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Antihypertensive and Vasoprotective Effects of Combined Pharmacotherapy in Patients with Arterial Hypertension and Prediabetes

Aim	To evaluate effects of different types of combination drug therapy on indexes of 24-h blood pressure monitoring (24-h BPM), arterial stiffness, and central aortic pressure (CAP) in patients with arterial hypertension (AH) and prediabetes.
Materials and methods	The study included 120 patients with AH and prediabetes. After randomization using envelopes, three treatment groups were formed: group 1, patients receiving perindopril, indapamide SR, and metformin (n=40); group 2, patients receiving perindopril, moxonidin, and metformin (n=40); and group 3, patients receiving perindopril, indapamide SR, and amlodipine (n=40). 24-h BPM, determination of arterial stiffness, and measurement of CAP were performed for all patients.
Results	After 24 weeks of treatment, patients of all groups showed statistically significant improvements of most indexes of 24-h BPM, arterial stiffness, and CAP. In groups 2 and 3, the treatment was associated with significantly more pronounced beneficial changes in 24-BPM, arterial stiffness, and CAP compared to group 1. Antihypertensive and vasoprotective effects of the perindopril+moxonidin+metformin and perindopril+indopamide SR+amlodipine combinations were comparable.
Conclusion	The observed statistically significant antihypertensive and vasoprotective effects of the perindopril+moxonidin+metformin combination along with its known positive metabolic effect allow recommendation of this combination therapy to patients with AH and prediabetes as an effective strategy for BP control.

Keywords	Arterial hypertension; prediabetes; vascular stiffness; central aortic pressure; perindopril; moxonidin; metformin
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Hypertension and disorders of carbohydrate metabolism are currently among the most common diseases in Russia. According to the national epidemiological ESSE-RF study, hyperglycemia was registered respectively in about 45% of male and 40% of female patients with hypertension at the age of 55–64 years [1]. Epidemiological data on the prevalence of early disorders of carbohydrate metabolism, i.e., impaired fasting glucose and impaired glucose tolerance, including patients with hypertension, are somewhat contradictory. The results of the Russian NATION study indicate that when glycated hemoglobin is used as a diagnostic criterion, prediabetes is diagnosed in 19.3% of patients [2]. At the same time, the international HAPIEE project showed that from 28.1 to 54.8% of Russian adults have elevated levels of fasting glucose [3].

A combination of hypertension plus prediabetes is not only accompanied by a higher risk of developing type 2 diabetes mellitus (DM) but is also associated with a 241% increased incidence of cardiovascular complications (CVCs) [4]. The higher risk of CVCs in patients with hypertension and hyperglycemia is likely due to early and significant changes in the target organs, the vascular wall in particular. Increased arterial stiffness and closely associated elevation of central aortic pressure (CAP) are known as prognostically significant indicators of pathological arterial remodeling [5, 6]. According to the ARIC study, prediabetes is associated with increased arterial stiffness [7]. Moreover, vascular stiffness is an independent predictor of CVCs in patients with both hypertension and impaired glucose tolerance [6, 8]. Thus, it is essential to use effective drug treatment in patients with hypertension and early disorders of carbohydrate metabolism, not only to achieve target levels of blood pressure (BP) but also to ensure clinically relevant vasoprotection.

According to the current guidelines for the treatment of hypertension, initial antihypertensive therapy includes an inhibitor of the renin-angiotensin-aldosterone system (RAAS) and a calcium channel blocker (CCB) or a

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thiazide/thiazide-like diuretic [9]. These combinations provide proven antihypertensive and anti-remodeling effects and ensure better prognosis in a large population of patients with hypertension, including those with disorders of carbohydrate metabolism.

However, the efficacy of drug treatment in patients with prediabetes is determined by the ability of an antihypertensive drug to correct pathogenic links of the mechanism of hypertension, insulin resistance, and hyperinsulinemia in particular, as well as a whole cascade of closely associated neurohumoral disorders. The biguanide, metformin, is traditionally used in cases of insulin resistance. Currently, experts recommend using metformin in patients with prediabetes to prevent type 2 DM and CVCs [10]. At the same time, the Russian guidelines for the treatment of hypertension give rightful preference in this situation to imidazoline receptor agonists (IRAs) [11]. Representatives of this class produce a pronounced antihypertensive effect, have a proven ability to reduce insulin resistance, and have additional pleiotropic cardio-, vaso-, and nephron-protective properties [12–14]. However, findings of the effect of IRAs, moxonidine in particular, on prognostically relevant parameters of 24-hour BP profile are scarce and contradictory. The efficacy of this class for regression of vascular stiffness and CAP in patients with hypertension and prediabetes has not been studied extensively.

Thus, the objective of this study was to evaluate the effect of different combination drug treatments on 24-hour ambulatory blood pressure monitoring (ABPM), vascular stiffness, and CAP in patients with hypertension and prediabetes.

Material and Methods

The study included 120 patients with grade 1 to 2 hypertension with concomitant prediabetes. The median age was 56 years (49–64 years). All patients included in the study signed an informed consent form. Early disorders of carbohydrate metabolism in patients with hypertension, i.e., impaired glucose tolerance and impaired fasting glucose, were established following current guidelines [15].

Exclusion criteria were: secondary hypertension, type 1 DM, history of myocardial infarction and/or myocardial revascularization, NYHA functional class II-IV chronic heart failure, acute cerebrovascular accident, complex heart rhythm and conduction disorders, severe liver and kidney dysfunction, intolerance of angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics (TDs), CCBs, IRAs, and biguanides.

The study design was open-label, randomized, comparative, parallel-group, prospective. For the comparative evaluation of antihypertensive and vasoprotective effects of different combination drug treatments, patients with hypertension and prediabetes were randomized into three groups using an envelope method:

- Group 1 (n = 40): a combination of ACE inhibitor perindopril (Prestarium A, Servier) at a starting daily dose of 5 mg in the evening, TD indapamide (Arion Retard, Servier) at a daily dose of 1.5 mg in the morning, and biguanide metformin (Glucophage, Nycomed/Merck) at a daily dose of 1000 mg in the evening;
- Group 2 (n = 40): ACE inhibitor perindopril (Prestarium A, Servier) at a starting daily dose of 5 mg in the evening, IRA moxonidine (Physiotens, Abbott Laboratories) at a starting daily dose of 0.2 mg in the morning, and biguanide metformin (Glucophage, Nycomed) 1000 mg in the evening;
- Group 3 (n = 40): ACE inhibitor perindopril (Prestarium A, Servier) at a starting daily dose of 5 mg in the evening, TD indapamide SR (Arifon Retard, Servier) at a daily dose of 1.5 mg in the morning, and dihydropyridine CCB amlodipine (Glucophage, Nycomed/Merck) at a starting dose of 5 mg in the morning.

The achievement of office target BP was evaluated at 4, 8, 12, and 24 weeks of treatment. Given that the study was planned and carried out until mid 2018, the target BP was <140/90 mmHg, according to the 2013 ESH/ESC guidelines [16]. In 4 weeks, the target BP was registered in 12 patients in Group 1, 14 patients in Group 2, 19 patients in Group 3. The dose of perindopril was increased to 10 mg/day for the rest of the patients. Later, at 8 and 12 weeks, doses of moxonidine and amlodipine were increased to 0.6 mg/day and 10 mg/day for patients in the respective groups who had not achieved the target BP. If the office BP levels were higher than 139/89 mm Hg within the next 4 to 6 weeks after doses of the antihypertensive drugs had been corrected, drug therapy was further corrected, and the patients were dropped from the study.

Initially and in 24 weeks, all patients underwent ABPM using BPLab Vasotens hardware. They were allowed to move freely. Measuring intervals were 25 minutes during the day-time and 55 minutes during sleep [17]. The main parameters evaluated were mean 24-hour, daytime, and nighttime systolic, diastolic, and pulse BP (SBP 24, SBPd, SBPn, DBP24, DBPd, DBPn, PBP 24, PBPd, PBPn), blood pressure load (SBPd load, SBPn load, DBPd load, DBPn load), BP variability (SBPdV, SBPnV, DBPdV, DBPnV), morning surge (SBPMS, DBPMS), the rate of morning surge (SBPMSR, DBPMSR), 24-hour index. Based on the 24-hour index, four types of BP curves were distinguished: dipper, non-dipper, over-dipper, and night-

peaker. Moreover, the mean 24-hour values of parameters characterizing vascular stiffness were determined: aortic pulse wave velocity (PWVao), reflected wave transit time (RWTT), arterial stiffness index (ASI), augmentation index (AIx), the maximum change in BP with time (dP/dtmax); the main parameters of the CAP were also assessed: 24-hour, daytime, and nighttime systolic, diastolic, and pulse BP (SBPao24, SBPaod, SBPaon, DBPao24, DBPaod, DBPaon), mean aortic pressure (MBPao24, MBPaod, MBPaon), aortic pulse pressure (PBPao24, PBPaod, PBPaon), aortic augmentation index (AIxao24, AIxaod, AIxaon), pulse pressure amplification (PPA24, PPAd, PPAn), ejection duration (ED24, EDd, EDn), subendocardial viability ratio (SEVR24, SEVRd, SEVRn).

Data were processed with Statistica 12.0 software. Quantitative values are expressed as medians and interquartile intervals. Inter-group comparisons of quantitative parameters were performed using non-parametric Mann–Whitney U-tests (independent groups) and Wilcoxon tests (dependent groups). Multiple qualitative comparisons were made using the Pearson's chi-squared test. Differences were considered significant if $p<0.05$.

Results

At the time of inclusion, the patient groups did not differ significantly in terms of anthropometric and clinical data, ABPM, arterial stiffness, and CAP.

During drug therapy, the target BP was recorded for a comparable number of patients in all groups: in Groups 1 and 2, 36 of 40 (90%) patients, and in Group, 3 37 (92.5%) of 40 patients ($p > 0.05$).

For all groups after 24 weeks of drug therapy, statistically significant positive changes of most parameters of ABPM were observed in all patients who achieved the target BP (Table 1).

In Groups 2 and 3, mean 24-hour, daytime and nighttime values OF SBP, DBP and PBP, IV SBP and VAR SBP at day and night times, SBP load and SBP variability at day and night times, DBPload and DBP variability mainly at night, decreased during treatment. SBP morning surge was statistically more significant vs the ABPM findings in Group 1. It is essential to note that the positive changes of all parameters studied after 24 weeks were comparable in Group 2 and Group 3 (see Table 1). This evidence shows the significant and equivalent antihypertensive efficacy of the commonly used combination of ACE inhibitor + TD + dihydropyridine CCB and in the presence of prediabetes, drug therapy using pathogenetically justified combination of ACE inhibitor, IRA, and biguanide.

In all patients groups, treatment was accompanied by a more than 2-fold, statistically significant increase in the number of patients with a sufficient reduction in nighttime BP, i.e., dippers (Figure 1). Moreover, significant decreases were registered by 24 weeks in the number of patients with a prognostically unfavorable 24-hour profile, i.e., non-dippers, irrespective of the therapy used (Figure 2). This type of 24-hour curve decreased by 67% in Group 2 and by 79% in Group 3, a 32% difference ($p < 0.05$). After 24 weeks of treatment, such pathological profiles as "night-peaker" and "over-dipper" were not registered in any group.

Statistically significant, positive dynamics of almost all parameters of arterial stiffness and CAP were observed during the administration of different drug

Table 1. Comparative effect of different combination drug treatments on the ABPM parameters in patients with hypertension and prediabetes

Parameter	Change from baseline, Δ%		
	Group 1 (n = 36)	Group 2 (n = 36)	Group 3 (n = 37)
SBP24, mm Hg	–11.7*	–16.4*, **	–16.6*, ***
SBPd, mm Hg	–7.3*	–11.7*, **	–12.2*, ***
SBPn, mm Hg	–12.2*	–16.0*, **	–17.3*, ***
DBP24, mm Hg	–6.5*	–10.7*, **	–12.8*, ***
DBPd, mm Hg	–4.7*	–10.2*, **	–12.2*, ***
DBPn, mm Hg	–6.8*	–11.4*, **	–14.6*, ***
PBP24, mm Hg	–11.7*	–17.1*, **	–17.7*, ***
PBPd, mm Hg	–9.4*	–17.4*, **	–17.5*, ***
PBPn, mm Hg	–11.4*	–16.9*, **	–17.9*, ***
SBPd load, %	–37.7*	–59.1*, **	–62.2*, ***
SADn load, %	–41.2*	–64.6*, **	–68.0*, ***
DBPd load, %	–28.5*	–43.0*	–45.5*
DBPn load, %	–22.3*	–38.9*, **	–45.2*, ***
SBPdV, mm Hg	–17.3*	–30.4*, **	–35.3*, ***
SBPnV, mm Hg	–22.1*	–35.6*, **	–40.0*, ***
DBPdV, mm Hg	–15.3*	–16.0*	–22.2*
DBPnV, mm Hg	–16.3*	–25.0*, **	–28.6*, ***
SBPMS, mm Hg	–9.4*	–24.8*, **	–26.9*, ***
SBPMSR, mm Hg	–16.6*	–28.9*	–30.6*
DBPMS, mm Hg	–12.7*	–17.0*	–17.9*
DBPMSR, mm Hg	–20.5	–24.4*	–28.6*

Statistically significant differences ($p < 0.05$): *, vs baseline; **, Δ% between Group 1 and Group 2; ***, Δ% between Group 1 and Group 3. SBP24, mean 24-hour systolic blood pressure; SBPd, mean day-time systolic blood pressure; SBPn, mean night-time systolic blood pressure; DBP 24, mean 24-hour diastolic blood pressure; DBPd, mean day-time diastolic blood pressure; DBPn, mean night-time diastolic blood pressure; PBP 24, mean 24-hour pulse blood pressure; PBPd, mean day-time pulse blood pressure; DBPn, mean night-time pulse blood pressure; V, variability; MS, morning surge; MSR, the rate of morning surge.

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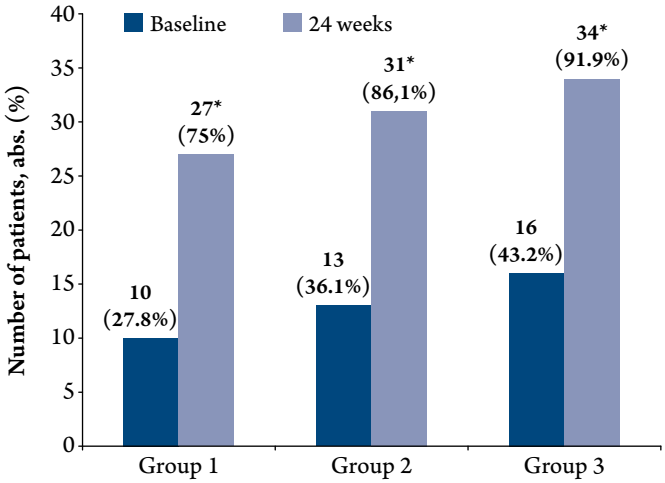
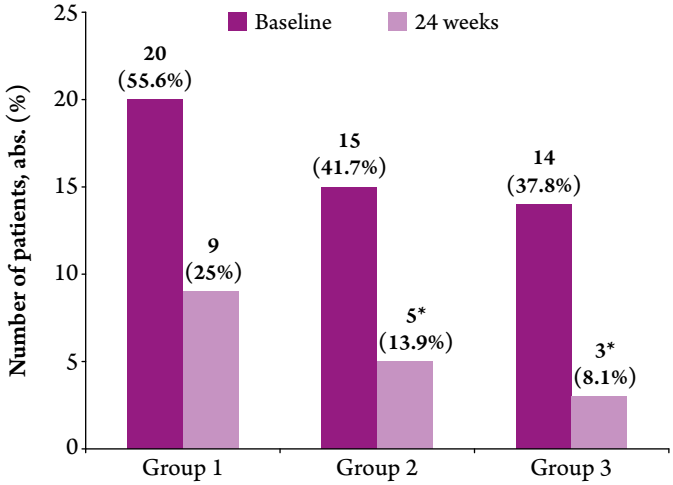
Figure 1. The number of patients with a "dipper" physiological profile at baseline and after 24 weeks of treatment



* – p<0.05 vs baseline findings.

Figure 2. The number of patients with a "non-dipper" pathological profile at baseline and after 24 weeks of treatment



* – p<0.05 vs baseline findings.

treatments in patients with hypertension and prediabetes (Tables 2 and 3). In addition, the combinations of perindopril + moxonidine + metformin and perindopril + indapamide SR + amlodipine produced more significant improvements in arterial stiffness and CAP vs the results in Group 1. The vasoprotective efficacy of combination drug therapy was comparable in Groups 2 and 3 (Tables 2 and 3). After 24 weeks of treatment, a decrease in the number of patients in all groups with both PWVao and SBPao24 exceeded threshold values ($p < 0.05$ vs baseline).

In this study, it was necessary to assess some additional parameters in addition to the traditional parameters of vascular stiffness and CAP. For example, there was a statistically significant decrease in the arterial stiffness index (ASI) in all groups during the treatment, which indicates a lower risk of the development and progression of coronary artery disease. Moreover, the risk of ischemic complications in patients in Groups 2 and 3 decreased more than in Group 1.

The use of all combination treatments also contributed to a reduction in the left ventricular ejection duration (ED), which can be explained by a decrease in aortic pressure. Moreover, the treatment increased the subendocardial viability ratio (SEVR), which might have been due to the improved endothelial function and reduced rigidity of coronary arteries.

Discussion

Our findings showed that the use of different combination drug treatments in patients with hypertension and prediabetes was accompanied by positive and statistically significant changes in most parameters of ABPM, CAP, and vascular stiffness. At the same time, the changes in almost all parameters studied were more pronounced during the administration of two combinations: perindopril + indapamide SR + amlodipine and perindopril + moxonidine + metformin. This appears to be relevant from a practical point of view, as it expands the possibilities of pathogenetically based drug treatment of patients with hypertension and prediabetes. On one hand, the efficacy of the combination of two antihypertensive drugs, perindopril, and moxonidine, was comparable to the combination of three drugs, perindopril, indapamide SR and amlodipine. Metformin clearly produces some

Table 2. Comparative effect of different combination drug treatments on vascular stiffness in patients with hypertension and prediabetes

Parameter	Change from baseline, Δ%		
	Group 1 (n = 36)	Group 2 (n = 36)	Group 3 (n = 37)
RWTT, ms	4.9*	7.0*, **	7.6*, ***
RWTT cor, ms	2.9*	4.7*, **	4.7*, ***
PWVao, m/s	–1.8*	–6.0*, **	–6.8*, ***
PWVao cor, m/s	–2.1*	–6.1*, **	–6.0*, ***
ASI, mm Hg	–10.6*	–17.7*, **	–21.7*, ***
ASI cor, mm Hg	–11.8*	–18.7*, **	–21.5*, ***
AIx, %	–11.3*	–32.5*, **	–33.3*, ***
AIx cor, %	–23.5*	–45.2*, **	–46.9*, ***
dP/dtmax, mmHg/sec	–7.2	–11.8*	–13.9*

Statistically significant differences ($p < 0.05$): *, vs baseline; **, Δ% between Group 1 and Group 2; ***, Δ% between Group 1 and Group 3. cor, corrected to SBP 100 mmHg and HR 60 bpm; RWTT, reflected wave transit time; PWVao, aortic pulse wave velocity; ASI, artery stiffness index; AIx, augmentation index; dP/dtmax, the maximum change in BP with time.

Table 3. Comparative effect of different combination drug treatments on CAP in patients with hypertension and prediabetes

Parameter	Change from baseline, Δ%		
	Group 1 (n = 36)	Group 2 (n = 36)	Group 3 (n = 37)
SBPao24, mm Hg	–11.2*	–17.9*, **	–18.2*, ***
SBPaod, mm Hg	–8.0*	–11.9*, **	–12.5*, ***
SBPaon, mm Hg	–12.7*	–16.2*, **	–17.4*, ***
DBPao24, mm Hg	–6.8*	–10.6*, **	–12.7*, ***
DBPaod, mm Hg	–5.2*	–10.6*, **	–13.0*, ***
DBPaon, mm Hg	–6.3*	–11.3*, **	–14.5*, ***
BPao24, mm Hg	–8.2*	–14.0*, **	–14.7*, ***
BPaod, mm Hg	–7.0*	–9.9*, **	–10.6*, ***
BPaon, mm Hg	–10.2*	–13.4*, **	–15.6*, ***
PBPao24, mm Hg	–15.0*	–11.7*	–20.0*
PBPaod, mm Hg	–8.9*	–17.1*, **	–20.5*, ***
PBPaon, mm Hg	–16.1*	–24.6*, **	–26.7*, ***
AIxao24, %	–22.4*	–41.1*, **	–54.9*, ***
AIxao24 cor, %	–29.4*	–50.7*, **	–56.1*, ***
AIxaod, %	–16.7*	–43.0*, **	–56.5*, ***
AIxaod cor, %	–23.5*	–48.9*, **	–55.6*, ***
AIxaon, %	–20.5*	–44.9*, **	–48.9*, ***
AIxaon cor, %	–29.9*	–56.9*, **	–57.5*, ***
PPA 24, %	4.3*	3.2*	4.6*
PPAd, %	3.8*	2.4*	3.8*
PPAn, %	4.9*	4.4*	4.9*
ED24, ms	–3.9*	–4.2	–4.8*
EDd, ms	–3.0*	–3.7	–4.3*
EDn, ms	–3.3*	–4.2	–4.9*
SEVR 24, %	3.7	3.9	3.5
SEVRd, %	3.7*	2.3	2.4
SEVRn, %	3.2	4.4	3.8

Statistically significant differences ($p < 0.05$): *, vs baseline; **, Δ% between Group 1 and Group 2; ***, Δ% between Group 1 and Group 3. Cor, values corrected to HR 75 bpm; SBPao24, mean 24-hour aortic systolic blood pressure; SBPaod, mean day-time aortic systolic blood pressure; SBPaon, mean night-time aortic systolic blood pressure; DBPao24, mean 24-hour aortic diastolic blood pressure; DBPaod, mean day-time aortic diastolic blood pressure; DBPaon, mean night-time aortic diastolic blood pressure; PBPao 24, mean 24-hour aortic pulse blood pressure; PADaod, mean day-time aortic pulse blood pressure; PADaon, mean night-time aortic pulse blood pressure; AIxao, aortic augmentation index; PPA, pulse pressure amplification; ED, left ventricular ejection duration; SEVR, subendocardial viability ratio.

antihypertensive effect, but it is mild [18, 19]. On the other hand, metformin is recommended by the current guidelines if non-drug measures are not effective in the presence of prediabetes [10].

As the number of drugs prescribed increases, this can naturally contribute to poor adherence. We can suggest that the use of perindopril, moxonidine, and metformin solves several problems at once: a clinically significant antihypertensive effect; correction of insulin resistance associated with disorders of carbohydrate metabolism; improvement of metabolic parameters; and improved patient compliance.

What can explain the statistically significant antihypertensive and vasoprotective efficacy of the combination treatment including ACE inhibitor, IRA, and biguanide as demonstrated in our study? Insulin resistance and hyperinsulinemia are known to be key mechanisms contributing to the development and stabilization of hypertension in prediabetes. Insulin and insulin resistance are currently considered to be actively involved in the regulation of blood pressure, primarily through the activation of the sympathetic-adrenal system [20]. Hypersympathicotonia, in turn, is closely related to increased activity RAAS. The combination of perindopril, moxonidine, and metformin targets the key mechanisms of hypertension in the presence of carbohydrate metabolism disorders, and the role of moxonidine could be essential. The antihypertensive action of IRAs is caused by the selective effect on I1 imidazoline receptors located in the medulla oblongata nuclei and adrenal glands, and resulting in clinically significant central and peripheral sympatholytic activity [21]. Moreover, stimulation of renal imidazoline receptors is accompanied by the suppression of over-activated RAAS. Activity of plasma renin decreases along with levels of angiotensin II and aldosterone [14]. It is also important that activation of renal I1 imidazoline receptors due to moxonidine increases sodium and water excretion, reduces "salt" appetite, and contributes to a decrease in the circulating blood volume, as well as to the reduction of vascular wall edema [22].

Antihypertensive efficacy of moxonidine was demonstrated in large-scale clinical trials, e.g., TOPIC, MERSY, ALMAZ [13, 23, 24]. However, the benefits of this drug include not only its ability to control BP, but also its positive metabolic effects, due to which moxonidine can be used extensively in patients with obesity, DM, and prediabetes. The CAMUS, MERSY, ALMAZ studies demonstrated that moxonidine could increase tissue sensitivity to insulin and improve carbohydrate and lipid metabolism [13, 24, 25]. Several reports showed a reliable decrease in fasting blood glucose during the administration of moxonidine [26, 27].

The positive metabolic effects of IRAs are caused not only by the correction of hypersympathicotonia. By acting on the pancreatic imidazoline receptors, moxonidine normalizes insulin secretion by beta cells and increases the expression of insulin receptor-1 (IRS-1) in the liver

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and skeletal muscles. IRS-1 is involved in the activation of phosphatidylinositol 3 kinase (PI3K) and stimulates the translocation of the intracellular glucose transporter GLUT4 [28, 29]. All of these effects contribute to reduced insulin resistance in the liver, muscle, and fat tissues.

This study also showed that therapy including moxonidine produces a clinically relevant vasoprotective effect. It would be reasonable to suggest that the positive impact of the treatment on parameters of vascular stiffness and blood pressure is caused by the sympatholytic effect of the drug and reduced glucotoxicity due to tissue resistance to insulin. By increasing tissue sensitivity to insulin, IRAs might inhibit the activity of mitogen-activated protein kinase and, thus, the proliferation of vascular smooth muscle cells [30]. It should also be noted that experimental and clinical studies have shown increased production of nitrogen oxide by the vascular wall and improved endothelial function [31]. Moreover, much attention is paid to the possibility of slowing the aging process in vascular walls during the use of IRAs. It is known that insulin resistance can contribute to the acceleration of telomere shortening in stem cells and premature aging of vessels [32]. The positive modeling of carbohydrate metabolism during the administration of moxonidine might be accompanied by regression of age-related changes in the vascular wall.

Our findings can be explained in part by the administration of metformin. A recent meta-analysis demonstrated that metformin is able to increase NO production through the phosphorylation of adenosine monophosphate-activated protein kinase and eNOS, and thus improve the elasticity of arteries [33]. A study including female patients with polycystic ovary syndrome showed a statistically significant decrease in the pulse wave velocity, AIx, SBPao, and DBPao after 12 weeks of therapy including metformin [34].

Thus, the combination treatment including perindopril, moxonidine and metformin may be recommended for patients with hypertension and prediabetes as an alternative to the traditional three-component combination of ACE inhibitor, diuretic, and CCB, since it produces comparable antihypertensive and vasoprotective effects, and contributes to the improvement of metabolic performance and correction of insulin resistance.

Conclusion

The use of all three combination drug treatments in patients with hypertension and prediabetes was accompanied by statistically significant positive changes of most parameters of 24-hour monitoring of blood pressure, vascular stiffness, and central aortic pressure. At the same time, the use of perindopril in combination

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with moxonidine and metformin produced clinically significant antihypertensive and vasoprotective effects which were comparable to standard therapy with a combination of perindopril, indapamide SR, and amlodipine. Moreover, the combination of perindopril, moxonidine, and metformin may be a preferred drug treatment for patients with hypertension and prediabetes due to the positive metabolic effects of this combination.

No conflict of interest is reported.

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