Review

ISSN 1738-5997 (Print) • ISSN 2092-9935 (Online)
Electrolyte Blood Press 13:41-45, 2015
http://dx.doi.org/10.5049/EBP.2015.13.2.41

Hypertension in Chronic Glomerulonephritis

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Chronic glomerulonephritis (GN), which includes focal segmental glomerulosclerosis and proliferative forms of GN such as IgA nephropathy, increases the risk of hypertension. Hypertension in chronic GN is primarily volume dependent, and this increase in blood volume is not related to the deterioration of renal function. Patients with chronic GN become salt sensitive as renal damage including arteriolosclerosis progresses and the consequent renal ischemia causes the stimulation of the intrarenal renin-angiotensin-aldosterone system (RAAS). Overactivity of the sympathetic nervous system also contributes to hypertension in chronic GN. According to the KDIGO guideline, the available evidence indicates that the target BP should be ≤140 mmHg systolic and ≤90 mmHg diastolic in chronic kidney disease patients without albuminuria. In most patients with an albumin excretion rate of ≥30 mg/24 h (i.e., those with both micro- and macroalbuminuria), a lower target of ≤130 mmHg systolic and ≤80 mmHg diastolic is suggested. The use of agents that block the RAAS system is recommended or suggested in all patients with an albumin excretion rate of ≥30 mg/24 h. The combination of a RAAS blockade with a calcium channel blocker and a diuretic may be effective in attaining the target BP, and in reducing the amount of urinary protein excretion in patients with chronic GN.

Key Words: Chronic glomerulonephritis, Volume dependent, RAAS blockade

Received: December 3, 2015
Accepted: December 14, 2015
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Prevalence of hypertension in chronic glomerulonephritis

Hypertension is a frequent finding in chronic kidney diseases. Almost all patients develop hypertension when the glomerular filtration rate (GFR) declines. Renal parenchymal hypertension develops in the setting of acute glomerulonephritis (GN), chronic GN, diabetic nephropathy, polycystic kidney disease, hypertensive nephrosclerosis, and renal microvascular disorders. Mild to moderate hypertension occurs in more than 75% of patients with acute forms of GN, such as poststreptococcal GN[1]. Patients with acute GN have hypertension primarily due to sodium retention leading to fluid overload, as evidenced by suppression of the renin-angiotensin-aldosterone (RAAS) system.

Causes of chronic GN with hypertension include IgA nephropathy (IgAN), membranous nephropathy, membranoproliferative GN, and focal segmental glomerulosclerosis[1]. According to one report, hypertension was frequently found in focal segmental sclerosis, membranous nephropathy, IgAN, and membranoproliferative GN[2]. Hypertension is a presenting feature in one third of patients with focal segmental sclerosis. Five years after renal biopsy, 92% of normotensive and 47% of hypertensive patients remained with normal renal function. These findings suggest that the high prevalence of hypertension in chronic GN is related to declining renal function. In IgAN, 9-53% and 7-15% of patients have hypertension and malignant hypertension, respectively. It was also reported that non-dipper hypertension was observed in 93% of the hypertensive IgAN patients[3]. Hypertension and the lack of a circadian rhythm can accelerate the progression of chronic GN which can, in turn, be slowed by the treatment of hypertension.

Pathophysiology of hypertension in chronic GN

There are three main factors contributing to the development of hypertension in patients with chronic GN, which are similar to those in essential hypertension, but more accentuated (Table 1). Sodium retention is of primary importance. Increased RAAS activity is responsible for the hypertension. Renal ischemia induced by microvascular damage is a potent stimulus of RAAS. Hypertension also results from overactivity of the sympathetic nervous system. Much evidence indicates increased sympathetic nervous activity in renal disease. Renal ischemia is probably a primary event leading to increased sympathetic nervous activity[4,5].

It was earlier reported that the blood volume was high in patients with IgAN, and that mean arterial pressure was correlated with blood volume, but not with plasma renin activity and GFR. Therefore, it has been suggested that hypertension in IgAN is primarily volume dependent, and that this increase in blood volume is not related to the deterioration of renal function[6]. Among IgAN patients with mild proteinuria, hypertension was associated with glomerular sclerosis, interstitial fibrosis/tubular atrophy, interstitial infiltration, and arteriosclerosis, but was not associated with the mesangial score. Arteriosclerosis was positive in 38.6% of hypertensives compared with 3.2% of normotensives. Hypertension affected the prognosis of mild proteinuric IgAN nephropathy through vascular lesions[7]. It was reported that in IgAN and membranous nephropathy, the patients with arteriolar hyalinosis and hypertension are characterized by higher values of glomerular sclerosis and tubulointerstitial damage, which are both responsible for reduced capillary bed perfusion pressure leading to a reduction of interstitial blood flow and consequent hypoxia in the interstitial compartment[8]. Furthermore, the sodium sensitivity index and scores for glomerular sclerosis and tubulointerstitial damage were higher in IgAN patients with normal to high-normal blood pressure (BP) or hypertension than in those with optimal BP[9]. The mean pressure-natriuresis curve was steeper in the optimal group than that in the normal to high-normal or hypertensive IgAN groups. The sodium sensitivity index was significantly correlated with glomerular sclerosis and tubulointerstitial damage. The increased sodium sensitivity appeared before hypertension and sodium restriction lowered BP to the optimal range and decreased proteinuria. We reported in 234 patients with IgAN that 121 patients (52%) had systolic BP $\geq$130 mmHg and 74 (32%) $\geq$140 mmHg. Systolic BP was positively correlated with serum uric acid concentrations and with pathological findings, including glomerulomegaly and the degree of tubulointerstitial fibrosis and deposits of IgM and C3, and negatively with post-glomerular filtration rate and the slope of change in 1/serum creatinine for 2 years (Table 2). Patients with systolic BP $\geq$130 mmHg compared with those <130 mmHg were older and showed more severe clinico-pathological findings such as pre- and post-serum creatinine, amount of proteinuria, glomerulomegaly, tubulointerstitial fibrosis, and deposits of IgM and C3[10-12].

It was observed in patients with IgAN that urinary angiotensinogen levels, renal tissue angiotensinogen expression and angiotensin II immunoreactivity were significantly higher, and that urinary angiotensinogen reflects

Table 1. Pathogenesis of hypertension in chronic glomerulonephritis

1) Sodium and water retention: Sodium sensitivity increases as glomerulosclerosis and tubulointerstitial damage progress
2) Excessive activity of RAAS system: Renal ischemia is a potent stimulus of renin secretion
3) Increased activity of the sympathetic nervous system: The afferent signal may arise within the kidneys

Table 2. Relationship between blood pressure and clinicopathological findings in patients with IgA nephropathy

1) Systolic blood pressure correlates positively with: serum uric acid tubulo-interstitial fibrosis deposits of IgM and C3 mean glomerular surface area
2) Systolic blood pressure correlates negatively with: post-glomerular filtration rate delta 1/SCr/2 year

the activity of the intrarenal RAAS system[13]. Even though the IgAN patients did not show massive renal damage, immunoreactivity of hemeoxygenase-1 and angiotensinogen were increased in these patients at this time point. These data suggest that intrarenal reactive oxygen species and RAAS activation play a pivotal role in the development of IgAN during the early stages and provide a supportive foundation for the effectiveness of RAAS blockade in IgAN[14]. We observed that urine angiotensinogen levels correlate with the urine protein-to-creatinine ratio and serum creatinine concentrations in patients with IgAN[11]. Finally, increased urinary angiotensinogen levels induced by salt and associated renal damage leads to the development of salt-sensitive hypertension in patients with IgAN[15].

Therefore, it can be speculated that patients with chronic GN become salt sensitive as renal damage progresses, and the consequent reduction of interstitial blood flow and hypoxia causes the stimulation of the intrarenal RAAS which, in turn, contributes to the development of salt-sensitive hypertension.

Several studies have shown the gene polymorphisms contributing to hypertension and the relationship between BP-related genes and disease progression in patients with IgAN. Men with AGT M235T TT were found to be at an increased risk of IgAN progression compared to those with the other genotypes[16]. CD14 -159CC and ACE DD were independently associated with hypertension[17]. There was a significant difference in the therapeutic response to ARB between the DD/ID genotype and the II genotype[18].

New aspects of anti-hypertensive therapy in patients with chronic GN

According to the KDIGO guideline[19], the available evidence indicates that in chronic kidney disease patients without albuminuria the target BP should be ≤140 mmHg systolic and ≤90 mmHg diastolic. In most patients with an albumin excretion rate of ≥30 mg/24 h (i.e., those with both micro- and macroalbuminuria), a lower target of ≤130 mmHg systolic and ≤80 mmHg diastolic is suggested (Table 3). In achieving BP control, the value of lifestyle changes and the need for multiple pharmacological agents is acknowledged. However, the JNC VIII and ESH/ESC guidelines recommend a systolic BP goal of <140 mmHg in patients with chronic kidney disease[20,21]. Thus, the most appropriate targets for systolic BP to reduce cardiovascular morbidity and mortality among persons are still uncertain.

Table 3. The target blood pressure in the KDIGO clinical practice guidelines in non-diabetic chronic kidney disease

1) In patients with proteinuria 30-300 or ≥300 mg/24 hr: blood pressure ≤130/80 mmHg
2) In patients with proteinuria <30 mg/24 hr: blood pressure ≤140/90 mmHg

Intensive BP treatment was examined in the several studies, such as ACCORD[22], HALT-PKD[23] and SPRINT[24]. It was recently reported in the SPRINT trial that among non-diabetic patients at high risk for cardiovascular events, targeting a systolic BP of <120 mm Hg, as compared with <140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and of death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. Among patients with polycystic kidney disease in the HALT-PKD study, as compared with standard BP control, rigorous BP control was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion. The ACCORD study, on the contrary, showed in older patients with type 2 diabetes that intensive antihypertensive therapy did not significantly reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. An intensive strategy reduced the new development of microalbuminuria by 16%, but had no significant effect on other microvascular end points or composites. So far, the evidence suggests that a lower target of ≤130 mmHg systolic and ≤80 mmHg diastolic may be appropriate for patients with chronic GN and both micro- and macroalbuminuria if they are not old and do not have high cardiovascular risk factors.

Which is the best anti-hypertensive drug? According to the KDOQI guideline, hypertensive people with diabetes and chronic kidney disease stages 1-4 should be treated with an ACE inhibitor or an angiotensin receptor blocker, usually in combination with a diuretic[25]. An approach to diabetic nephropathy based on RAAS blockade in type II diabetes is projected to result in a lower incidence of end-stage renal disease (66%) compared with placebo patients. It is also suggested that using an ACE inhibitor or an angiotensin receptor blocker in normotensive patients with diabetes and albuminuria levels ≥30 mg/g is more beneficial. In the KDIGO guideline, the use of agents that block the RAAS system is recommended or suggested in all patients with an albumin excretion rate of ≥30 mg/24 h[19]. The ESH /ESC hypertension guideline announced that RAS blockers are more effective in reducing albuminuria than other antihypertensive agents[21]. The ONTARGET study showed that both angiotensin receptor blockers and ACE inhibitors were equally effective in improving outcome (dialysis, doubling of serum creatinine, and death), and the number of events for the composite outcome was similar for both[26]. Because of the reduction in renal function, the use of diuretics is mainly important in patients with chronic kidney disease who are usually volume overloaded.

The attainment of target BP in patients with chronic kidney disease typically requires multidrug therapy as seen in several clinical studies. It is commonly accepted that a combination of an ACE inhibitor with a calcium channel blocker is superior to placebo and equivalent or superior to ACE inhibitors alone for inhibiting the progression of diabetic kidney disease. The ACCOMPLISH study showed that the combination of an ACE inhibitor with a calcium channel blocker is superior to the combination of ACE inhibitors with a beta blocker[27].

A number of trials and meta-analyses have shown that the combination of ACE inhibitor/angiotensin receptor blocker therapy has a greater anti-proteinuric effect than either agent alone. However, in the dual-therapy group of the Ontarget study, even though there was a significant reduction in proteinuria, there was an increase in adverse effects and worsening renal outcomes[26]. Whether the combination of ACE inhibitor/angiotensin receptor blocker therapy may be beneficial for the cardio-renal outcomes in non-elderly patients with chronic GN who do not have high cardiovascular risk remains unresolved.

In summary, the combination of an ACE inhibitor/angiotensin receptor blocker with a calcium channel blocker (long-acting dihydropyridine or non-dihydropyridine) and a diuretic may be effective to attain the target BP and to reduce the amount of urinary protein excretion in patients with chronic GN.

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