AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 2, Issue 1, 2024 ISSN (E): 2993-2149

Current Views and the Correct Approach to the Treatment of Arterial Hypertension in Patients with Diabetes Mellitus

Raza Muhammad Kalim
Resident Master's student, Samarkand State Medical University

Abstract: Arterial hypertension is about twice as common in patients with diabetes mellitus as in the general population. The incidence of arterial hypertension among patients with diabetes mellitus ranges from 20 to 60% depending on the criteria used for elevated blood pressure (BP) and the type of diabetes mellitus.

Keywords: arterial hypertension, type 2 diabetes mellitus, macro-microangiopathy, cardiovascular complications.

Introduction. The main cause of mortality in diabetes mellitus is vascular complications, in the pathogenesis of which the main role belongs to hyperglycaemia and its metabolic effects. The risk of macro- and microangiopathy in patients with type 2 diabetes mellitus directly depends on the level of glycaemia. Arterial hypertension has a significant impact on the fate of patients with diabetes, significantly increasing the risk of cardiovascular and renal complications, which are the main causes of premature death. Thus, according to the data of the Fremingham study, arterial hypertension increases mortality 5 times in patients with diabetes mellitus [1]. In patients with diabetes mellitus with arterial hypertension, effective drug therapy significantly prevents the development of cardiovascular complications and renal failure. Antihypertensive drugs are recommended for all adult patients with diabetes mellitus with BP 130/85 mmHg or more [2].

Forms of arterial hypertension in patients with diabetes mellitus.

Two forms of arterial hypertension are most common in diabetic patients:

1) hypertension and 2) hypertension associated with diabetic nephropathy. In addition, stenotic lesions of renal arteries (unilateral and bilateral), diffuse glomerulonephritis, chronic pyelonephritis, renal papillae necrosis may be the causes of arterial hypertension in diabetic patients. Hypertension is the predominant form of arterial hypertension in patients with insulin-independent diabetes mellitus (type II). In about 10 - 20% of patients with type II diabetes mellitus, diabetic nephropathy is the cause of arterial hypertension. In some cases arterial hypertension may be associated with stenosing lesions of one or both renal arteries.

Table 1. Effect of different antihypertensive drugs on glucose metabolism.

Drug	Glucose level	Insulin secretion	Tissue sensitivity to insulin
Thiazide diuretics		Ï	Ï
Indapamide	0	0	0
b-Adrenoblockers:			
Non-selective		Ï	Ï
b1-selective	0/	0/Ï	Ï/0
Calcium antagonists	0	0	0

ACE inhibitors	0/Ï	0	0/
AT1-receptor blockers	0	0	0
a1-Adrenoblockers	0/Ï	0	0/
Agonists of a2-adrenoreceptors	0	0/c	0
I1-receptor agonists	0		

In the vast majority of patients with insulin-dependent diabetes mellitus (type I), in the first years after the onset of the disease BP is within the age-related normal range. Approximately 10 - 15 years from the onset of the disease in 50% of patients with type I DM develop diabetic nephropathy, which is characterized by persistent proteinuria, arterial hypertension and progressive renal dysfunction (decreased glomerular filtration rate below 80 ml/min, increased serum levels of creatinine). At the preclinical stage, diabetic nephropathy is manifested by increased glomerular filtration rate (more than 130 - 140 ml/min) and microalbuminuria (30 - 300 mg/day or 20 - 200 µg/min). BP may be either normal or elevated, but average BP levels in patients with latent diabetic nephropathy are significantly higher than in healthy individuals of the same age.

Selection of an antihypertensive drug for the treatment of arterial hypertension in a patient with diabetes mellitus. As mentioned above, antihypertensive drugs should be prescribed to all patients with diabetes mellitus with a BP level of at least 130/85 mmHg according to repeated measurements. When choosing a drug for long-term therapy of arterial hypertension in patients with diabetes mellitus, one should take into account not only the severity of its antihypertensive action, but also the possible effect on carbohydrate metabolism and pathogenetic mechanisms of arterial hypertension. Currently, the following groups of antihypertensive drugs are used for the treatment of hypertension: thiazide diuretics, b-adrenoblockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, AT1-angiotensin receptor blockers, a1-adrenoreceptor blockers, central a2-adrenoreceptor agonists and I1-imidazoline receptor agonists.

Effect of antihypertensive drugs on carbohydrate metabolism

In individualised doses, drugs belonging to different pharmacological groups have the same effect on BP, but they differ in their effect on carbohydrate metabolism, urinary albumin excretion and renal function.

Antihypertensive drugs can be divided into three main groups depending on their effect on carbohydrate metabolism:

1. Drugs that have an unfavourable effect on carbohydrate metabolism (diuretics, except indapamide, and b-adrenoblockers);

2. Drugs with no significant effect on carbohydrate metabolism (indapamide, b-adrenoblockers with vasodilating properties, calcium antagonists, AT1-angiotensin receptor blockers, central a2-adrenoreceptor agonists);

3. Drugs with some favourable effect on carbohydrate metabolism (ACE inhibitors, a1-adrenoblockers and I1-imidazoline receptor agonists).

Thiazide diuretics and b-adrenoblockers, usually recommended for use in patients with uncomplicated hypertension, are not well suited for the treatment of arterial hypertension in diabetic patients. Firstly, thiazide diuretics and b-adrenoblockers may impair glucose tolerance. Secondly, according to some observations, they predispose to the onset and possibly progression of diabetes mellitus in hypertensive patients.

Thiazide diuretics in high doses (50 mg hydrochlorothiazide or equivalent doses of other diuretics) increase fasting glucose levels and glycosylated haemoglobin concentration, and impair tolerance to oral and intravenous glucose load. Cases of development of non-ketonemic hyperosmolar coma during treatment with thiazide diuretics in diabetic patients have been

described. Suggested mechanisms of impaired glucose tolerance during treatment with thiazide diuretics include decreased insulin secretion and decreased tissue sensitivity to insulin action (insulin resistance) [3] . In diabetic patients they aggravate hyperglycemia and in some cases may cause the development of non-ketonemic hyperosmolar coma. The most unfavourable effect on glucose metabolism is produced by non-selective b-adrenoblockers (propranolol, nadolol, timolol) and b1-selective blockers (atenolol, metoprolol, etc.) in high doses. On the other hand, b-adrenoblockers with intrinsic sympathomimetic activity (oxprenolol, pindolol, etc.) have little effect on carbohydrate metabolism. Suggested mechanisms of impaired glucose tolerance during treatment with b-adrenoblockers include inhibition of insulin secretion, decreased tissue sensitivity to insulin action (insulin resistance), inhibition of glucose utilisation in peripheral tissues and increased secretion of growth hormone [3]. Along with impaired glucose tolerance, the ability of b-adrenoblockers to mask clinical manifestations of hypoglycaemia and inhibit mobilisation of glucose from the liver in response to hypoglycaemia is of clinical importance. Many of the signs and symptoms of hypoglycaemia are known to be due to increased activity of the sympathetic-adrenal system. All b-adrenoblockers, suppressing clinical manifestations of hypersympathicotonia, may complicate the diagnosis of hypoglycemic states in diabetic patients, b-Adrenoblockers inhibit the mobilization of glucose from the liver in response to hypoglycaemia, both spontaneous (e.g. after intense exercise or prolonged fasting) and induced by insulin or oral glucose-lowering drugs. Mobilisation of glucose from the liver is mediated by b2-adrenoreceptors. Therefore, hypoglycaemic reactions to insulin and oral sugar-reducing drugs are more often observed during treatment with non-selective b-adrenoblockers.

Thus, in diabetes mellitus b-adrenoblockers (especially non-selective), on the one hand, impair glucose tolerance, and on the other hand, predispose to the development of hypoglycaemia and complicate the timely diagnosis of hypoglycaemic states. Several population studies have shown that thiazide diuretics and b-adrenoblockers increase the likelihood of diabetes mellitus in middle-aged and elderly hypertensive patients. Thus, C. Bengtsson et al. [4] reported a 3.5-fold increase in the risk of diabetes mellitus in women with hypertension treated with thiazide diuretics compared to untreated patients. According to a 10-year study, thiazide diuretics increase the risk of developing type II diabetes mellitus independently of other risk factors [5]. In a comparative study, the incidence of diabetes mellitus was 2 to 3 times higher in elderly hypertensive patients treated with b-adrenoblockers or thiazide diuretics compared with untreated patients [6]. Finally, according to a retrospective study, thiazide diuretics accelerate the development of diabetic nephropathy in diabetic patients with arterial hypertension [7]. The assumption about the adverse effect of thiazide diuretics and b-adrenoblockers on the occurrence and progression of diabetes mellitus in patients with arterial hypertension, based on the results of retrospective and uncontrolled prospective studies, has recently been confirmed in the SARRP study (Captopril Prevention Project, 1998).

In this controlled study, the incidence of diabetes mellitus during 6 years of follow-up was significantly higher in the group of hypertensive patients treated with diuretics and b-adrenoblockers compared with patients receiving the ACE inhibitor captopril. Taking into account the effect of antihypertensive drugs on carbohydrate metabolism, ACE inhibitors, a1-adrenoreceptor blockers and I1-imidazoline receptor agonists should be used in the treatment of arterial hypertension in diabetic patients without concomitant heart and kidney damage (see Table 1). However, the ability of antihypertensive drugs to prevent cardiovascular and renal complications in diabetic patients is much more important than their effect on carbohydrate metabolism.

Effect of antihypertensive drugs on cardiovascular complications in patients with diabetes mellitus. Unfortunately, the prophylactic efficacy of various antihypertensive drugs in patients with diabetes mellitus has not been sufficiently studied in long-term studies. In controlled studies, the ability of thiazide diuretics and b-adrenoblockers to prevent cardiovascular complications in diabetic patients with arterial hypertension, despite their unfavourable effect on glucose metabolism, has been proven [2]. The recently published results of the CARRP study

(1998) suggest that in hypertensive patients with diabetes mellitus, the ACE inhibitor captopril is more effective in preventing cardiovascular complications than diuretics and b-adrenoblockers. Two other controlled studies have shown the superiority of ACE inhibitors over "vasoselective" calcium antagonists in the prevention of cardiovascular complications in patients with hypertension combined with type II diabetes mellitus. Thus, in the controlled study ABCD (Appropriate Blood Pressure Control Diabetes) [8], myocardial infarction and other cardiovascular complications developed significantly less frequently in patients with type II diabetes mellitus with arterial hypertension treated with the ACE inhibitor enalapril than in the group of patients receiving the calcium antagonist nisoldipine. In the FACET (Fosinopril versus Amlodipine Cardiovascular Events randomised Trial) randomised trial [9], cardiovascular complications developed significantly less frequently in the group of patients with hypertension combined with type II diabetes treated with the ACE inhibitor fosinopril compared to patients receiving the calcium antagonist amlodipine. The ability of a1-adrenoblockers and I1-imidazoline receptor agonists to improve long-term prognosis in diabetic patients with arterial hypertension has not, to our knowledge, been investigated. Therefore, given the results of the controlled trials KAPPP, ABCD and FACET, ACE inhibitors can be considered the drugs of choice for the treatment of hypertension in patients with type II diabetes mellitus. If the antihypertensive efficacy of ACE inhibitors is insufficient, calcium antagonists and/or diuretics are added. Recent studies have demonstrated the cardioprotective effect of the combination of an ACE inhibitor and dihydropyridine calcium antagonists such as amlodipine and felodipine-retard.

b1-Selective b-adrenoblockers (atenolol, betaxolol, bisoprolol, metoprolol, etc.) still play an important role in the treatment of arterial hypertension in patients with diabetes mellitus combined with CHD. After all, patients with CHD have a particularly high risk of sudden death and the development of myocardial infarction, which are prevented by b-adrenoblockers. Effect of antihypertensive drugs on proteinuria and renal function in patients with diabetes mellitus. Antihypertensive drugs have different effects on urinary albumin excretion, which reflects the severity of renal damage and is a prognostically unfavourable sign in type I diabetes mellitus.

ACE inhibitors and "cardioselective" calcium antagonists (verapamil and diltiazem) when administered as monotherapy to the greatest extent reduce micro- and macroalbuminuria in patients with diabetes mellitus (on average by 20 - 60%). In combination with verapamil or diltiazem ACE inhibitors reduce urinary excretion of albumin by almost 80%. Among diuretics, indapamide is comparable to ACE inhibitors in its effect on urinary albumin excretion in patients with diabetic nephropathy.

Numerous controlled studies have established the ability of ACE inhibitors to slow the progression of diabetic nephropathy in patients with type I diabetes. Thus, E. Lewis et al. [10] showed that long-term therapy with captopril approximately 50% reduces the risk of renal complications in diabetic patients with overt nephropathy. Captopril was equally effective in patients with elevated and normal BP.

Other studies have found a favorable effect of inhibitors on the progression of latent diabetic nephropathy (urinary albumin excretion rate from 30 to 300 mg/day) in patients with type I diabetes. According to the pooled data of three long-term studies, treatment with ACE inhibitors more than 4 times reduces the probability of transformation of latent diabetic nephropathy into manifest diabetic nephropathy (urinary albumin excretion rate of more than 300 mg/day) [11].

The evidence of renoprotective effect of ACE inhibitors in patients with type II diabetes mellitus with manifest nephropathy is not so convincing. For example, M. Ravid et al. [12] found that the ACE inhibitor enalapril with long-term use prevents the development of renal dysfunction in patients with type II diabetes mellitus with microalbuminuria.

In short-term comparative studies, "cardioselective" calcium antagonists had the same favourable effect on urinary albumin excretion rate and renal function in patients with overt diabetic

nephropathy as ACE inhibitors. The results of studies on the renal effects of "vasoselective" long-acting antagonists are contradictory.

Thus, in patients with diabetic nephropathy, ACE inhibitors, as well as verapamil and diltiazem can be considered first-line antihypertensive drugs. If ACE inhibitor monotherapy is not effective enough, a calcium antagonist (verapamil or diltiazem) or diuretic (primarily indapamide) should be added.

Targets of antihypertensive therapy in patients with diabetes mellitus. Until recently, it was recommended that BP be maintained at or below 130/85 mmHg in patients with diabetes mellitus. In a controlled trial of HTP (Hypertension Optimal Treatment), it was shown that it is reasonable to reduce BP to a lower level in diabetic patients. In this study, mortality and the incidence of cardiovascular complications were the lowest in the group of patients whose diastolic BP was maintained at 80 mm Hg or lower. The MDRD (Modification of Diet in Renal Disease) study shows that in patients with renal damage of various etiologies, the desired level of BP reduction depends on the severity of proteinuria. In patients with proteinuria more than 1 g/day the optimal level of BP in terms of progression of renal dysfunction is 125/75 mm Hg and lower, and in patients with daily proteinuria from 0.25 to 1.0 g - 130/80 mm Hg. In patients with proteinuria less than 0.25 g/day, it is sufficient to maintain BP at a level not higher than 130/85 mm Hg. . Consequently, in most cases in patients with diabetes mellitus, BP should be maintained at a level not higher than 130/80 mm Hg. Only in patients with diabetic nephropathy and significant proteinuria it is important to reduce BP to a lower level.

Conclusions: Thus, the presented literature data indicate that the approaches to the treatment of arterial hypertension in patients with diabetes mellitus differ significantly from those for uncomplicated hypertension. Not thiazide diuretics and b-adrenoblockers should be primarily used to treat arterial hypertension in patients with diabetes mellitus, but ACE inhibitors, the preventive efficacy of which in diabetes mellitus has been proven in three controlled studies. In patients with diabetes mellitus, antihypertensive drug therapy should be initiated at lower BP levels that are not formally considered elevated. The BP levels that should be sought to be maintained with antihypertensive medication are also lower in diabetic patients than in hypertensive patients without diabetes mellitus.

Literature:

1. Wilson PW, Cupples CF, Kannel WB. Is hyperglycemia associated with cardiovascular disease? The Framingham Study. - Amer. Heart J 1991;121:586-90.
2. The sixth report of the Joint National Committee on prevention, detection, evaluation abd treatment of high blood pressure - Arch. Intern. Med 1997;157 (11):2413-46.
3. Houston MC. The effects of antihypertensive drugs on glucose intolerance in hypertensive nondiabetic and diabetics -Amer Heart J 1988;115(3):640-56.
4. Bengtsson C, Blohme G, Lapidus L, Lundgren H. Diabetes in hypertensive women: an effect of antihypertensive drugs or the hypertensive state per se? - Diabetes Med. 1988;5:261-4.
5. Skarfors ET, Selinus KI, Lithell HO. Risk factors for development of noninsulin-dependent diabetes in middle-aged men - Brit. Med. J 1991;303:755-60.
6. Mykkanen L, Kuusisto J, Pyorala K. et al. Increased risk of non-insulin-dependent diabetes mellitus in elderly hypertensive subjects - J. Hypertens 1994;12:1425-32.
7. Walker WG, Herman J, Yin DP. et al. Diuretics accelerate diabetic nephropathy in hypertensive insulin-dependent and non-insulin-dependent subjects - Trans. Amer. Assoc. Phys. 1987;100:305-15.
8. Estacio RO, Jeffers BW, Hatt WR. et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with enalapril on cardiovascular outcomes in patients

with non-insulin-dependent diabetes and hypertension - New Engl. J. Med. 1998;338 (10):645-52.

9. Tatti P, Guarisco R, Pahor M. et al. Outcome results of the fosinipril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM - Diabetes Care 1998;21 (4):597-603.
10. Lewis EJ, Hunsicker LO, Baix R. et al. The effects of angiotensin-converting enzyme inhibition on diabetic nephropathy - New Engl. J. Med 1993;329 (20):1456-62.
11. Parving HH, Rossing P. The use of antihypertensive agents in prevention and treatment of diabetic nephropathy - Curr. Opin. Nephrol. Hypertrytens. 1994;3:292-300.
12. Ravid M, Brosh D, Levi Z. et al. Use of enalapril to attenuate decline in renal function in normotensive normoalbuminuric patients with type 2 diabetes mellitus - Ann. Intern, Med 1998;128 (12):982-8.
13. Hansson L, Zanchetti A, Carruthers SG. et al. Effects of intensive blood pressure-lowering and low-dose aspirin in patients with hypertension: principle results of the Hypertension Optimal Treatment (HOT) randomised trial - Lancet 1998;351 (9118):1755-62.
14. Peterson JC, Adler S, Burkart JM. et al. Blood pressure control, proteinuria, and the progression of renal disease - Ann. Intern. Med. 1995;123 (10):754-62.