ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-5 | MAY - 2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HYPERTENSION AND CHRONIC KIDNEY DISEASE

Medical Science

Stanislava Zlateva Private Laboratory Ramus Ltd, Sofia, Bulgaria.

Zlatina Atanasova Private Laboratory Ramus Ltd, Sofia, Bulgaria.

KEYWORDS:

Arterial hypertension, chronic kidney disease, classification of hypertension, end-stage renal failure

High blood pressure or primary essential hypertension, or arterial hypertension (AH), or hypertension alone is a chronic disease with the highest incidence in the world. The main characteristic of hypertension is the increase in systolic and particularly, in diastolic arterial pressure. AH is essential (primary) in 90-95% of the cases and secondary in the rest 5-10%. In industrialized countries, every fifth adult is hypertensive (1, 2, 3). The disease is common in both developed (333 million hypertensives) and developing countries (639 million hypertensives). However, the number of hypertensives varies considerably in the different regions. It is the lowest - 3.4% (men) and 6.8% (women) - in the rural regions of India and the highest - 68.9% (men) and 72.5% (women) - in Poland. By 2025, AH will rise by only 5.7% in the EU, but the number of people living with hypertension will increase by 15.3%. Hypertension is the most important preventable risk factor for premature death worldwide. Hypertension is the third detrimental to health factor after smoking and poor nutrition worldwide (1, 3, 4, 5). In the US, 75 million or 29% of the adult population is hypertensive. Approximately 30% of the hypertensives are unaware of their disease. In adults (over 60 years), hypertension is about 50%. Nearly 40% of the hypertensives do not receive therapy, and about 23% fail to reach the target values despite the received therapy (4, 5, 6). In Bulgaria, there are over 1.8 million hypertensives and every year their number increases by 9,000 persons, i.e. 21.3% of the population suffers from AH, and the age limit continues to fall inexorably. In Bulgaria, AH affects 42.8% of the men and 39.7% of the women of working age (between 24 and 65 years). Every third hypertensive, aged between 35 and 44 years, is unaware of his/her disease. The risk factors for hypertension include genetic predisposition, familial history, age, gender, overweight, poor nutrition, salt abuse, insufficient potassium intake, immobilization, alcohol abuse, obstructive sleep apnea (4, 7-10). According to the JNC7 (Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure), AH can be classified as follows:

Reference Card From JNC 7 (11)

Blood pressure (mmHg)	Systolic	Diastolic
Normal	90 – 119	60 – 79
Pre-hypertension	120 – 139	80 – 89
Phase 1 of hypertension	140 – 159	90 – 99
Phase 2 of hypertension	≥160	≥100

The pathogenesis of hypertension is multifactorial and extremely complex (12, 13). Normal blood pressure regulation is a complex process. One of the hypotheses on the etiology of hypertension focuses on genetic predisposition, high salt intake and adrenergic tone (12, 14). AH is the result of an imbalance between cardiac output and peripheral vascular resistance. In healthy subjects, this interaction is autoregulated. Contraction of arterioles raises arterial pressure by increasing the total peripheral resistance, while contraction of veins leads to redistribution of the peripheral intravascular volume. Multiple factors modulate the blood pressure - humoral mediators, structural changes in the heart and small vessels, vascular reactivity, blood viscosity, circulating blood volume and autonomic nervous system (12, 13, 15). Once the blood pressure has been raised, a cycle of endothelial damage starts in the small arterioles. Local intravascular activation of the thrombocytic cascade, fibrinoid necrosis of the small blood vessels and release of more vasoconstrictors occur. There is evidence that structural changes in the heart and vessels precede the onset of AH (14, 15). Left ventricular hypertrophy, myocardial interstitial fibrosis and coronary angiopathy are important structural changes. Left ventricular hypertrophy is the result of genetic abnormalities that lead to changes in the renin-angiotensin-aldosterone system, the natriuretic peptide and adrenoceptor signaling. AH is also characterized by increased vascular resistance and high coronary perfusion pressure. Damages in vessels affect mainly the arterial wall and microcirculation. Peripheral vascular resistance is a consequence of the narrowed lumen and increased wall/lumen ratio. There are many assumptions on the mechanisms responsible for the increased resistance in AH. Emphasis is placed on disturbances in renal exchange of salt and water, in particular, abnormalities of the intrarenal renin-angiotensin system. Cardiac output is influenced by the intake of sodium, renal function and mineralocorticoids (12, 14, 16). Disruption of sympathetic and parasympathetic cardiovascular regulation also plays an important role. Abnormal increases in circulating plasma levels of adrenergic neurotransmitters, norepinephrine and epinephrine, have been demonstrated repeatedly in normotensive subjects with familial history of hypertension (12, 16, 17). This occurs in individuals with a certain genetic background or a specific phenotype. Sympathetic hyperactivity is probably accompanied by impaired vagal impact on the heart. Adrenergic activation is an early manifestation in the course of the disease and becomes more pronounced with the severity of hypertension. Peripheral vascular resistance depends on the sympathetic nervous system, humoral factors and local autoregulation. Sympathetic nervous system produces its effects through the vasoconstrictory alpha effect or vasodilatory beta effect. Humoral activities on peripheral resistance are also affected by mediators, such as vasoconstrictors (angiotensin, catecholamines) or vasodilators (prostaglandins, kinins), blood viscosity, vascular wall condition and blood flow rate (12, 16, 17, 18, 19).

The onset and development of AH are closely related with genetic and social factors. One of the mechanisms for the development of elevated arterial pressure is seen in high-debit AH, where the minute volume of the heart is increased as a result of reduced peripheral vascular resistance and increased sympathetic stimulation. A second model of AH includes normal or decreased cardiac output and increased systemic vascular resistance due to increased vascular reactivity. Another pathophysiologic mechanism for raising the arterial pressure, partly overlapping the first model, is the increased re-absorption of salt and water by the kidneys. This is the salt-sensitive hypertension, where the circulating blood volume increases. On the other hand, cortisol reactivity may represent a link between the increased psychosocial stress and the development of AH. Pulse pressure (the difference between systolic and diastolic blood pressure) is frequently increased in elderly hypertensives. This may be manifested by excessive systolic and normal or low diastolic pressure. This condition is called isolated systolic hypertension (12, 14, 16).

The development of AH passes through various stages. Typically, the initial stage involves pre-hypertension in persons aged 10-30 years (with increased heart output). It is followed by the onset of hypertension in persons aged 20-40 years (with increased peripheral resistance). Only then, persistent hypertension occurs in persons aged between 30-50 years. And finally, complicated hypertension appears in persons aged 40-60 years. After a long, unchanging, asymptomatic period, persistent hypertension leads to complications (3, 12, 20, 21, 22). Typically, after a 10-year period, hypertensives develop damages to certain organs. Firstly, the heart and kidneys are damaged (20, 21, 22). After then, changes in the aorta and small arteries, brain, retina, etc. occur. Single organ involvement is found in approximately 83% of the patients, dual organ - in 14% and multi-organ involvement (>3 organ systems) in about 3% of the hypertensive patients (1, 6, 12, 20, 23).

In this review, **we present literature data** on AH- induced kidney damage, without considering secondary renal hypertension. Kidneys are protected from acute increases in blood pressure by auto-regulatory mechanisms. AH is a risk factor for chronic kidney disease (CKD) and its end stage (20, 21, 22). The risk of kidney damage appears to be more closely related with systolic than diastolic blood pressure. Typically, after a 10-year period of uncontrolled hypertension, damage to the kidneys is observed, leading to chronic kidney disease (CKD). Considering the two main indicators for CKD (GFR and microalbuminuria), more recent studies have shown that damage to the kidneys may start much earlier (12, 23, 24, 25). The incidence of CKD in the different European countries is 5-10%, and in Bulgaria it approximates 12%. The most common cause of CKD is diabetes in 35% of the cases and the second one is AH in about 30% (5, 11, 24, 25). The increase in blood pressure - occasional or permanent, leads to proportional autoregulatory vasoconstriction of renal arterioles. Vascular pre-glomerular resistance increases. This process involves mainly the afferent arterioles. Early renal blood flow, glomerular filtration rate (GFR) and the pressure of glomerular capillaries (PGC) remain relatively constant. After a time, they also change (12, 26, 27). The majority of patients with primary essential hypertension have preserved autoregulation. Glomerular capillaries are protected from barotrauma and significant proteinuria is not observed. However, the pre-glomerular vasculature, exposed to hypertension, develops slowly and progressively vascular pathology. The extent of hypertension-induced kidney damage is proportional to the degree of blood pressure in the renal microvasculature.

Changes in automatic control (genetic or acquired) lead to an increase in renal perfusion pressure (12, 15, 20, 23, 28, 29). Hypertension, associated with vascular lesions in the kidney, affects mainly pre-globular arterioles. There are ischemia-induced changes in glomerular and post-glomerular structures. Hyper-perfusion damages the glomeruli. Glomerular pathology progresses to glomerulosclerosis. Kidney tubules can also become ischemic and gradually, atrophic. Angiotensin II increases the ischemic damage. Glomerular filtration of proteins increases and this also leads to glomerular collapse, segmental necrosis and glomerulosclerosis. Hyper-filtration of proteins causes tubular reabsorption of proteins and mesangial proliferation, leading to tubulo-interstitial inflammation and glomerulosclerosis. Hyper-filtration results in a trans-glomerular loss of proteins that promote the release of cytokines and growth factors from the mesangial cells (25, 26, 30, 31). According to another mechanism, there is endothelial dysfunction and loss of endogenous vasodilators. Both mechanisms lead to hypoxic-ischemic damage. This is followed by activation of intrarenal renin-angiotensin system and increased release of cytokines and growth factors (12, 17, 30, 32). The lumen of arterioles narrows, due to hypertrophy of the smooth muscle cells. Glomerular hypertension has a direct effect on glomerular structures. Adaptive mechanisms include contraction, transcriptional activity, proliferation, remodeling and fibrosis. The increase in inflammatory cells stimulates apoptosis and causes loss of normal kidney cells. Matrix production increases and this finally results in progressive glomerular and interstitial fibrosis.

AH is a major independent risk factor for end stage renal disease in part of the hypertensive patients (22, 26, 27). Both AH and subsequent CKD require continuous control of certain biomarkers. These include mostly complete lipid profile, macroalbuminuria, creatinine, cystatin C, albumin/creatinine ratio, glucose, glycated hemoglobin, CBC, etc. (16, 28). Monitoring of early markers of kidney damage may suggest to proper treatment and avoidance of end-stage renal failure.

This review presents data on the relationship between hypertension and renal impairment and the possible underlying etiology and pathogenesis.

References:

1. Eichmann F, Potthoff P, Schmidt M, et al. PCV115Burden of Hypertension in Selected EU Countries. 2010-2025. http://dx.doi.org/10.1016/j.jval.2012.08.1058
2. Pirkle JL1, Freedman BI. Hypertension and chronic kidney disease: controversies in pathogenesis and treatment. Minerva Urol Nefrol, 65, 2013 Mar, N 1,37-50. PMID: 23538309 PMCID: PMC4030753
3. Merai R, Siegel C, Rakotz M, Basch P, Wright J, Wong B; DHSc., Thorpe P. CDC Grand Rounds: A Public Health Approach to Detect and Control Hypertension. MMWR Morb Mortal Wkly Rep, 65, 2016, N 45, 1261-1264. doi: 10.15585/mmwr.mm6545a3.
4. Chobanian A., Bakris G., Black H. et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension, 42, 2003,N 6,1206-1252 http://hyper.ahajournals.org/content/42/6/1206.long
5. Mihajlov R, Stoeva D, Pencheva B, et al. Albuminuria and Glomerular Filtration in patients with Essential Hypertension. Clin.Lab, 61, 2015, N 7, 677-685
6. Beevers G, Lip G, O'Brien E. ABC of hypertension: The pathophysiology ofHypertension. BMJ, 322, 2001, N 2791, 912-916. doi:10.1136/bmj.322.7291.912
7. Ostchega Y, Dillon CF, Hughes JP, et al. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. J Am Geriatr Soc, 55,2007, N 7, 1056-1065. DOI:10.1111/j.1532-5415.2007.01215.x. c. 1056 – 1065.
8. Know Your Risk Factors for High Blood Pressure. American Heart Assotiation. Jan 12,2017
9. Collart F, de Timary P, Dom G, et al. Alcohol-induced hypertension: an important healthcare target in Belgium. Acta Clin Belg, 70, 2015 , N 6, 389-395. doi: 10.1179/2295333715Y.0000000039. Epub 2015 Jul 2.
10. Delsart P, Takla M, Marboeuf P, et al. Evaluation of blood pressure control in an obstructive sleep apnea population followed in cardiology.High Blood Press Cardiovasc Prev, 22, 2015 Jun, N 2, 159-164. doi: 10.1007/s40292-015-0088-1.PMID: 25894017
11. Chobanian AV, BakrisGL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension, 42, 2003,1206-1252 https://doi.org/10.1161/01.HYP.0000107251.49515.c2
12. Dreisbach AW, Batuman V. Pathophysiology of Hypertension. Medscape Updated: Dec 28, 2015 .
13. Di Lullo L, Bellasi A, De Pascalis A, et al. Hypertension, type Ⅳ cardiorenal syndrome and chronic kidney disease: Pathophysiological and therapeutical approach. World J Hypertens , 7, 2017 February 23, N 1: 10-18. Available from: URL: http://www.wjgnet.
14. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell, 104, 2001 Feb 23, N 4, 545 – 556.
15. De Jong AM, Maass AH, Oberdorf-Maass SU, et al. Cyclical stretch induces structural changes in atrial myocytes. J Cell Mol Med, 17, 2013, N 6, 743–753. Published online 2013 Apr 26. doi: 10.1111/jcmm.12064
16. Mihaylov R, Stoeva D, Pencheva B. Early diagnostics of diabetic nephropathy. Int J Sci Research, 6, 2017, N 1,
17. Manrique C, Lastra G, Gardner M, et al. The Renin Angiotensin Aldosterone System in Hypertension: Roles of Insulin Resistance and Oxidative Stress. Med Clin North Am, 93, 2009 May, N 3, 569–582. doi: 10.1016/j.mcna.2009.02.014
18. Esler M, Lambert E, Schlaich M. Point: Chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension. J. Appl. Physiol, 109,2010, N 6, 1996-1998. December 2010. DOI:10.1152/japplphysiol. 00182.2010. c.
19. Mancia G, Grassi G. REVIEWS. The Autonomic Nervous System and Hypertension. Circ Res, 114, 2014 May 23, N 11,:1804-1814.
20. Arora P, Batuman V. Chronic Kidney Disease. Medscape. Updated: Jul 24, 2016
21. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl , 3, 2013, N 4, 368–371. Published online 2013 Nov 27. doi: 10.1038/kisup.2013.79
22. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA, 289, 2003, N 18, 2363-2369. PMID: 12746359 DOI: 10.1001/jama.289.18.2363 22.
23. Iseki K. Factors influencing the development of end-stage renal disease. Clin Exp Nephrol, 9, 2005, N 1,5–14. 10.1007/s10157-005-0341-3 .
24. Михайлов Р. .Цистатин С - нов биомаркер за оценка на бъбречната функция. Мед.Мар., 2013, 14 – 17
25. How High Blood Pressure Can Lead to Kidney Damage or Failure. American Heart Association, Jan 18,2017
26. Nguyen H, Odelola OA, Rangaswami J, et al. A Review of Nutritional Factors in Hypertension Management. Int J Hypertension, 2013,2013, Article ID 698940, 12 pageshttp://dx.doi.org/10.1155/2013/69894026.
27. Mihailov M, Pencheva B, Stoeva D. Estimation of GFR through various formulas. Compres rendue del Academie Bulgarie des scienes,69, 2016, N 7, 935-944.
28. Kuil A, Engberink MF, Verberne LD, et al. Protein intake in relation to risk of hypertension and microalbuminuria in patients with type 1 diabetes: the EURODIAB Prospective Complications Study. J Hypertens, 31,2013, N 6,1151-1159. doi: 10.1097/HJH.0b013e328360418e.
29. Михайлов Р.Микроалбуминурия и съотношение албумин/креатинин. Мед.Мар., 2013, 18 – 21.

30. Mihailov R, Stoeva D, Pencheva B .Оценка на гломерулната филтрация чрез различните формули. Nefrol., dial., i transpl., 20,2014 N4, ISSN 1312-5257, c.20-30, 5tabl., 1fig. Sum. Bulg., Engl., 28 ref.
31. Mihailov R.The new biomarker cystatin C and albuniuria. Compres rendue del Academie Bulgarie des scienes, 67, 2014, N 11, 935-944.
32. Ponnuchamy B, Khalil RA. Cellular mediators of renal vascular dysfunction in hypertension. Am J Physiol, 296, 2009, N 4, R1001–1018. doi:10.1152/ajpregu.90960.2008. PMC 2698613Freely accessible. PMID 19225145. Retrieved 2009-06-23.