The role of arterial hypertension in the progression of non-diabetic glomerular diseases

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Abstract

Arterial hypertension (AH) per se is, together with diabetes mellitus, the most important cause of renal failure and of dialysis in the western world. AH is also a well known consequence of chronic renal disease, and at the same time one of the main factors which causes diabetic and/or non-diabetic chronic renal failure progression. AH is mostly registered in patients with focal segmental glomerulosclerosis and with membranoproliferative glomerulonephritis. The pathophysiology and the mechanism of AH within primary glomerular diseases are complex, including activation of the sympathetic nervous system, the renin–angiotensin system (RAS), sodium retention, volume expansion and decreased synthesis of vasodilatatory substances. As autoregulation of glomerular pressure in chronic glomerular disease is disturbed, the increment in systemic blood pressure leads to the rise in glomerular pressure. Glomerular hypertension results in glomerular capillary wall stretch, endothelial damage and a rise in protein glomerular filtration. These processes, in turn, cause changes of mesangial and proximal tubular cells, ultimately resulting in the replacement of functional by non-functional connective tissue and the development of fibrosis. One of the most important factors in the progression of chronic renal failure is activation of the RAS. Its effect is not only elevated blood pressure, but also the promotion of cell proliferation, inflammation and matrix accumulation. Many studies, first in experimental animals and later in humans, have shown that the lowering of blood pressure (and proteinuria) is associated with a slower progression of kidney disease. It seems that angiotensin-converting enzyme inhibitors (ACEIs) are more renoprotective than other antihypertensives (the protection beyond the antihypertensive effect), although some studies have also confirmed a comparatively beneficial effect of non-dihydropiridine calcium channel blockers (CCBs) and angiotensin II receptor blockers (ARBs). Moreover, it seems that a combination of antihypertensives (e.g. ACEI + CCB, ACEI + ARB) has a more effective action than either of the drugs alone. However, the effects depend first on the degree of blood pressure reduction. According to comprehensive studies, the achievement of adequate blood pressure (not higher than 130/85 mmHg) is the most important factor. An even lower blood pressure (125/75 mmHg) has been suggested as the limit value in patients with proteinuria of > 1 g/24 h and in Blacks.

Keywords: glomerular diseases; hypertension

Introduction

Arterial hypertension per se is, together with diabetes mellitus, the most important cause of renal failure and of the introduction of dialysis treatment. It is also a well-known consequence of chronic renal failure. Arterial hypertension is (with age, sex, race, proteinuria, hyperlipidaemia, smoking, etc.) also one of the main causes of the progression of diabetic and non-diabetic chronic renal failure. This progressive renal failure develops especially in patients with glomerular kidney disease and clinically manifest proteinuria [1–5]. This process is slow in general, but sometimes the damage to the kidneys can develop very rapidly, with an immediate need for dialysis [6]. The Multiple Risk Factor Intervention Trial (MRFIT) has shown that the increasing risk of development of end-stage renal failure (ESRF) correlates significantly with the rise in blood pressure. If systolic blood pressure was > 200 mmHg, the risk of end-stage renal disease (ESRD) was 48.2 times higher than if it was < 120 mmHg. If diastolic blood pressure was > 120 mmHg, the risk was
30.9 times higher than when it was < 70 mmHg. The Hypertension Detection and Follow-up Program (HDFP) showed that creatinine was higher in subjects with a higher blood pressure. The creatinine values were three times higher in those with diastolic blood pressure > 115 mmHg than in those whose diastolic blood pressure was 90–114 mmHg. The same data have been obtained in other larger studies, e.g. in the ‘Maryland’ study, ‘Veterans Administration’ study and the study conducted by Tierney and co-workers [1]. The ‘Modification of Diet in Renal Disease’ study has also confirmed a higher incidence of renal failure associated with a higher blood pressure. The authors of that study found that 83% of the investigated patients had arterial hypertension; in those whose glomerular filtration were < 10 ml/min, arterial hypertension was observed in 95% of the subjects [1].

Prevalence of arterial hypertension in primary glomerulonephritis

In patients with chronic glomerular kidney disease with no renal failure, arterial hypertension was noted in 15–80% [4]. This shows that some changes in kidney function activate vasoactive hormonal systems and sodium excretion, which are responsible for the development of arterial hypertension before any detectable change in glomerular filtration. The prevalence of arterial hypertension varied depending on the type of glomerular disease, on the country where the study was performed and also on the time of the investigation (‘new’ vs ‘old’ studies). Most often, arterial hypertension was found in membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis and in endo- and extracapillary glomerulonephritis. This, of course, has influenced the natural course of the disease [7].

Pathophysiology of arterial hypertension in glomerular diseases

The pathophysiology and the mechanism of development of arterial hypertension in primary glomerular disease are complex. They involve activation of the sympathetic nervous system, the renin–angiotensin system (RAS), sodium retention, volume expansion and the decreased synthesis of vasodilatory substances. As the autoregulation of glomerular pressure is damaged in chronic glomerular disease, elevated systemic blood pressure leads to the rise in glomerular pressure. This hypothesis of kidney damage by arterial hypertension is the opposite of the classical view which saw glomerular ischaemia to be caused by hypertensive preglomerular arteries and arterioles. Glomerular hypertension results in glomerular capillary stretching, endothelial damage and elevated glomerular protein filtration. These processes cause the changes in mesangial and proximal tubular cells. These cells become immunocompetent, secreting cytokines, growth factors and other inflammatory mediators, which finally result in the replacement of active kidney tissue by connective tissue and fibrosis. One of the most important factors leading to progression of renal failure is the activation of the RAS [the renoprotective effects of angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) indirectly support this statement]: its effect is not only blood pressure elevation; but angiotensin II (Ang II) promotes cell proliferation, inflammation and matrix accumulation [2–4,8]. For a better understanding of Ang II, it is important to recognize its activation of nuclear factor-κB (NF-κB), as well as its effects on the production and secretion of transforming growth factor-β1 (TGF-β1) [4,9]. Ang II activates NF-κB in vascular smooth muscles and in mesangial cells. NF-κB plays a pivotal role in the control of few genes, e.g. the genes for cytokines, chemokines, adhesion molecules, nitric oxide (NO) synthesis, cyclooxygenase 2 and angiotensinogen, all involved in the pathogenesis of vascular damage. The inhibition of NF-κB reduced the organ damage with Ang II in the heart and kidneys by preventing production of the mediators [4,9]. The other most important factor whose production may be modulated by the intrarenal RAS, i.e. Ang II, and is very important in the pathogenesis of nephropathy is TGF-β1, the factor involved in the development of fibrosis in many kidney and other organs diseases. This factor directly stimulates the synthesis of individual components of the extracellular matrix and blocks the degradation of matrix-stimulating protease inhibitors, e.g. plasminogen activator inhibitor-1. Furthermore, TGF-β1 stimulates endothelin-1 (ET-1) production. This substance is a potent vasoconstrictor with a key role in the control of vascular tonus and with a potential role in the development of chronic renal failure. TGF-β1 inhibits the production of NO from the endothelium [4].

Antihypertensive drug treatment

Many studies, first with experimental animals and later in humans, have confirmed the effectiveness of the lowering of blood pressure (as well as proteinuria) on the progression of renal failure. Antihypertensive treatment decreases the rate of renal failure in diabetic (e.g. UKPDS study) and non-diabetic kidney disease (REIN study, AIPRI study, AIPRI extension study) [10–14]. It seems that drugs which inhibit the RAS are more effective in renoprotection than other antihypertensives, although there are studies showing that non-dihydropyridine calcium channel blockers (CCBs) and ARBs posses the same effect [1–4,8,11]. Moreover, it seems that the drug combinations (e.g. ACEI + CCB, or ACEI + ARB) are more effective than monotherapy [8–12]. The renoprotective effect of ACEIs is explained by their antiproteinuric effect [1–4]. It should be mentioned...
here that an effect can also be explained through its action on NF-κB and TGF-β. Ultimately, however, it seems that the renoprotective action depends first of all on the magnitude of the blood pressure reduction. In one of the newer studies, investigators have noted that a higher antiproteinuric effect was achieved when patients were treated with an ACEI alone or with the combination of an ACEI and CCB, but not with other antihypertensives (e.g. β-blockers). However, this difference was lost if blood pressure was not strictly controlled [11]. Another recommendation is the use of higher doses of ACEIs [13]. Arterial hypertension in patients with renal failure is not easily controlled; there is a need to use more than one antihypertensive drug—more than 50% of patients with renal insufficiency need three or more antihypertensives. In the MDRD study, it was shown that 1.9 drugs were needed to reach the blood pressure target of 125/75 mmHg, and 1.5 drugs to reach 140/90 mmHg in patients with no renal failure. In patients with chronic renal insufficiency, these figures were 2.1 and 1.8, respectively [1]. These data were confirmed in the HOT (Hypertension Optimal Treatment) study [14]. According to large studies, it is most important to reach the ‘target’ blood pressure. According to JNC VI, blood pressure should not exceed 130/85 mmHg in patients with chronic renal failure. Moreover, a lower blood pressure (125/75 mmHg) is suggested for patients with proteinuria of more than 1g/24h and for Blacks [15].

References

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