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Blood Pressure Control in Patients with Glomerulonephritis

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1. Introduction

Although the expanding prevalence of lifestyle-related diseases such as diabetes mellitus and hypertension which ultimately cause renal dysfunction, glomerulonephritis still remains as one of the major causes of end-stage renal failure in most countries all over the world. In addition to the immunological therapy using corticosteroids and immunosuppressants, management of non-immunological risk factors such as hypertension, obesity and disorders of glucose and lipid metabolism greatly affect the prognosis of renal function in the treatment of patients with glomerulonephritis. Especially, hypertension is a pivotal risk factor for the progression of renal injuries and the adequate blood pressure control is a matter of primary importance in order to prevent the development of renal dysfunction.

In this chapter, the importance of blood pressure control is stressed referring the evidence thus far, and current topics and future prospects are discussed as to the matters such as target blood pressure levels and choices of antihypertensive agents.

2. Target blood pressure

Generally, hypertension is diagnosed when the systolic blood pressure is higher than 140mmHg and/or the diastolic blood pressure is higher than 90mmHg. However, this is an arbitrary definition and the linear relation between the blood pressure level and the risk of renal dysfunction can be extended even in the normotensive range in epidemiological studies. Figure 1 shows the relations of blood pressure level categories and the risk of developing end-stage renal failure in 17-year follow-up study of Okinawa prefecture residents in Japan (1). Naturally, hypertension increases the risk of renal failure with elevating grade of blood pressure levels. Moreover, blood pressure levels lower than 140/90mmHg but higher than 130/85mmHg, namely the high-normal blood pressure, offers a significant risk for future development of renal failure.

As for the target blood pressure level in the treatment of glomerulonephritis patients, Figure 2 depicts the outcomes of Modification of Diet in Renal Disease (MDRD) study (2) in which the blood pressure control level less than 125/75mmHg brought about slower GFR reduction than the level less than 140/90mmHg in subjects with nondiabetic renal diseases especially when the proteinuria was prominent. Similarly, Figure 3 plots the annual decrease rates of GFR against achieved blood pressure levels in hypertensive subjects with

renal diseases (3). In patients whose hypertension was not treated, GFR decreased by more than 10mL/min per year. When the blood pressure was lowered to 140/90mmHg, the rate of annual GFR decline was reduced by half. However, considering that the physiological annual GFR decline with aging is about 1mL/min, the annual GFR decline in 140/90mmHg subjects is faster than the natural rate. As compared with this, strict blood pressure lowering to 130/85mmHg or 130/80mmHg yielded retardation of GFR decline to a nearly physiological level in subjects with renal diseases.

Fig. 1. Relationship between the incidence of end-stage renal failure and the blood pressure level (1). The incidence of end-stage renal failure is increased not only in hypertensive subjects but also in subjects with high-normal blood pressure ranging 130-139/85-89 mmHg as compared with lower normal blood pressure subjects.

Fig. 2. The annual decrease in glomerular filtration rate (GFR) in nondiabetic renal disease patients of The Modification of Diet in Renal Disease(MDRD) Study. (2)

Thus, it is suggested that the blood pressure should be lowered below the high-normal level in glomerulonephritis patients in order to maximally slow the progression of renal dysfunction. Therefore, the American, European and Japanese guidelines for the management of hypertension recommend the target blood pressure level of less than 130/80mmHg in patients with chronic kidney disease (CKD) (4-6).

Fig. 3. Relationship between the annual decrease in glomerular filtration rate (GFR) and the achieved mean blood pressure level in studies treated hypertensive patients with renal diseases (3). The GFR decline rate was suppressed to the level near to the physiological decrease with aging in patients whose blood pressure was lowered under 130/85mmHg.

3. Glomerular hypertension and hyperfiltration

According to the hyperfiltration theory proposed by Hostteter and Brenner (7,8), increases in glomerular capillary pressure, referred to as glomerular hypertension, play an important role in the development and the progression of glomerular injuries ultimately resulting in glomerular sclerosis and the loss of its nephron. As indicated in Figure 4, not only high blood pressure but also increased salt intake and decreased urinary sodium excretion resulting in body fluid volume expansion raise intraglomerular capillary pressure and cause glomerular hypertension. In addition, the increases in protein intake and glomerular efferent arteriolar resistance are also the factors that contribute to the elevation of intraglomerular capillary pressure. Long-lasting of sustained glomerular hypertension impairs glomerular capillary endothelium and allows filtration of plasma protein molecules, followed by widening of mesangial area, obstruction of capillary lumen, hyalinosis of glomerular tuft and finally resulting in glomerular sclerosis, abolition of blood flow and filtration function. The loss of glomeruli brings about the atrophy of following renal tubules and nephrons themselves. Once a certain proportion of nephrons fall into atrophy, the intraglomerular capillary pressure and the single nephron filtration glomerular filtration rate of remaining glomeruli increase in order to compensate the reduced renal blood flow and maintain the glomerular filtration rate, which consequently promote further development of glomerular hypertension.

Fig. 4. Relations of factors contributing to the increase in intraglomerular capillary pressure and progression of glomerular sclerosis.

In order to stop the progression of this vicious cycle, comprehensive control of factors influencing the intraglomerular capillary pressure elevation such as arterial hypertension and intakes of salt and protein is needed. As mentioned concerning the target blood pressure, strict blood pressure control is important in patients with glomerulonephritis. In controlling the blood pressure, it should be kept in mind that reduction of intraglomerular capillary pressure as well as systemic arterial pressure is essential in order to achieve maximally effective inhibition of glomerular injuries and renal dysfunction. With regard to the hemodynamic aspect of renal microcirculation, intraglomerular capillary pressure is regulated by the balance between vascular resistances of afferent and efferent glomerular arterioles as depicted in Figure 5. A number of neural and humoral factors are known to affect the contraction and dilation of glomerular arterioles. Among them, the renin-angiotensin-aldosterone (RAA) system indicated in Figure 6 is assumed to play a pivotal role in the regulation of glomerular hemodynamics. Especially, angiotensin II, a peptide exhibiting prominent bioactivities in the RAA system, induce strong contraction of efferent rather than afferent glomerular arterioles. In addition, angiotensin II facilitates mesangial cell proliferation, increases oxidative stress by activating NAD(P)H oxidase, and induce proinflammatory transcription factor NF- κ B (9,10). These versatile effects of angiotensin II also contribute to the progression of renal tissue injuries.

On the other hand, angiotensin II stimulates the adrenal cortex to secrete aldosterone, a major mineralocorticoid, which facilitates renal tubular reabsorption of sodium resulting in blood and body fluid volume expansion and blood pressure elevation. Besides this well-known effect, aldosterone has been shown to promote renal tissue fibrosis and production of extracellular matrices such as collagen (9-11). Moreover, aldosterone injures endothelial,

epithelial and mesangial cells of glomeruli. In addition, aldosterone, like angiotensin II, constricts the efferent arterioles preferably to the afferent arteriole and increase the intraglomerular capillary pressure and filtration of plasma protein molecules. Thus, aldosterone is also assumed to be a factor exerting detrimental effects to the progression of glomerular diseases.

Fig. 5. The structure of glomeruli and factors relating to the hemodynamics and hydraulic pressure of glomeruli and glomerular arterioles.

Fig. 6. Outlines of the renin-angiotensin-aldosterone system and the biological actions elicited by its components.

Several other hormones and autacoids are known to elicit dilation or contraction of the glomerular arterioles. Atrial natriuretic peptide (ANP), produced by the heart, dilates the afferent arteriole and preserves renal and glomerular blood flow in the state of heart failure (12). This action is supposed to work also in glomerulonephritis patients with reduced renal function because the plasma ANP level is increased by body fluid volume increase and reduced clearance in the kidney. Vascular endothelium produces vasoactive substances such as nitric oxide (NO) and endothelin (ET). NO preferentially dilates and ET preferentially contract the afferent arterioles (13,14). NO is supposed to participate in the mechanism of increased glomerular filtration in the early stage of diabetic nephropathy, however, the NO synthase inhibition has been shown to increase intraglomerular capillary pressure in experimental glomerulonephritis (15,16). The pathophysiological implication of ET in the glomerular circulation is not well understood. The kidney has abundant ability to produce prostaglandins (PG) from arachidonic acid and PGE₂ which facilitates natriuresis and dilates the afferent arterioles is the major PG produced in the kidney. As compared with this, PGI₂ produced by vascular endothelium dilates both the afferent and the efferent arterioles (17). Nonsteroidal anti-inflammatory drugs such as indomethacin, which inhibit cyclooxygenase and PG production, can cause renal dysfunction as the adverse effect. The inflammatory process in the pathogenesis of glomerulonephritis is supposed to stimulate PG production in the kidney. This possibly increases glomerular and renal blood flow on one hand, however, may rather increase intraglomerular pressure on the other hand by preferentially dilating the afferent arterioles. However, it has been reported that the long-term administration of PGI₂ analogue mitigated the progression of renal dysfunction without increasing intraglomerular capillary pressure in patients with chronic glomerulonephritis (18).

Taken these together into consideration, it is suggested that the enhancement of RAA system is harmful to the glomeruli and the kidney via the noxious actions of angiotensin II and aldosterone. Reductions in renal function generally cause an increase in body fluid volume which inhibits plasma renin activity and concentrations of angiotensin II and aldosterone. Therefore, the circulating components of RAA system is supposed to be rather suppressed in patients with advanced glomerulonephritis. However, the renal and cardiovascular cells have been shown to produce components of RAA system such as renin, angiotensin converting enzyme (ACE) and aldosterone. In addition, angiotensinogen produced by the liver is abundant in plasma. Therefore, it is thought that angiotensin II and aldosterone are locally produced in the renal and cardiovascular systems and their concentrations in the tissues may be higher than in plasma. And, it is possible that the renal tissue RAA system is rather enhanced and contributes to the progression of renal injuries in patients with advanced glomerulonephritis although the circulating components of RAA system are suppressed.

4. Inhibitors of renin-angiotensin-aldosterone system in antihypertensive drug therapy for patients with glomerulonephritis

The precedent sections stressed the importance of strict blood pressure control and the implications of RAA system in the management of renal diseases in order to prevent the progression of renal dysfunction efficiently and effectively. In this context, inhibitors of RAA system such as ACE inhibitors and angiotensin II receptor antagonists (ARB) are supposed to provide renoprotective effects in addition to their hypotensive effects by inhibiting the detrimental actions of angiotensin II and aldosterone. Especially, these inhibitors of RAA system preferentially dilate the efferent arterioles as compared to the

afferent arterioles and thereby lower intraglomerular capillary pressure effectively (Figure 5). Anderson et al. (19) have shown that an ACE inhibitor lowers intraglomerular capillary pressure, reduces proteinuria and inhibits the progression of glomerular sclerosis more prominently than other antihypertensive drugs in rats with reduced renal mass in which the circulating RAA system is thought to be suppressed.

In human, it is a distinctive feature that the intraglomerular capillary pressure is elevated and the GFR is increased at the early stage of diabetic nephropathy. This glomerular hypertension facilitates the progression of diabetic nephropathy stages, namely, microalbuminuria, overt proteinuria, a GFR reduction, a serum creatinine increase and end-stage renal failure. Taguma et al. (20) have first reported that an ACE inhibitor reduces proteinuria in patients with diabetic nephropathy, and it is suggested that the suppression of angiotensin II generation brings about alleviation of glomerular hypertension and reduce hydrauric transcapillary filtration pressure of protein. After that, Lewis et al. (21) performed the multi-center collaborative prospective study evaluating the renoprotective effects of an ACE inhibitor in patients with type 1 diabetes mellitus presenting overt proteinuria and demonstrated that captopril inhibited the serum creatinine increase and the incidence of end-stage renal failure. As well as ACE inhibitors, multiple lines of later clinical studies have indicated that ARB are effective in retarding the progression of nephropathy at each stage in patients with type 2 diabetes (22-24).

With regard to the non-diabetic renal disease such as glomerulonephritis, the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) study (25) and Ramipril Efficacy in Nephropathy (REIN) study (26) showed that ACE inhibitors delay the progression of renal insufficiency in European patients with non-diabetic renal disease. Furthermore, African American Study of Kidney Disease and Hypertension (AASK) (27) suggested that ACE inhibitors slow renal disease progression in African American patients with hypertensive renal disease. Also as for the Asian population, we have reported that an ACE inhibitor and an ARB are effective in reducing proteinuria and slowing the deterioration of renal function in Japanese patients with chronic glomerulonephritis (28,29). Namely, an ACE inhibitor, benazepril, or an ARB, valsartan, inhibited the increase in serum creatinine and reduced proteinuria by 30-40% as compared with placebo (Figure 7,8). In addition, there is another study reported that an ACE inhibitor improved renal outcomes in Chinese patients with advanced stage of non-diabetic renal disease whose serum creatinine ranged 3.1 to 5.0mg/dL (30).

Fig. 7. Changes in serum creatinine concentrations and urinary protein excretions in glomerulonephritis patients given the ACE inhibitor or the placebo (28).

Fig. 8. Changes in serum creatinine concentrations and urinary protein excretions in glomerulonephritis patients given the angiotensin II receptor blocker (ARB) or the placebo (29).

As compared with ACE inhibitors and ARB, clinical evidence of other inhibitors of RAA system, such as renin inhibitors and aldosterone blockers seems less abundant regarding their renoprotective effects in patients with glomerulonephritis. In the cascade of RAA system indicated in Figure 6, conversion of angiotensinogen to angiotensin I by the enzymatic action of renin is assumed to be a rate-limiting step. Therefore, renin inhibitors such as aliskiren are thought to be theoretically effective in suppressing the activity of RAA system. Aliskiren, alone or in combination with ARB, has been shown to reduce albuminuria and proteinuria in patients with diabetic nephropathy (31,32), however, its efficacy in patients with glomerulonephritis is to be studied.

ACE inhibitors are widely used in the treatment of hypertension and renal disease. They reduce plasma levels of angiotensin II and aldosterone. However, it has been shown that the plasma aldosterone concentration rather increases in a certain portion of patients after month of long-term administration and this phenomenon is recognized as aldosterone breakthrough. Sato et al. (33) have reported that the long-term ACE inhibitor treatment failed to reduce albuminuria in patients with diabetic nephropathy who had developed aldosterone breakthrough, however, the albuminuria significantly reduced after adding spironolactone, an aldosterone blocker. Although spironolactone can cause adverse effects by its partially estrogenic actions such as gynecomastia and menstrual disorder which sometimes hamper the continuation of administration, eplerenone, a newly developed aldosterone blocker, is much more specific to the mineralocorticoid receptor and almost free from such estrogenic side effects. There is paucity of clinical evidence as to the effects of aldosterone blockers in glomerulonephritis patients, however, the use of an aldosterone blocker in addition to an ACE inhibitor or an ARB would be expected to exhibit protective effects against the progressions of glomerular injuries and renal dysfunction.

5. Calcium channel blockers in antihypertensive drug therapy for patients with glomerulonephritis

Although the guidelines for hypertension management recommend strict blood pressure control in order to prevent organ injuries and cardiovascular diseases, the target blood

pressure is generally achieved only in less than a half of hypertensive patients under treatment. In terms of lowering blood pressure, the hypotensive effect of CCB, directly dilating vascular smooth muscle, is consistently reliable in various conditions including glomerulonephritis patients. Therefore, the addition of CCB to RAA system inhibitors is expected to bring about effective blood pressure reduction with few chances to cause impeding adverse effects.

Ca channels residing in the plasma membrane of cells are composed five subunits; $\alpha 1$, $\alpha 2$, β , γ and δ . Among them, the $\alpha 1$ subunit conforming Ca^{2+} ion pathway has isoforms of L, N, P/Q, R and T. There are three isoforms of $\alpha 1$ subunit, L, N and T in the cardiovascular tissues, and Table 1 shows their distributions, functions and pharmacological blockers. Dihydropyridine (DHP) CCB, which are generally used as hypertensive drugs, blocks the L-type Ca channels existing in the arterial smooth muscle. With regard to the glomerular arterioles, because the afferent but not the efferent arterioles have the L-type channels, DHP CCB generally preferentially dilate the afferent arterioles. Therefore, it is supposed that the reduction in intraglomerular capillary pressure may not be so prominent as compared with the reduction in systemic arterial pressure. In this respect, the N-type and the T-type channels exist both in the afferent and the efferent arterioles and the blockers of these Ca channels are assumed to dilate both glomerular arterioles. This property is expected to contribute to the reduction in intraglomerular capillary pressure. Indeed, the N-type CCB, cilnidipine, and the T-type CCB such as efonidipine and azelnidipine have been shown to reduce proteinuria significantly in patients with glomerulonephritis as compared with L-type CCB (Figure 9), suggesting these CCB are effective in alleviating glomerular hypertension (34-36).

Fig. 9. The glomerular filtration rate (GFR) and the urinary excretions of protein in glomerulonephritis patients given the L-type Ca channel blocker (CCB), amlodipine, or the L- and T-type CCB, efonidipine (35).

As listed in Table 1, T-type Ca channels exist also in the adrenal and the in vitro experiments using cultured adrenal cells have shown that the T-type CCB suppress the expression of

aldosterone synthase gene (CYP11B2) and production of aldosterone (37,38). In harmony with this, clinical studies in healthy subjects and hypertensive patients have shown that the acute or the chronic administrations of T-type CCB lower plasma aldosterone levels (39,40). We have compared the effects of L- and T-type CCB efonidipine and L-type CCB amlodipine in patients with glomerulonephritis and observed that efonidipine reduces plasma aldosterone concentration as compared with amlodipine while the plasma angiotensin II concentrations were comparable (Figure 10)(35). It is mentioned in the previous section of this chapter that aldosterone is supposed to promote the progression of glomerular injuries and the aldosterone blocker can reduce albuminuria. Considering that the mechanism of aldosterone suppression by T-type CCB is different from those by ACE inhibitors, ARB and aldosterone blockers, this property of T-type CCB would be expected to provide an additive benefit, when combined with the RAA system inhibitors, against the progression of renal dysfunction in the antihypertensive treatment of glomerulonephritis patients.

Ca channel	Tissue distribution	Function	Blocker
L-type	vascular smooth muscle intestinal smooth muscle	vasocontraction intestinal contraction	nifedipine nicardipine nitrendipine amlodipine etc.
N-type	brain nerve end	facilitation of signal transmission	cilnidipine
T-type	vascular smooth muscle cardiac muscle adrenal	vasocontraction stimulation of excitement conduction aldosterone secretion	manidipine efonidipine benidipine azelnidipine mibefradil

Table 1. Subtypes of Ca channel and their locations, functions and blockers.

Fig. 10. The plasma concentrations of angiotensin II and aldosterone in glomerulonephritis patients given the L-type Ca channel blocker (CCB), amlodipine, or the L- and T-type CCB, efonidipine (35).

6. Summary and conclusions

Strict blood pressure control over 24 hours is of primary importance in preventing progression of renal injuries and deterioration of renal function in patients with glomerular diseases. In addition, it is important to lower not only systemic blood pressure but also intraglomerular capillary pressure in order to protect glomeruli from sclerosis because the increase in intraglomerular capillary pressure, glomerular hypertension, causes filtration of albuminuria and proteinuria which are dose-dependently related to the progression of renal injuries. Therefore, the antihypertensive therapy in patients with glomerulonephritis should aim not only the normalization of blood pressure but also the reduction of proteinuria and albuminuria. In order to lower intraglomerular capillary pressure, inhibitors of RAA system such as ACE inhibitors and ARB are effective as antihypertensive drugs because angiotensin II greatly contribute to the contraction of the efferent arterioles of glomeruli. In addition, interests are attracted as to the usefulness aldosterone receptor blockers and renin inhibitors as novel agents protecting the kidney. CCB are potent hypotensive agents, however, they rather dilate the afferent arterioles and may not be so effective as RAA system inhibitors in lowering intraglomerular capillary pressure. In this respect, some dihydropyridine CCB which block not only L-type Ca channel but also N- or T-type Ca channel have been shown to dilate efferent arterioles in addition to dilating afferent arterioles and are expected to be beneficial to protect glomeruli as well as lowering blood pressure effectively.

Prognosis of renal function in glomerulonephritis may be largely dependent on the nature of its pathohistological diagnosis and the therapeutic effects of immunosuppressive agents. In addition to these, efforts to lessen and minimize risk factors for renal injuries should be continuously made in order to inhibit the deterioration of renal function. Such efforts would be expected to contribute to inhibit not only the development of renal failure but also the incidence of cardiovascular diseases and to improve the prognosis of glomerulonephritis patients. Among the various risk factors for renal injuries hypertension has great influence and the adequate blood pressure control is a pivotally important issue.

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An Update on Glomerulopathies - Clinical and Treatment Aspects

Edited by Prof. Sharma Prabhakar

ISBN 978-953-307-673-7

Hard cover, 468 pages

Publisher InTech

Published online 02, November, 2011

Published in print edition November, 2011

An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

How to reference

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Toshihiko Ishimitsu (2011). Blood Pressure Control in Patients with Glomerulonephritis, An Update on Glomerulopathies - Clinical and Treatment Aspects, Prof. Sharma Prabhakar (Ed.), ISBN: 978-953-307-673-7, InTech, Available from: <http://www.intechopen.com/books/an-update-on-glomerulopathies-clinical-and-treatment-aspects/blood-pressure-control-in-patients-with-glomerulonephritis>

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