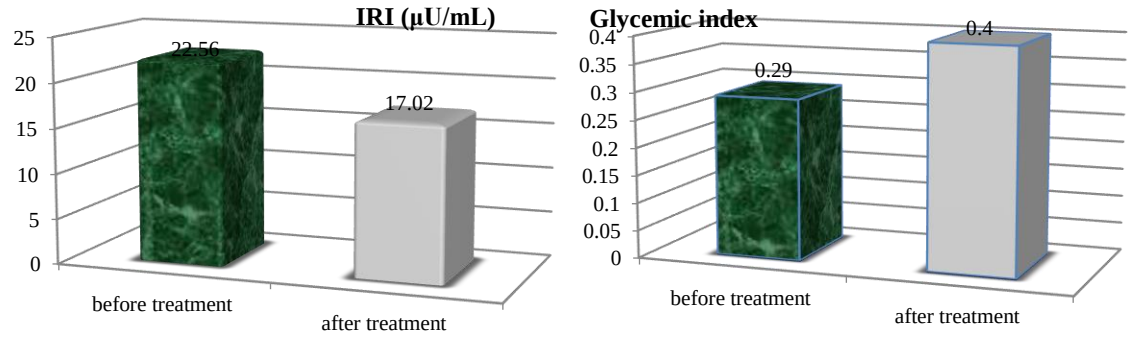

Fig. 2. Dynamics of carbohydrate metabolism indices in hypertensive patients with MSin combination antihypertensive therapy

Combined antihypertensive therapy led to a significant improvement in lipid metabolism. Thus, the level of total cholesterol decreased from 6.38±1.32 to 5.77±1.21 mmol/L ($p<0.05$); LDL cholesterol – from 5.63±1.12 to 5.11±1.48 mmol/L ($p<0.05$); TG – from 2.48±1.52 to 1.89±0.78 mmol/L ($p<0.05$). The level of HDL cholesterol underwent a significant increase from 1.27±0.28 to 1.44±0.36 mmol/L ($p<0.05$) (Fig. 3).

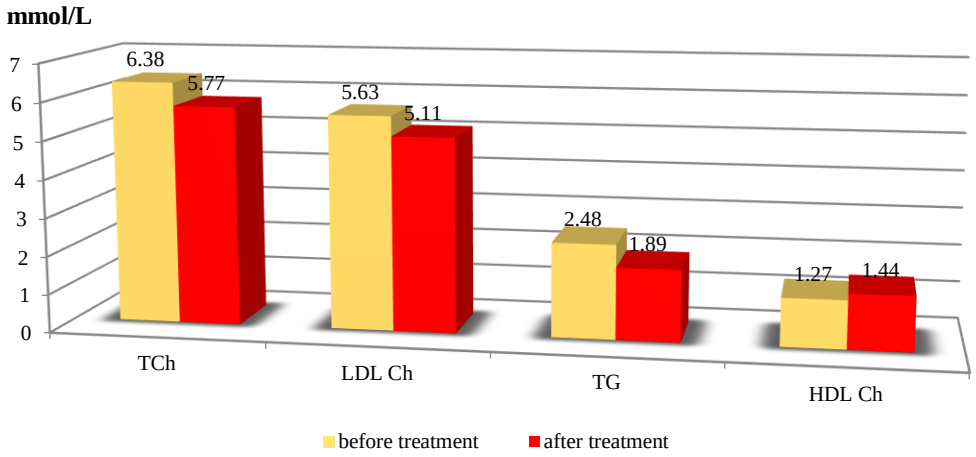

Fig. 3. Dynamics of lipid metabolism indices in hypertensive patients with MS against the background of combined antihypertensive therapy

12-week treatment with combined AHT led to changes in adipose tissue hormones, in particular leptin and adiponectin (ADN). Thus, the initially elevated level of leptin (45.5±3.81 ng/L) moderately and significantly decreased (25.7±1.64 ng/L; $p<0.001$) (Fig. 4). At the same time, the initially decreased level of ADN (4.78±2.2 μg/mL), on the contrary, significantly increased to 8.02±3.4 μg/mL ($p<0.001$) (Fig. 4).

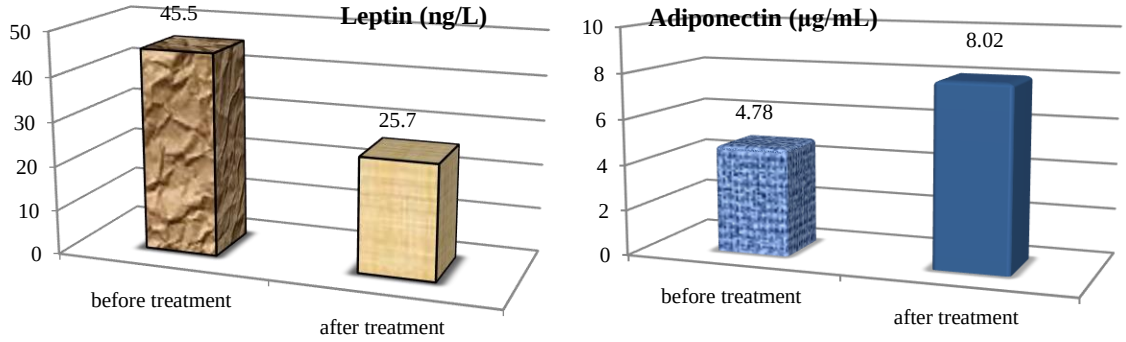

Fig. 4. Dynamics of leptin and adiponectin levels in hypertensive patients with MS in combination antihypertensive therapy

There were positive changes in vascular endothelial dysfunction. It was noted that combined AHT led to a significant decrease in the level of endothelin-1 from 13.4±1.7 to 9.2±1.5 ng/L ($p<0.01$) and CDE from 15.9±2.1 to 6.9±1.2 cells/100 µL ($p<0.001$) (Fig. 5).

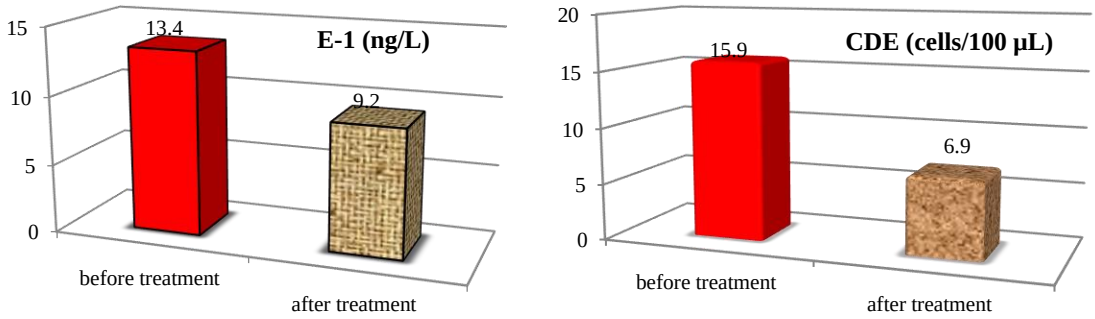

Fig. 5. Dynamics of endothelial dysfunction indices in hypertensive patients with MS on the background of combined antihypertensive therapy

Discussion

The results of the studies have demonstrated a sufficient hypotensive effect of combined antihypertensive therapy and an improvement in the target blood pressure level in patients with stage II hypertension with MS. In 95.5% of patients, the target BP level was achieved.

The clinical efficacy of combined AHT has been proven in a number of foreign works. Some authors compared the efficacy and tolerability of moxonidine with hydrochlorothiazide – it was shown that both drugs are equally effective in terms of lowering blood pressure [3]. Others – with a β-blocker – atenolol and against the background of the hypoglycemic drug metformin [3,9]. Third authors, in a comparative study of moxonidine, enalapril and irbesartan, showed identical antihypertensive activity of the studied drugs [10]. The effectiveness of moxonidine has also been confirmed in long-term studies [8,9]. Thus, the ALMAZ study showed a high clinical efficacy of moxonidine, which caused a pronounced decrease in BP in more than 50% of patients with monotherapy [8].

The results of our work showed that moxonidine, which has a pronounced sympatholytic effect, has a positive effect both on carbohydrate and lipid metabolism, and on hormones of

adipose tissue and endothelial function. Thus, in relation to carbohydrate metabolism, the indicators of blood glucose (by 2.2%) and glycated hemoglobin (by 3.2%) changed insignificantly and insignificantly, but the level of IRI significantly decreased (by 24.6%) and the glycemic index increased (by 37,9%), which is consistent with foreign data [3,11,15]. A significant improvement in lipid metabolism was revealed: the level of total cholesterol decreased by 10.6%, LDL cholesterol – by 10.2%, triglycerides – by 23.8%, and the level of HDL cholesterol increased by 13.4%. Apparently, the effect of moxonidine on carbohydrate and lipid metabolism is mediated through an increase in tissue sensitivity to insulin [12,13].

Moxonidine, in addition to its main antihypertensive effect, is able to reduce IR [15]. It reduces sympathetic activity, which leads to a decrease in the hydrolysis of fats and free fatty acids, a decrease in the proportion of insulin-resistant fibers in skeletal muscles, and an increase in the transfer and metabolism of glucose. All this leads to an increase in tissue sensitivity to insulin and an improvement in carbohydrate and lipid metabolism [12,15]. The absence of significant dynamics of glucose in the blood during therapy with moxonidine in patients with MS with improved indicators of IRI and tissue sensitivity to insulin, as well as indicators of the lipid spectrum, suggests that lipid metabolism reacts much faster to changes in insulin sensitivity than carbohydrate metabolism [1,2,3]. This assumption is confirmed by our research [6].

The improvement in endothelial function, which we noted in MS patients who took moxonidine, is obviously due to an increase in insulin sensitivity. It is known that the vascular endothelium is the main target organ under IR conditions [1,4,5]. This increases the secretion of the vasoconstrictor endothelin [7]. In our work, against the background of the use of moxonidine, the level of endothelin-1 significantly decreased.

The increase in insulin sensitivity can probably also explain the significant decrease in body weight, which was noted in our work.

An interesting finding of our study is that during therapy with moxonidine, the level of adipose tissue hormones changed – leptin (decreased by 43.5%) and adiponectin (increased by 67.8%). Leptin, like insulin, by affecting central mechanisms, leads to an increase in SNS activity and reflects peripheral leptin resistance [3,15]. Adiponectin is a risk factor for the development of IR and atherosclerotic vascular disease. Hypoadiponectinemia is directly related to obesity and may serve as an additional marker of IR [11,12]. The normalization of the secretory activity of adipose tissue is another confirmation of the need to prescribe imidazoline agonists in MS [14].

Conclusion

Thus, the combined antihypertensive therapy ARBII (valsartan) + imidazoline receptor agonists (moxonidine) in hypertensive patients with MS affected the main links of MS pathogenesis, namely, achieved a pronounced hypotensive and sympatholytic effect, increased tissue sensitivity to insulin, balanced the level of adipose tissue hormones, improved lipid metabolism and the functional state of the endothelium. In our opinion, the combination of antihypertensive drugs used in hypertensive patients with MS is the preferred combination of choice in the treatment and prevention of this category of patients.

References

[1] Gaponova N.I., Abdrakhmanov V.R., Baratashvili V.L. Analysis of the efficacy and safety of moxonidine in patients with arterial hypertension and hypertensive crises. Cardiology2011; 6: 91-96. Russian (Гапонова Н.И., Абдрахманов В.Р., Бараташвили В.Л. Анализ эффективности и безопасности применения моксонидина у пациентов с артериальной гипертензией и гипертоническими кризами. Кардиология 2011; 6: 91-96).

[2] Minushkina L.O. Possibilities of using moxonidine in the treatment of arterial hypertension in patients with metabolic syndrome and diabetes mellitus. Cardiology2011; 4: 74-78. Russian (Минушкина Л.О. Возможности применения моксонидина в лечении артериальной гипертонии у больных с метаболическим синдромом и сахарным диабетом. Кардиология 2011; 4: 74-78).

[3] Mychka V.B., Masenko V.P., Chazova I.E. Features of the therapeutic approach to the treatment of arterial hypertension in patients with insulin resistance. Endocrinology problems2006; 52 (5): 5-10. Russian (Мычка В.Б., Масенко В.П., Чазова И.Е. Особенности терапевтического подхода к лечению артериальной гипертонии у пациентов с инсулинорезистентностью. Проблемыэндокринологии. 2006; 52(5): 5-10).

[4] Recommendations for the treatment of arterial hypertension. ESH/ESC 2018. Rus. cardiol. magazine2019; 105 (1): 7-94.Russian (Рекомендации по лечению артериальной гипертонии. ESH/ESC 2018. Рос. кардиол. журнал 2019; 105(1): 7-94).

[5] RSSC recommendations for the management of patients with metabolic syndrome. Moscow: Medicine 2013; 1-62. Russian (Рекомендации ВНОК по ведению больных с метаболическим синдромом. М.: Медицина 2013;1-62).

[6] Uzbekova N.R., Khuzhamberdiev M.A., Usmanova D.N., Abdullaeva D.Kh., Kityan S.A. On the question of the effect of moxonidine on metabolic parameters in patients with arterial hypertension with metabolic syndrome. Infection, Immunity and Pharmacology (Uzbekistan) 2014; 2: 82-88. Russian (Узбекова Н.Р., Хужамбердиев М.А., Усманова Д.Н., Абдуллаева Д.Х., Китьян С.А. К вопросу о влиянии моксонидина на метаболические показатели у больных артериальной гипертонией при метаболическом синдроме. Инфекция, иммунитет и фармакология 2014; 2: 82-88).

[7] Chazova I.E., Mychka V.B. Metabolic syndrome. Moscow: Media Medica 2008; 1-349. Russian (Чазова И.Е., Мычка В.Б. Метаболический синдром.М.: Медиа Медика2008; 1-349).

[8] Betteridge D.J. Risk Management with Moxonidine: Focus on ALMAZ and other Trials in Insulin Resistance. ESC 2006;1-138.

[9] Chazova I.E.,Almazov V.A.,Shlyakhto E.V.Moxonidine improves glycemic controlin mildly hypertensive,overweightpatients: a comparison withmetformin. DiabetObes.Metabol.2006; 8: 456-465.

[10] Derosa G., Cicero A.F., D'Angela A. Metabolic and antihypertensive effects of moxonidine and moxonidine plus irbesartan in patients withtype 2 diabetes mellitus and mild hypertension: a sequentialrandomized, double-blind clinicaltrial. Clin. Ther.2007; 29: 602-610.

[11] Ebinc H., Ozkurt Z.N., Ebinc F.A. Effects of sympatholytic therapy with moxonidine on serum adiponectin levels in hypertensive women. J.lnt. Med.Res. 2008; 36: 80-87.
[12] Funahashi T. Hypoadiponectinemia in obesity andtype 2 diabetes: close association with insulin resistance and hyperinsulinemia. J. Clin. Endocrinol. Metab. 2006; 86(5): 257-263.
[13] Shuldiner A. R., Rongze Y., Gong D.W. Resistin, obesity and insulin resistance– the emerging roleif the adipocyte as an endocrine organ. N. Engl. J. Med.2007; 345(18): 1345-1346.
[14] Van Zwieten P.A., Mancia G. Background and treatment of metabolicsyndrome: a therapeutic challenge. Semin. Cardiothorac. Vasc. Anesth. 2006; 10: 206-214.
[15] Zimmet P. Etiology of the metabolic syndrome: potential role of insulin resistance, leptinresistance and other players. Ann. N.Y. Acad. Sci. 2009; 892: 25-44.