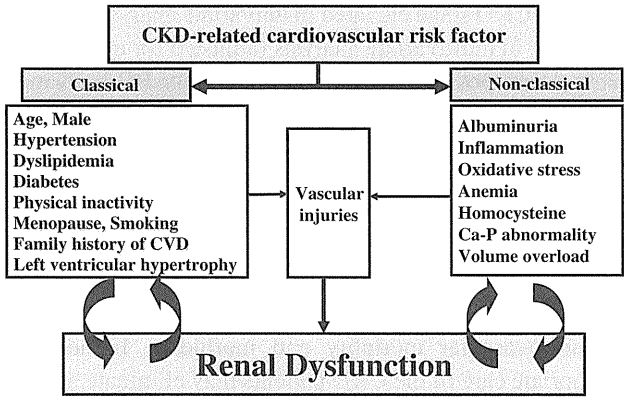


Fig. 2 Vicious cycle between vascular injuries and renal dysfunction

factors, as well as non-classical risk factors, thereby forming a vicious cycle. Both classical and non-classical risk factors are powerful accelerators of atherosclerosis. It has been shown that even moderate renal dysfunction is associated with enhanced oxidative stress and inflammation, which in turn accelerates atherosclerosis in the general circulation.

On the other hand, it has been shown that atherosclerotic vascular lesions are more prevalent in CKD patients than in non-CKD patients [9]. Thus, CKD reflects atherosclerosis, and CKD also accelerates atherosclerosis. This vicious cycle is present even in moderate reductions of GFR, and therefore, patients with CKD are more likely to die of CVD than to progress to ESRD.

Albuminuria as a cardiorenal risk

Among various components of CKD, microalbuminuria is of particular interest, because it is a significant risk factor not only in diabetic and hypertensive subjects but also in the general population [10–14]. Studies have now shown that albuminuria even within the normal range is associated with a higher incidence and prevalence of stroke and CVD [15, 16]. Albuminuria has been shown to cluster with a number of risk factors including hypertension, dyslipidemia, renal dysfunction, hyperhomocysteinemia and various inflammatory and oxidative stress markers [17, 18]. After adjustment of these factors, however, albuminuria is still an independent predictor for adverse cardiovascular events, and this risk increases in a continuous fashion with the degree of albuminuria [16]. Furthermore, recent clinical trials have shown that reduction of albuminuria is significantly related to improved outcomes in albuminuric subjects [10, 19, 20].

The mechanisms of the association between albuminuria and CVD are still largely unknown and are a focus of intensive research and debate [21–23]. It has been suggested that albuminuria not only reflects glomerular damage, but is also a sensitive indicator of generalized endothelial dysfunction and capillary vasculopathy that leads to penetration of atherosclerotic lipoproteins into the arterial walls [24–26]. Studies showed that albuminuria was associated with endothelial dysfunction in the systemic circulation [26], but not all studies support this contention [27]. The issue of whether the endothelial dysfunction in the general circulation can be deduced from the presence of albuminuria is the subject of considerable debate, because glomerular endothelial cells are quite distinct from those of general circulation. Endothelial dysfunction of the glomerulus alone may not cause albuminuria unless it affects functions of basement membrane or podocytes [21].

Microalbuminuria results from glomerular injuries and/or reduced tubular reabsorption of filtered albumin. It is unlikely that all 2 million nephrons within the kidney contribute equally to such a miniscule amount of albumin leaking into urine. It is more probable that some nephrons are damaged, leaking a substantial amount of albumin, while the majority of others are not. The question is whether the nephron damage occurs randomly among all the nephrons or according to some principle. A random phenomenon would be difficult to explain such a close linkage between microalbuminuria and CVD, because there is no logical necessity. However, if there is a principle that causes nephron damage in certain subpopulations, and if the same principle applies to some mechanisms of CVD, then it would be able to explain the close linkage.

The strain vessel hypothesis

In hypertensive renal injury, considerable heterogeneities exist among different nephron populations [28–31]. Specifically, tissue injury is most obvious in the juxtamedullary region and outer medulla in spontaneously hypertensive rats (SHRs) [28], Dahl salt-sensitive hypertensive rats [29], renovascular hypertension [30] and angiotensin II (Ang II)-induced hypertension [31]. In addition, it has been shown that in SHRs glomerular lesions first appear predominantly in the juxtamedullary nephrons and then extend toward more superficial nephrons [28]. Such distinct localization of renal injuries and mode of progression may be related to anatomical and functional heterogeneities of different nephron populations.

Figure 3 illustrates the anatomical relationships of the renal vasculature and tubular segments. The juxtamedullary glomeruli are located deep in the cortex and their afferent arterioles arise from either the initial segment of the interlobular artery or directly from the arcuate artery. In more superficial nephrons, their glomerular afferent

arterioles branch off from the more distal segments of the interlobular arteries. Since glomerular capillary pressure is normally maintained at about 50 mmHg by autoregulation in all nephrons [32], the pressure gradient across the afferent arteriole would be greatest in the juxtamedullary nephron. In other words, the juxtamedullary afferent arteriole is exposed to unusually high pressure for a vessel of its size (about 20 μm), and is destined to maintain strong vascular tone in order to provide this large pressure gradient in a short distance between the large arcuate artery and the glomerulus. In contrast, in the superficial nephrons, a more gradual pressure reduction occurs along the greater length of vasculature including the entire interlobular artery and afferent arterioles. It is of note that the interlobular artery also participates in renal autoregulation [33, 34], and therefore the feeding pressure of superficial afferent arterioles is substantially lower than that of juxtamedullary afferent arterioles [33].

There are many diseases and mechanisms proposed to cause microalbuminuria [21]. As discussed above, however, regardless of the pathogenesis of microalbuminuria, the anatomical sites that are injured initially or more severely are the juxtamedullary afferent arterioles and glomeruli [29–31]. It would be reasonable to expect that in the early stages of hypertension, diabetes or aging, renal injury occurs predominantly in the juxtamedullary nephrons, while the majority of other nephrons remain relatively intact. This would be expected to result in only minimal increases of urinary albumin excretion. Indeed, we observed that in type 2 diabetic Otsuka Long-Evans Tokushima Fatty rats, podocyte injuries were evident only in the juxtamedullary, and not the superficial glomeruli, in the early stage of developing albuminuria (unpublished observation).

From the hemodynamic point of view, the juxtamedullary afferent arterioles are small short vessels that are exposed to a high pressure and destined to maintain strong vascular tone in order to provide a large pressure gradient in a short distance. We refer to these kinds of vessels as 'strain vessels' [35]. Thus, microalbuminuria may be an early marker of vascular damage of strain vessels within the body. Other 'strain vessels' exist most notably in the central nervous system where many perforating arteries arise directly from large high-pressure arteries such as anterior, middle or posterior cerebral arteries, and penetrate into the brain tissues (Fig. 3) [36]. As in the case of juxtamedullary afferent arterioles, these perforating arteries are exposed to high pressure and destined to maintain large pressure gradients from their parent arteries to brain tissue capillaries [37]. It is well known that the sites of hemorrhage or infarction in the brain are frequently the areas of blood supply governed by these perforating arteries [36, 38]. Thus, 'strain vessels injuries' may explain the link between vascular damage and microalbuminuria in the kidney and stoke.

There may be similar, albeit not the same, hemodynamic conditions existing in the coronary circulation [39]. It is well known that coronary blood flow depends primarily on diastolic and not on systolic BP. Coronary arteries arise directly from the aorta, and during the systolic phase there is little coronary blood flow because intramyocardial vessels are compressed due to myocardial contraction. This creates a unique situation that during the systolic phase the entire epicardial segments of coronary arteries, including small arteries just before their entering the myocardium, are exposed to very high pressure, because there is little outflow. Studies have shown that coronary arteries (particularly small-sized segments) exhibit myogenic responses

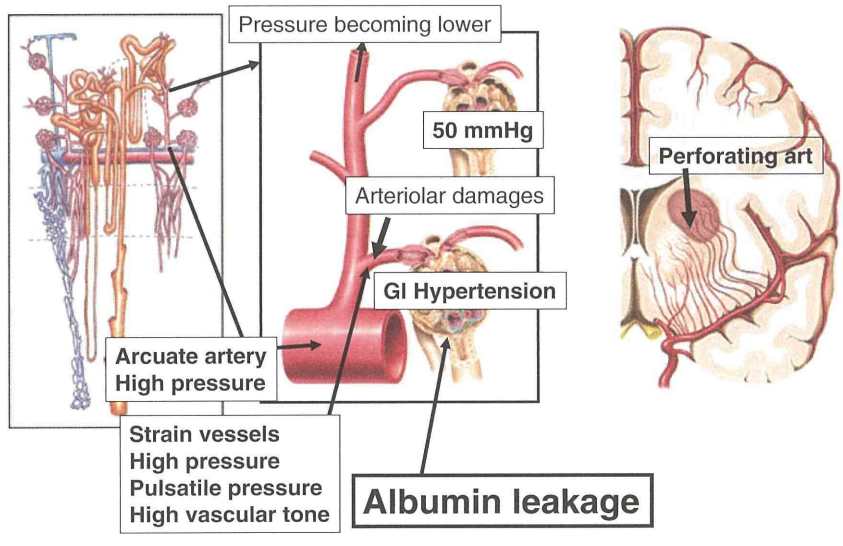


Fig. 3 Anatomical structures of the renal vasculatures and the tubular segments as well as perforating arteries in the central nervous system. Details are described in the text

[40], so that when intraluminal pressure is elevated, they would contract strongly in order to maintain vascular integrity. Therefore, although coronary arteries do not provide a pressure gradient, they would still be under high-pressure hemodynamic conditions with a strong vascular tone, which would be similar, though not the same, to those of strain vessels in the kidney and central nervous system.

According to our hypothesis, the importance of arterial stiffness for the association between cerebro-CVDs and albuminuria may be explained [41] by the fact that the strain vessels are directly influenced by the hemodynamics of large arteries. Unlike other small vessels in peripheral circulation where blood flow and pressure are rather constant, the strain vessels are exposed to pulsatile pressure and flow, and therefore stiffness of large arteries would have great impacts on the burden imposed on strain vessels [42, 43].

CKD components as cardiorenal risks

Figure 4 illustrates the relationship between CKD components and cardiorenal risks. As mentioned above, in such diseases as hypertension, diabetes and obesity, microalbuminuria would be a significant risk because it may reflect significant injuries of strain vessels. As endothelial and vascular damage become advanced, more and more glomeruli are injured, resulting in a substantial amount of albuminuria and reduced GFR. Therefore, microalbuminuria, which would indicate the presence of advanced glomerular as well as systemic vascular lesions, is a very strong risk of both renal and cardiovascular events in subjects with hypertension, diabetes and/or obesity.

On the other hand, macroalbuminuria does not seem to be a significant risk of CVD in primary glomerular diseases. Urine abnormality is the first sign of primary glomerular diseases, and its manifestation is often proteinuria (macroalbuminuria) rather than microalbuminuria. The degree of urine abnormalities reflects the degree of glomerular injuries. In addition, proteinuria induces tubulointerstitial damage within the kidney, thereby contributing to a decline of GFR. Indeed studies have established that the heavier the proteinuria, the faster the decline in renal function. Thus, in primary glomerular diseases, proteinuria is a significant renal risk, but it alone may not be a risk for CVD because strain vessels are not the primary sites of injuries.

Albuminuria and salt sensitivity of BP

One of the features of microalbuminuria is the close association with salt sensitivity of BP [44, 45], and this association is observed even in normotensive subjects [44]. Salt-sensitive hypertension is characterized by glomerular hypertension, microalbuminuria [46] and a higher mortality and morbidity of cardiovascular events [46, 47]. Interestingly, the association between microalbuminuria and CVD has been shown not only in diabetic or hypertensive populations but also in apparently healthy subjects [10–14].

There are many mechanisms involved in salt sensitivity of BP, and one of the mechanisms may be impaired pressure natriuresis. According to our strain vessel hypothesis, microalbuminuria indicates the existence of damage in juxtamedullary afferent arterioles and glomeruli, and therefore impairment of the downstream medullary

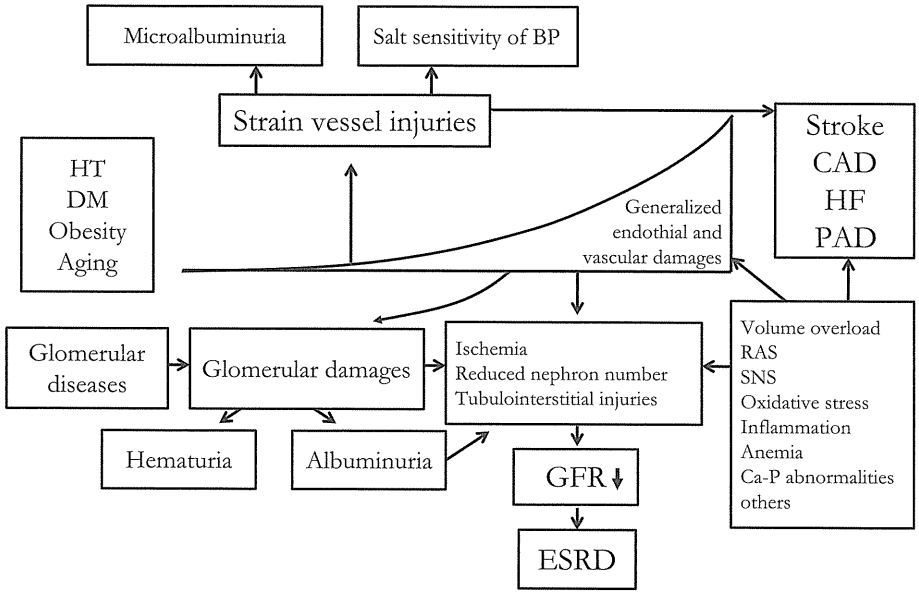


Fig. 4 Relationship among causes of CKD, endothelial and vascular injuries, urine abnormality, reduced GFR and cardiorenal events. *HT* hypertension, *DM* diabetes mellitus, *CAD* coronary artery disease, *HF* heart failure, *PAD* peripheral artery disease, *RAS* renin angiotensin system, *SNS* sympathetic nervous system

circulation. Since the medullary circulation plays a crucial role in the mechanisms of pressure natriuresis [48, 49], microalbuminuria may be related to impaired pressure natriuresis, and therefore, salt sensitivity of BP. In addition, in early stages of juxtamedullary glomerular injuries, there may be functional alterations in vasa recta. Namely, microalbuminuria could be caused by glomerular hypertension/hyperfiltration of juxtamedullary nephrons due to afferent arteriolar dysfunctions and impaired autoregulation. This hyperfiltration in the juxtamedullary glomeruli may cause constriction of descending vasa recta and thereby, functionally impair renal medullary circulation. It is of note that medullary thick ascending limb (mTAL) is anatomically located in the vicinity of the vasa recta that supply blood to the medulla. Studies have demonstrated the presence of tubulovascular cross talk in which nitric oxide or superoxide produced by the mTAL can diffuse into pericytes of descending vasa recta [50, 51]. By microperfusing mTAL segments in vitro, Abe et al. [52] demonstrated that an increase in sodium chloride concentration of the tubular perfusate stimulates superoxide anion production and decreases nitric oxide. Thus, hyperfiltration in juxtamedullary nephrons would increase sodium delivery to their own mTAL and stimulate superoxide production, which in turn may cause vasoconstriction of descending vasa recta (Fig. 5). Thus, our strain vessel hypothesis may explain the close interrelationships among microalbuminuria, salt sensitivity of BP and cerebro-cardiovascular mortality and morbidity. It should be noted, however, that other factors, such as the RAS and insulin sensitivity, also play a role in salt sensitivity of BP.

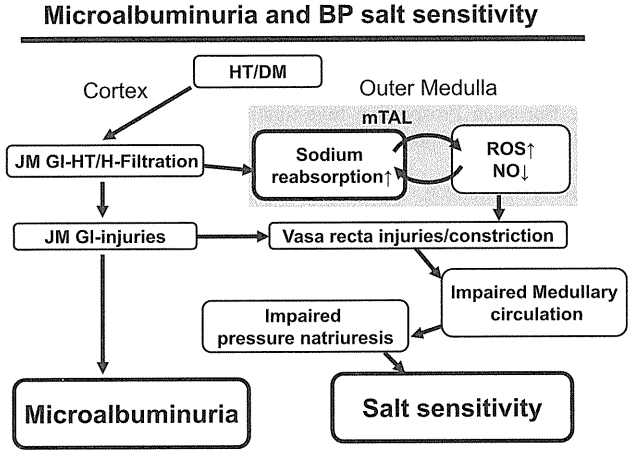


Fig. 5 Possible mechanism linking albuminuria and salt sensitivity of BP. Medullary blood flow is supplied via vasa recta, the downstream of the juxtamedullary glomerulus. In the phase of albuminuria, juxtamedullary glomeruli are injured, and therefore circulation of the downstream vasa recta is impaired. This in turn causes blunted pressure natriuresis and consequently an enhanced salt sensitivity of BP

Inhibitors of the RAS in the treatment of CKD

The inhibitors of the RAS have been shown to decrease both BP and urinary albumin excretion and to slow the progression of renal dysfunction significantly in diabetic and non-diabetic patients with CKD [53–56]. The renoprotective effects of RAS inhibitors are most prominent in patients with substantial amount of albuminuria [57]. Importantly, studies have reported that baseline as well as change in albuminuria during follow-up is closely associated with both renal outcome and cardiovascular mortality and morbidity [58–60]. Thus, it is recommended that strict BP control and reduction of albuminuria are the two important treatment goals for cardiorenal protection in CKD patients.

In contrast to the case for albuminuric patients, there is no convincing evidence that the benefits of RAS inhibitors extend to patients with less albuminuria [57]. Indeed, recent studies reported that a strong inhibition of the RAS may not be useful in certain populations. In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [61], a combination of high doses of ramipril and telmisartan did not offer any additional cardiovascular benefit beyond monotherapy with either drug alone, but it resulted in more adverse renal events of acute dialysis. In the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSEND), treatment with a high dose of telmisartan, as compared with placebo, resulted in a significantly higher renal event rate, which was primarily driven by increased rate of doubling of serum creatinine [62]. Interestingly, subanalyses of these studies have clarified that those who experienced adverse renal events were normotensive, had normal renal function and normoalbuminuria [62, 63]. The underlying mechanism for this may be based on complex interplays among RAS, salt balance and renal function [64]. It is known that inhibition of RAS would lead to a greater chance of hypotension and acute renal failure under such conditions as acute illness, dehydration, sodium depletion with excessive use of diuretics or major surgical procedures. This may be the case particularly in normotensive subjects with normal renal function in whom the circulating RAS responds very sensitively to changes in sodium balance, thereby maintaining circulatory homeostasis. Furthermore, repetition of subtle renal insult, even if it was partially reversible, may have resulted in doubling of serum creatinine in such subjects who had high cardiovascular risks and may also have unrecognized intrarenal vascular lesions. In contrast to subjects with normal renal function, the circulating RAS is less responsive to changes in sodium balance in subjects with reduced renal function or microalbuminuria, because their BP is salt sensitive and body fluid volume is expanded under regular sodium intake.

Thus, the known benefits of RAS inhibition should be placed within the context of an expected risk of adverse effects. In CKD, modifying levels of albuminuria still remains an important strategy for renal and cardiovascular protection. However, for those at low renal risk and with low levels of albuminuria, RAS inhibition may not offer any renal benefit. It is advised that RAS inhibitors be used more judiciously, with dose titration and better monitoring of kidney function as well as BP. Although the RAS is deemed to cause vascular injuries independent of BP, we should keep in mind that the RAS is a critically important biological component in maintaining homeostasis of body fluid volume and BP.

An evolutionary point of view and perspectives

Why do we have such vulnerable structures as 'strain vessels' or the RAS that may cause organ damage? From the evolutionary point of view, we speculate that unique structures such as strain vessels in vital organs as well as neurohormonal systems such as the RAS would have been essential for creatures on the land in order to survive under their natural environments [35]. All creatures in their natural environment were constantly facing the danger of circulatory collapse. Given the generally difficult access to salt and a high risk of wound injuries, hypotension and hypoperfusion of vital organs were the principal challenges with which they had to cope, and the potent vasoconstrictor and sodium-retaining actions of RAS were indispensable for this purpose. In addition, in order to maintain the perfusion of the vital tissues such as brainstem, it was necessary to develop circulatory systems in which vessels branch off directly from the large arteries and deliver blood to the tissue. Taken together, the close link between microalbuminuria and CVD may be viewed as an inevitable consequence destined by evolution. In other words, while human beings enjoy the benefits of the many developments of the industrial revolution we have to keep in mind that our fate is still governed by the natural law of evolution. The 'strain vessel' hypothesis may explain why hypertension and diabetes, unforeseen in the concept of evolution, preferentially affect vital organs such as brain, heart and kidney.

References

1. Sarnak MJ, Levey AS, Schoolwerth AC, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003;42:1050–65.
2. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009;13(6):621–30.
3. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164(6):659–63.
4. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int. 2004;65(6):2380–9.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
6. Bouchi R, Babazono T, Nyumura I, Toya K, Hayashi T, Ohta M, et al. Is a reduced estimated glomerular filtration rate a risk factor for stroke in patients with type 2 diabetes? Hypertens Res. 2009;32(5):381–6.
7. Gerstein HC, Mann JF, Pogue J, Dinneen SF, Hallé JP, Hoogwerf B, et al. Prevalence and determinants of microalbuminuria in high-risk diabetic and nondiabetic patients in the Heart Outcomes Prevention Evaluation Study. The HOPE Study Investigators. Diabetes Care. 2000;23:B35–9.
8. Nakayama M, Sato T, Sato H, Yamaguchi Y, Obara K, Kurihara I, et al. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study. Clin Exp Nephrol 2010;14:333-9.
9. Weiner DE, Tabatabai S, Tighiouart H, Elsayed E, Bansal N, Griffith J, et al. Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. Am J Kidney Dis. 2006;48(3):392–401.
10. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. Diabetes Care. 2006;29:595–600.
11. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777–82.
12. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, et al. Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. J Intern Med. 2004;255:247–56.
13. Ravera M, Ratto E, Vettoretti S, Viazzi F, Leoncini G, Parodi D, et al. Microalbuminuria and subclinical cerebrovascular damage in essential hypertension. J Nephrol. 2002;15:519–24.
14. Wada M, Nagasawa H, Kurita K, Koyama S, Arawaka S, Kawanami T, et al. Microalbuminuria is a risk factor for cerebral small vessel disease in community-based elderly subjects. J Neurol Sci. 2007;255:27–34.
15. Klausen KP, Scharling H, Jensen JS. Very low level of microalbuminuria is associated with increased risk of death in subjects with cardiovascular or cerebrovascular diseases. J Intern Med. 2006;260:231–7.
16. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, HOPE Study Investigators, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–6.
17. Fliser D, Buchholz K, Haller H, European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis (EUTOPIA) Investigators. Antiinflammatory effects of angiotensin II subtype

1 receptor blockade in hypertensive patients with microinflammation. Circulation. 2004;110:1103–7.
18. Ogawa S, Mori T, Nako K, Kato T, Takeuchi K, Ito S. Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy. Hypertension. 2006;47:699–705.
19. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med. 2001;249:519–26.
20. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110:2809–16.
21. Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? Diabetologia. 2008;51:714–25.
22. Nosadini R, Velussi M, Brocco E, Abaterusso C, Piarulli F, Morgia G, et al. Altered transcapillary escape of albumin and microalbuminuria reflects two different pathogenetic mechanisms. Diabetes. 2005;54:228–33.
23. de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. J Am Soc Nephrol. 2006;17:2100–5.
24. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet. 1992;340:319–23.
25. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. J Am Soc Nephrol. 2006;17:2106–11.
26. Malik AR, Sultan S, Turner ST, Kullo IJ. Urinary albumin excretion is associated with impaired flow- and nitroglycerin-mediated brachial artery dilatation in hypertensive adults. J Hum Hypertens. 2007;21:231–8.
27. Diercks GF, Stroes ES, van Boven AJ, van Roon AM, Hillege HL, de Jong PE, et al. Urinary albumin excretion is related to cardiovascular risk indicators, not to flow-mediated vasodilation, in apparently healthy subjects. Atherosclerosis. 2002;163(1):121–6.
28. Iversen BM, Amann K, Kvam FI, Wang X, Ofstad J. Increased glomerular capillary pressure and size mediate glomerulosclerosis in SHR juxtamedullary cortex. Am J Physiol. 1998;274:F365–73.
29. Johnson RJ, Gordon KL, Giachelli C, Kurth T, Skelton MM, Cowley AW Jr. Tubulointerstitial injury and loss of nitric oxide synthases parallel the development of hypertension in the Dahl-SS rat. J Hypertens. 2000;18:1497–505.
30. Eng E, Veniant M, Floege J, Fingerle J, Alpers CE, Menard J, et al. Renal proliferative and phenotypic changes in rats with two-kidney, one-clip Goldblatt hypertension. Am J Hypertens. 1994;7:177–85.
31. Mori T, Cowley AW Jr. Role of pressure in angiotensin II-induced renal injury: chronic servo-control of renal perfusion pressure in rats. Hypertension. 2004;43:752–9.
32. Ericson AC, Sjöquist M, Ulfendahl HR. Heterogeneity in regulation of glomerular function. Acta Physiol Scand. 1982;114:203–9.
33. Heyeraas KJ, Aukland K. Interlobular arterial resistance: influence of renal arterial pressure and angiotensin II. Kidney Int. 1987;31:1291–8.
34. Takenaka T, Suzuki H, Okada H, Hayashi K, Ozawa Y, Saruta T. Biophysical signals underlying myogenic responses in rat interlobular artery. Hypertension. 1998;32:1060–5.
35. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res. 2009;32(2):115–21.
36. Greenberg SM. Small vessel, big problem. N Engl J Med. 2006;354:1451–7.
37. Auer RN, Sutherland GR. Primary intracerebral hemorrhage: pathophysiology. Can J Neurol Sci. 2005;32:S3–12.
38. Dubas F. Small vessel pathology and cerebral hemorrhage. J Neuroradiol. 2003;30:298–302.
39. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007;356:830–40.
40. Cornelissen AJ, Dankelman J, VanBavel E, Stassen HG, Spaan JA. Myogenic reactivity and resistance distribution in the coronary arterial tree: a model study. Am J Physiol Heart Circ Physiol. 2000;278(5):H1490–9.
41. Hashimoto J, Aikawa T, Imai Y. Large artery stiffening as a link between cerebral lacunar infarction and renal albuminuria. Am J Hypertens. 2008;21(12):1304–9.
42. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46:200–4.
43. Struijker Boudier HA, Cohuet GM, Baumann M, Safar ME. The heart, macrocirculation and microcirculation in hypertension: a unifying hypothesis. J Hypertens. 2003;21:S19–23.
44. Cubeddu LX, Hoffmann IS, Aponte LM, Nuñez-Bogesits R, Medina-Suniaga H, Roa M, et al. Role of salt sensitivity, blood pressure, and hyperinsulinemia in determining high upper normal levels of urinary albumin excretion in a healthy adult population. Am J Hypertens. 2003;16:343–9.
45. Nesović M, Stojanović M, Nesović MM, Cirić J, Zarković M. Microalbuminuria is associated with salt sensitivity in hypertensive patients. J Hum Hypertens. 1996;10:573–6.
46. Campese VM. Salt sensitivity in hypertension. Renal and cardiovascular implications. Hypertension. 1994;23:531–50.
47. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension. 2001;37:429–32.
48. Dickhout JG, Mori T, Cowley AW Jr. Tubulovascular nitric oxide crosstalk: buffering of angiotensin II-induced medullary vasoconstriction. Circ Res. 2002;91:487–93.
49. Cowley AW Jr. Long-term control of arterial blood pressure. Physiol Rev. 1992;72:231–300.
50. Mori T, Cowley AW Jr, Ito S. Molecular mechanisms and therapeutic strategies of chronic renal injury: physiological role of angiotensin II-induced oxidative stress in renal medulla. J Pharmacol Sci. 2006;100:2–8.
51. Mori T, Cowley AW. Angiotensin II-NAD(P)H oxidase-stimulated superoxide modifies tubulovascular nitric oxide cross-talk in renal outer medulla. Hypertension. 2003;42:588–93.
52. Abe M, O'Connor P, Kaldunski M, Liang M, Roman RJ, Cowley AW Jr. Effect of sodium delivery on superoxide and nitric oxide in the medullary thick ascending limb. Am J Physiol Renal Physiol. 2006;291:F350–7.
53. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456–62.
54. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–9.
55. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet. 1997;349(9069):1857–63.
56. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al. Effect of ramipril vs amlodipine on renal outcomes in

hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285(21):2719–28.
57. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135(2):73–87.
58. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. Hypertension. 2005;45(2):198–202.
59. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int. 2004;65(6):2309–20.
60. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;110(8):921–7.
61. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
62. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372(9638):547–53.
63. Mann JF, Schmieder RE, Dyal L, McQueen MJ, Schumacher H, Pogue J, et al. Effect of telmisartan on renal outcomes: a randomized trial. Ann Intern Med. 2009;151(1):1–10.
64. Ito S. Usefulness of RAS inhibition depends on baseline albuminuria. Nat Rev Nephrol. 2010;6(1):10–1.

Hypertension Research (2011) 34, 1106–1110

www.nature.com/hr

ORIGINAL ARTICLE

Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study

Masaaki Nakayama[1,2], Toshinobu Sato[3], Mariko Miyazaki[1], Masato Matsushima[1,4], Hiroshi Sato[1,5], Yoshio Taguma[1,3] and Sadayoshi Ito[1]

To examine the clinical significance of hypertensive nephropathy (HN) among non-diabetic chronic kidney disease (CKD) patients. The study comprised 2692 CKD patients recruited from 11 outpatient nephrology clinics; these included 1306 patients with primary renal disease (PRD), 458 patients with HN, 283 patients with diabetic nephropathy (DN) and 645 patients with other nephropathies (ONs). All patients fulfilled the criteria of CKD, with a persistent low estimated glomerular filtration rate (eGFR) $<60\,ml\,min^{-1}$ per $1.73\,m^2$ or proteinuria as determined by a urine dipstick test. The risk factors for cardiovascular disease (CVD), such as ischemic heart disease, congestive heart failure and stroke; all-cause mortality; and progression to end-stage renal failure (dialysis induction) were analyzed using a Cox proportional hazards model in each group. During a mean follow-up period of 22.6 months from recruitment, 100 patients were lost to follow-up and 192 patients began chronic dialysis therapy. A total of 115 CVD events occurred (stroke in 37 cases), and 44 patients died. Regarding CVD events and death, there were significant differences in the hazard ratios (HRs) for the groups of patients with different underlying renal diseases as determined by both univariate and multivariate analysis adjusted for confounding factors including estimated glomerular filtration rate: PRD, 1.0 (reference); HN, 3.33 (95% confidence interval, 1.82–6.09); DN, 5.93 (2.80–12.52); and ON, 2.22 (1.22–4.05). However, there were no differences in the hazard ratio for dialysis induction for the groups of patients with different underlying renal diseases. HN is associated with an increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.
Hypertension Research (2011) **34**, 1106–1110; doi:10.1038/hr.2011.96; published online 28 July 2011

Keywords: cardiovascular disease; chronic kidney disease; hypertensive nephropathy

INTRODUCTION

Chronic kidney disease (CKD)[1] is a well-known independent risk factor for cardiovascular disease (CVD), including stroke, progression to end-stage renal failure and all-cause mortality in the general population.[2–8]

The relation between excess CVD morbidity and mortality, and decreased kidney function has been well demonstrated in diabetic patients[9,10] in specific sub-populations with preexisting heart disease,[11,12] hypertension[13] and dislipidemia,[14] and in the elderly.[15]

Patients with primary or secondary kidney diseases are exposed to several unique factors that increase the frequency of CVD events. These factors include hyperlipidemia and coagulopathy due to nephritic syndrome, systemic inflammation-associated vasculitides, underlying collagen or infectious disease, and the use of therapeutic agents such as steroids.[16–18] Even though patients with hypertensive nephropathy (HN, nephrosclerosis) are believed to be at high risk for progression to kidney failure,[19] the impact of HN on the frequency of CVD events compared with the impact of other nephropathies (ONs) has not been clearly demonstrated.

Accordingly, in terms of risk stratification of patients, it is crucially important to clarify the clinical outcomes of CKD with respect to the underlying renal diseases, especially for CKD cases that are not the result of diabetes. Only a few reports have examined this issue, including our preliminary report.[20–22]

The present study aimed to address this issue in a cohort of patients from nephrology clinics.

METHODS

Study population (Gonryo CKD cohort)

The Gonryo CKD project is a prospective survey of the patient characteristics and outcomes of individuals who visit outpatient nephrology clinics in the Miyagi Prefecture (Northeast area of Japan), the details of which have been

[1]Tohoku University Graduate School of Medicine, Center for Advanced Integrated Renal Science, Sendai, Japan; [2]Fukushima Medical University School of Medicine, Fukushima, Japan; [3]Sendai Shakaihoken Hospital, Kidney Center, Sendai, Japan; [4]The Jikei University School of Medicine, Department of Clinical Research, Tokyo, Japan and [5]Tohoku University Graduate School of Pharmacology, Department of Clinical Pharmacology, Sendai, Japan
Correspondence: Dr M Nakayama, Tohoku University Graduate School of Medicine, Center for Advanced Integrated Renal Science, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
E-mail: mnakayama@med.tohoku.ac.jp
Received 21 January 2011; revised 23 March 2011; accepted 11 April 2011; published online 28 July 2011

reported elsewhere.[22] Eleven affiliated hospitals with Tohoku University, including one university hospital (Tohoku University Hospital), are participating in the project. Patient registration was originally requested for all patients who provided informed consent for participation in the project. The study protocol was approved by the institutional review board of the Tohoku University School of Medicine and by the respective participating hospitals.

Registration was conducted from May 2006 to November 2008, and 4015 patients were registered. Among the original registered patients, certain subjects were excluded from the present analysis—150 cases lacking data on serum creatinine levels and 241 cases with unknown underlying renal diseases. Among patients with essential hypertension and estimated glomerular filtration rates (eGFRs) above 60 ml min^{-1} per 1.73 m^2, those who did not have positive proteinuria findings at registration (n=836) and those lacking urinary testing results (n=96) were excluded. As a result, 2692 patients with complete CKD criteria were selected[1] and were subjected to analysis.

Patient classification and primary outcomes

Patients were classified according to one of four underlying renal diseases diagnosed by the attending physicians at the participating hospitals (Table 1): primary renal disease (PRD), defined by primary glomerulonephritis and tubulointerstitial nephritis, including biopsy-proven cases (81%); HN, defined by a history of hypertension and the absence of other possible disorders, including cases of biopsy-proven nephrosclerosis (20.8%); diabetic nephropathy, defined by a history of diabetes accompanying nephropathy and the absence of other possible renal disorders or presenting with nephropathy with diabetic retinopathy and the absence of other possible renal disorders, including biopsy-proven diabetic nephropathy (24.9%); and ONs, defined by ONs not included in the other three groups, including biopsy-proven cases (24.9%). The HN cases included in the present classification were in those patients who had an eGFR below 60 ml min^{-1} per 1.73 m^2 or positive proteinuria as determined by a dipstick test.

The primary outcomes of this survey included CVD events, such as angina pectoris, acute myocardial infarction, congestive heart failure, stroke (cerebral bleeding and infarction), and all-cause death before commencement of chronic dialysis therapy. Outcomes within 12 months after registration were surveyed using the medical records of the hospitals, death certificates and interviews with attending physicians at the time of annual checkups. An episode of CVD was defined as disease of the circulatory system (International Classification of Disease, 10th revision: I00 to I99), and the number of patients with angina pectoris or acute myocardial infarction included those who had received coronary stenting, angioplasty or bypass surgery, or who had a definite clinical course of acute myocardial infarction. In patients with congestive heart failure, only those who were admitted for treatment were counted. Diagnosis of stroke and stroke subtypes was based on the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke,[23] and only cases confirmed by computed tomography or magnetic resonance imaging of the brain were counted.

Table 1 Patient characteristics

	All	*PRD*	*ONs*	*HN*	*DN*
n	2.694	1.306	643	462	283
Age (years)	60.0 ± 16.2	55.7 ± 16.6	58.6 ± 15.7	70.3 ± 11.4	66.5 ± 12.6
Gender (male)	1441 (53.5%)	716 (54.8%)	275 (42.8%)	262 (56.7%)	188 (66.4%)
BMI	23.5 ± 3.8	23.4 ± 3.8	22.9 ± 3.7	24.2 ± 3.8	24.1 ± 3.8
Blood pressure (mmHg)					
Systolic	130.95 ± 16.2	129.21 ± 15.1	129.33 ± 15.8	134.68 ± 17.4	136.64 ± 17.5
Diastolic	76.7 ± 10.9	77.3 ± 10.4	76.7 ± 10.7	76.4 ± 11.8	74.0 ± 11.6
CKD stage (%)					
Stage 1+2	40.3	49.1	47.4	17.7	20.4
Stage 3	37.6	35.7	31.1	57.6	28.3
Stage 4	13.4	10.3	14.5	15.8	21.6
Stage 5	8.7	4.9	7.0	8.9	29.7
Comorbidities (%)					
Cardiac disease	12.8	7.5	12.3	21.2	24.7
Stroke	6.5	3.5	5.9	11.9	12.7
Diabetes	27.4	15.5	18.0	34.2	100.0
Hypertension	77.1	72.8	70.6	93.7	89.4
Hyperlipidemia	42.6	44.6	36.8	42.2	51.6
Pharmacotherapy (%)					
ARB/ACEI	62.7	62.1	52.6	70.1	76.3
Statin	34.7	36.1	30.0	32.3	43.1
ESA	6.5	3.6	4.8	7.8	21.9
Steroid	25.3	32.9	36.2	2.8	2.1
Proteinuria (%)	49.6	47.3	41.2	49.8	78.9
Hemoglobin (g dl^{-1})	12.8 ± 2.1	13.2 ± 1.9	12.6 ± 2.0	12.7 ± 2.1	11.6 ± 2.3
Total cholesterol (mg dl^{-1})	197.6 ± 38.7	198.7 ± 35.9	203.5 ± 41.3	190.99 ± 39.9	190.4 ± 41.4
Smoker (%)	16.2	15.8	14.6	16.2	21.6
Renal biopsy proven (%)	62.7	81.0	53.5	20.8	24.9
					mean ± s.d.

Abbreviations: ARB/ACEI, angiotensin receptor blocker/angiotensin-converting enzyme inhibitor; BMI, body mass index; DN, diabetic nephropathy; ESA, erythropoiesis stimulating agent; HN, hypertensive nephropathy; ONs, other nephropathies; PRD, primary renal disease.

Data collection

Serum creatinine levels were measured using the enzyme assay method. Kidney function was determined using the formula for eGFR for Japanese individuals.[24] Positive results for urinary protein were identified using the dipstick test for spot urine or an autoanalyzer. Patients were considered to be positive for macroalbuminuria when the dipstick result was positive or greater, corresponding to a urinary protein level $>30\,mg\,dl^{-1}$.[25] Blood pressure was measured at local medical centers in outpatient clinics using an automatic sphygmomanometer based on the Korotkoff sound technique with the subject in a seated position. Information on medications at baseline and each patient's history of CVD, diabetes mellitus, hypertension and hyperuricemia were obtained from the medical records or from the results of blood examinations at registration. Subjects receiving lipid-lowering drugs or displaying serum cholesterol levels $>220\,mg\,dl^{-1}$ were considered to have hypercholesterolemia. Subjects with fasting glucose levels $>126\,mg\,dl^{-1}$ or non-fasting glucose levels $>200\,mg\,dl^{-1}$ or who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Data analysis

Associations between primary outcomes and either baseline kidney function or underlying renal disease were examined using Cox proportional hazard model analysis adjusted for confounding factors.

Data are shown as means ± s.d. A *P*-value <0.05 indicated statistical significance. All statistical analyses were conducted using STATA version 10.0 software (StataCorp LP, College Station, TX, USA).

RESULTS

During an observation period of 22.6 ± 11.9 months, 100 patients were lost because of a switch to other medical services or to the patient quitting due to social reasons, and the follow-up of 192 patients was ended because of the initiation of maintenance dialysis therapy. There were 115 cases of CVD events (37 cases of stroke) and 44 cases of all-cause death (Table 2).

Table 2 Number of events

CKD stage	*CVD*	*Stroke*	*Death*	*ESRD*
Primary renal disease				
CKD1+2	2	1	1	—
CKD3	7	2	6	2
CKD4	2	1	2	8
CKD5	—	—	1	40
Hypertensive nephropathy				
CKD1+2	4	—	1	1
CKD3	12	8	6	—
CKD4	7	4	3	6
CKD5	3	2	3	24
Diabetic nephropathy				
CKD1+2	4	3	—	1
CKD3	7	1	3	1
CKD4	8	—	5	18
CKD5	10	3	4	54
Other nephropathies				
CKD1+2	2	7	2	—
CKD3	3	4	3	3
CKD4	6	1	4	9
CKD5	1	—	—	25

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease (dialysis induction).

In terms of CVD events and all-cause mortality, significant increases in hazard ratios were seen with increasing CKD stage using univariate analysis (Figure 1); however, these trends disappeared after multivariate adjustment (Table 3a). Significant differences in hazard ratios were seen with respect to underlying renal diseases using univariate analysis, and these differences were significant even after adjusting for confounding factors including eGFR (Table 3b).

Dialysis was started only for those patients who had a CKD stage 4 to 5 at the time of entry (Figure 2; CKD1+2: 0.2%, CKD3: 0.6%,

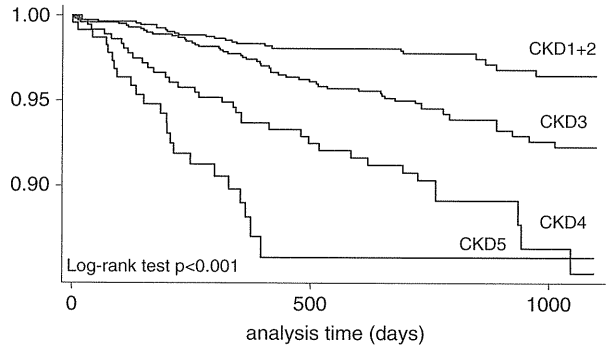


Figure 1 Event-free survival for cardiac disease, apoplexy and all cause of death for patients at different chronic kidney disease (CKD) stages.

Table 3a Risk for endpoints of CVD, stroke and death by CKD stage in all patients

				Univariate analysis		*Multivariate analysis*[a]	
CKD stage	*CVD*	*Stroke*	*Death*	*HR*	*95% CI*	*HR*	*95% CI*
CKD 1+2	12	11	4	1.00		1.00	
CKD 3	29	15	18	2.21	1.37–3.55	1.06	0.64–1.77
CKD 4	23	6	14	4.39	2.62–7.36	1.76	1.00–3.12
CKD 5	14	5	8	7.47	4.22–13.24	2.29	1.17–4.49

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease (such as angina pectoris, acute myocardial infarction and congestive heart failure); HR, hazard ratio.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors.

Table 3b Risk for endpoints of CVD, stroke and death by underlying renal diseases in all patients

Underlying				*Univariate analysis*		*Multivariate analysis*[a]	
renal disease	*CVD*	*Stroke*	*Death*	*HR*	*95% CI*	*HR*	*95% CI*
PRD	11	4	10	1.00		1.00	
ONs	12	12	9	3.17	1.78–5.62	2.22	1.22–4.05
HN	26	14	13	7.12	4.18–12.14	3.33	1.82–6.09
DN	29	7	12	10.88	6.29–18.84	5.93	2.80–12.52

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DN, diabetic nephropathy; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

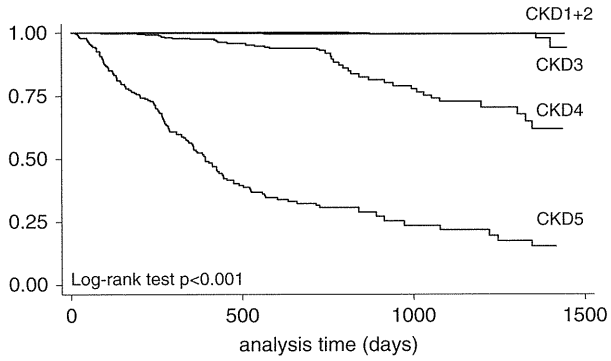


Figure 2 Event-free survival for progression to end-stage renal disease (dialysis induction) for patients at different chronic kidney disease (CKD) stages.

Table 4 Risk of progression to ESRD (dialysis induction) by underlying renal disease

Underlying		*Univariate analysis*		*Multivariate analysis*[a]	
Renal disease	*ESRD*	*HR*	*95% CI*	*HR*	*95% CI*
PRD	50	1.00		1.00	
ONs	37	1.43	0.94–2.19	1.11	0.70–1.76
HN	31	1.09	0.70–1.71	1.13	0.69–1.88
DN	74	5.25	3.66–7.53	1.25	0.68–2.28

Abbreviations: CI, confidence interval; DN, diabetic nephropathy; ESRD, end-stage renal disease; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

CKD4: 11.4%, CKD5: 61.1%), and no significant differences were observed with respect to underlying renal diseases after adjusting for confounding factors, including eGFR (Table 4).

DISCUSSION

This study aimed to clarify the impact of underlying renal diseases on CVD events and death before the initiation of dialysis treatment by analyzing the outcomes of 2692 CKD outpatients from 11 nephrology clinics. After 22.6 months of follow-up, there was a significant difference in the frequencies of CVD events and mortality among groups of patients with different underlying renal diseases, even after adjusting for possible confounding factors including kidney function. These findings showed that patients with HN represent a high-risk group, except for diabetic nephropathy patients, followed by ONs and PRD. In contrast, in terms of chronic dialysis induction, no significant differences were observed based on underlying renal diseases.

Both traditional and non-traditional mechanisms underlie the increased risk of CVD among CKD patients. Traditional factors include hypertension, diabetes, hyperlipidemia and smoking, whereas non-traditional factors include specific factors related to the uremic milieu, such as fluid overload, calcium/phosphate abnormalities, anemia, malnutrition, enhanced inflammation and oxidative stress, and the accumulation of uremic toxins.[26–34] Therefore, subjects with vasculopathy demonstrated by traditional factors are thought to undergo accelerated vascular damage along with progression of the CKD stage. Hypertension is a predominant risk factor for CVD in the general population, and it is logical that long-standing exposure to pathological conditions such as hypertension may have resulted in an increased frequency of CVD and mortality among non-diabetic subjects with HN. Several factors could have contributed to the better CVD outcomes in the group with PRD. First, half of the patients with PRD had immunoglobulin A nephropathy; glucocorticoid therapy does not increase the risk of CVD for these patients.[34] Blood pressure was also more adequately controlled in these patients than in patients in the other groups (Table 1). In addition, prevalent vasculopathy was not predominant in pre-dialysis PRD patients, as has been indicated for pediatric patients.[35,36] These results indicate that CKD staging cannot be applied on its own to predict which subjects are at high risk of CVD without taking into account the type of underlying renal disease. These results also suggest that individuals with HN should be the primary targets of CVD prevention measures among non-diabetic CKD patients.

In contrast, the present study revealed that the differences among underlying renal diseases did not have any influence on the frequency of the induction of dialysis after adjusting for confounding factors, including eGFR. In addition, dialysis induction was limited to subjects with CKD5. This result may confirm the clinical notion that CKD5 is the primary criterion for dialysis induction, as recommended in published guidelines.[37–39]

In the present study, several clinical issues that might have biased the analytical results must be considered. First, because all of the included patients were recruited from nephrology clinics, our patient selection may have introduced a bias toward relatively better medical compliance among those patients with modifiable factors, including the uremic milieu and blood pressure. Second, among patients with hypertension or diabetes, patients who had presented with proteinuria before entry into the study and who had responded to medical treatment thereafter were excluded from the study unless their eGFR was $<60\,ml\,min^{-1}$ per $1.73\,m^2$. Thus, the patients with diabetes or HN included in the present study may have been relatively resistant to conventional therapies. This resistance may have made their outcomes relatively worse, even though we adjusted for positive findings for proteinuria. Finally, data on microalbuminuria were not available in the present study. Because the clinical significance of microalbuminuria has been well demonstrated, further study is needed to determine the effect of microalbuminuria in these patients.

In conclusion, the present study demonstrated that patients with HN are at increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by a grant from Astellas Pharm, Inc. The authors express special thanks to Mrs. Makiko Nakayama and Jun Sakaino for their assistance with the study.

Study contributors: Yuji Yamaguchi (Japanese Red Cross Sendai Hospital), Katsuya Obara (Tohoku Kosai Hospital), Isao Kurihara (Tohoku Kosai Miyagino Hospital), Yasumichi Kinoshita and Kazuto Sato (Japanese Red Cross Ishinomaki Hospital), Jin Seino (Miyagi National Hospital), Akira Sugiura and Masahiro Miyata (Osaki Citizen Hospital), Kazuhisa Takeuchi (Koujinkai Central Hemodialysis Clinic), Kenji Nakayama and Naoki Akiu (Sendai City Hospital), Tetsuya Otaka (Katta General Hospital), Osamu Hotta, Hiroo Noshiro, Kazuyuki Suzuki, Mitsuhiro Sato, Norio Ieiri, Yoshinori Tsuchiya, Kozo Sato, Tomoyoshi Kimura, and Aki Ishida (Sendai Shakaihoken Hospital), and Tasuku Nagasawa, Noriko Miyazawa, and Takuma Hosoya (Tohoku University School of Medicine).

1 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney disease outcome quality initiative. *Am J Kidney Dis* 2002; **39**(2 Suppl 2): S1–S246.
2 Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003; **41**: 47–55.
3 Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; **164**: 659–663.
4 GO AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and the hospitalization. *New Engl J Med* 2004; **351**: 1296–1305.
5 Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M. Choronic kidney disease and cardiovascular disease in a general Japanese population: the hisayama study. *Kidney Int* 2005; **68**: 228–236.
6 Irie F, Sairenchi T, Fukasawa N, Yamagishi K, Ikehara S, Kanashiki M, Saito Y, Ota H, Nose T. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. *Kidney Int* 2006; **69**: 1264–1271.
7 Nakayama M, Metoki H, Terawaki H, Ohkubo T, Kikuya M, Sato T, Nakayama K, Asayama K, Inoue R, Hashimoto J, Totsune K, Hoshi H, Ito S, Imai Y. Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population-the Ohasama study. *Nephrol Dial Transplant* 2007; **22**: 1910–1915.
8 Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003; **63**: 1468–1474.
9 So WY, Kong AP, Ma RC, Ozaki R, Szeto CC, Chan NN, Ng V, Ho CS, Lam CW, Chow CC, Cockram CS, Chan JC, Tong PC. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. *Diabetes Care* 2006; **29**: 2046–2052.
10 Islam TM, Fox CS, Mann D, Muntner P. Age-related associations of hypertension and diabetes mellitus with chronic kidney disease. *BMC Nephrol* 2009; **10**: 17.
11 Wattanakit K, Coresh J, Muntner P, Marsh J, Folsom AR. Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction. *J Am Coll Cardiol* 2006; **48**: 1183–1189. Epub 2006 Aug 28.
12 Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007; **99**: 393–398.
13 Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, Higashiyama A, Kamide K, Kawanishi K, Okayama A, Kawano Y. Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita Study. *Stroke* 2009; **40**: 2674–2679.
14 Tsimihodimos V, Dounousi E, Siamopoulos KC. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. *Am J Nephrol* 2008; **28**: 958–973.
15 Roderick PJ, Atkins RJ, Smeeth L, Mylne A, Nitsch DD, Hubbard RB, Bulpitt CJ, Fletcher AE. CKD and mortality risk in older people: a community-based population study in the United Kingdom. *Am J Kidney Dis* 2009; **53**: 950–960.
16 Deegens JK, Wetzels JF. Membranous nephropathy in the older adult: epidemiology, diagnosis and management. *Drugs Aging* 2007; **24**: 717–732.
17 Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. *J Am Soc Nephrol* 2007; **18**: 2221–2225.
18 Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, Crow MK, Schwartz JE, Paget SA, Devereux RB, Salmon JE. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; **349**: 2399–2406.
19 Perneger TV, Klag MJ, Feldman HI, Whelton PK. Projections of hypertension-related renal disease in middle-aged residents of the United States. *JAMA* 1993; **269**: 1272–1277.
20 Lechner BL, Bockenhauer D, Iragorri S, Kennedy TL, Siegel NJ. The risk of cardiovascular disease in adults who have had childhood nephrotic syndrome. *Pediatr Nephrol* 2004; **19**: 744–748.
21 Morgan MD, Turnbull J, Selamet U, Kaur-Hayer M, Nightingale P, Ferro CJ, Savage CO, Harper L. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. *Arthritis Rheum* 2009; **60**: 3493–3500.
22 Nakayama M, Sato T, Sato H, Yamaguchi Y, Obara K, Kurihara I, Sato K, Hotta O, Seino J, Miyata M, Takeuchi K, Nakayama K, Matsushima M, Otaka T, Kinoshita Y, Taguma Y, Ito S. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study. *Clin Exp Nephrol* 2010; **14**: 333–339.
23 National Institute of Neurological Disorders and Stroke *Ad Hoc* Committee. Classification of cerebrovascular disease. *Stroke* 1990; **21**: 637–676.
24 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, Collaborators Developing the Japanese Equation for Estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
25 Takahashi M, Fukuda Y, Iwata S. Fundamental evaluation and efficacy for protein to creatinine ratio by ATLAS kit cartridge PRO12 using automatic urine analyzer Clinitek ATLAS XL. *Igaku Yakugaku* 2002; **48**: 727–735. (in Japanese).
26 Yamamoto S, Kon V. Mechanisms for increased cardiovascular disease in chronic kidney dysfunction. *Curr Opin Nephrol Hypertens* 2009; **18**: 181–188.
27 Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 520–528; e-pub ahead of print 22 December 2004.
28 Honda H, Qureshi AR, Heimbürger O, Barany P, Wang K, Pecoits-Filho R, Stenvinkel P, Lindholm B. Serum albumin, C-reactive protein, interleukin 6, and fetuin a as predictors of malnutrition, cardiovascular disease, and mortality in patients with ESRD. *Am J Kidney Dis* 2006; **47**: 139–148.
29 Chan DT, Irish AB, Dogra GK, Watts GF. Dyslipidaemia and cardiorenal disease: mechanisms, therapeutic opportunities and clinical trials. *Atherosclerosis* 2008; **196**: 823–834. e-pub ahead of print 6 March 2007.
30 Kazory A, Ross EA. Anemia: the point of convergence or divergence for kidney disease and heart failure? *J Am Coll Cardiol* 2009; **53**: 639–647.
31 Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 2002; **62**: 1524–1538.
32 Vaziri ND, Rodriguez-Iturbe B. Mechanisms of disease: oxidative stress and inflammation in the pathogenesis of hypertension. *Nat Clin Pract* 2006; **2**: 582–593.
33 Ravani P, Tripepi G, Malberti F, Testa S, Mallamaci F, Zoccali C. Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach. *J Am Soc Nephrol* 2005; **16**: 2449–2455; e-pub ahead of print 8 June 2005.
34 Barreto FC, Barreto DV, Liabeuf S, Meert N, Glorieux G, Temmar M, Choukroun G, Vanholder R, European Uremic Toxin Work Group (EUTox). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2009; **4**: 1551–1558.
35 Cheng J, Zhang X, Zhang W, He Q, Tao X, Chen J. Efficacy and safety of glucocorticoids therapy for IgA nephropathy: a meta-analysis of randomized controlled trials. *Am J Nephrol* 2009; **30**: 315–322.
36 Wilson AC, Mitsnefes MM. Cardiovascular disease in CKD in children: update on risk factors, risk assessment, and management. *Am J Kidney Dis* 2009; **54**: 345–360.
37 Lilien MR, Groothoff JW. Cardiovascular disease in children with CKD or ESRD. *Nat Rev Nephrol* 2009; **5**: 229–235.
38 Peritoneal Dialysis Adequacy Work Group. Clinical practice guidelines and clinical recommendations 2006 update Clinical practice guidelines for peritoneal dialysis adequacy. *Am J Kidney Dis* 2006; **48**(Suppl 1): S98–S129.
39 Dombros N, Dratwa M, Feriani M, Gokal R, Heimbürger O, Krediet R, Plum J, Rodrigues A, Selgas R, Struijk D, Verger C, EBPG Expert Group on Peritoneal Dialysis. European best practice guidelines for peritoneal dialysis 2. The initiation of dialysis. *Nephrol Dial Transplant* 2005; **20**(Suppl 9): ix3–ix7.

Microinflammationの関与

Microinflammation in diabetic microvascular complications

梶谷展生[1]　四方賢一[2]

Key words：細胞接着分子，ケモカイン，サイトカイン，VEGF，マクロファージ

はじめに

糖尿病性腎症の腎組織では，マクロファージを主体とする炎症細胞浸潤，細胞接着分子やケモカインの発現および炎症性サイトカインの増加など，炎症と共通した特徴が認められる．また，糖尿病網膜症の網膜組織においても白血球の集積や細胞接着分子の発現増加などが認められ，糖尿病性細小血管症の病態に炎症が関与していることが示唆される．

糖尿病性細小血管症の病態形成における‘炎症’とは，関節リウマチなどの炎症性疾患にみられる‘発熱，発赤，腫脹，疼痛，機能障害’を主徴とする従来の炎症の概念とは異なっている．すなわち高感度測定系で検出されるCRP(高感度CRP)の軽度の上昇などに特徴づけられる，血管を首座とする軽度の炎症を意味しており，‘microinflammation’や‘low grade inflammation’などと呼ばれている．慢性高血糖状態では，ポリオール代謝異常，プロテインキナーゼC(PKC)活性化，糖化反応(グリケーション)や酸化ストレスの亢進，レニン・アンジオテンシン系の活性化などが認められ，これらの因子が複合的に関与して炎症を惹起し糖尿病性細小血管症の病態に関与するものと考えられている．

本稿では，糖尿病性細小血管症におけるmicroinflammationの役割について概説する．

1. 網膜症におけるmicroinflammation

糖尿病網膜症は，網膜血管障害が機転となり血管透過性の亢進や毛細血管閉塞から網膜の虚血が惹起され，脆弱な網膜新生血管の形成を経て増殖網膜症へ至る．

糖尿病網膜症を有する患者は網膜症を有さない患者に比べて血清中のCRPやICAM-1が有意に高値であると報告されている[1]．また糖尿病モデルラットの網膜では血管内皮細胞におけるICAM-1発現が増加し，網膜血管に多くの白血球が接着している[2]．ICAM-1およびその白血球側のリガンドであるCD18を欠損したマウスでは糖尿病状態における網膜血管の白血球増加，血管透過性の亢進や網膜血管の変性が抑制されたとの報告もあり，これらは糖尿病網膜症の発症進展におけるmicroinflammationの関与を示唆するものと考えられる．

網膜におけるmicroinflammationを惹起するkey moleculeの一つとしてvascular endothelial growth factor(VEGF)が考えられている．VEGFは網膜の内皮細胞，色素上皮細胞，ミュラー細胞や周皮細胞など種々の細胞に発現が認められ，主として虚血により誘導される．糖尿病においては虚血所見が明らかになる前からVEGFの発現亢進が認められるが，その誘引として高血糖やそれに引き続くPKC経路の活性化，糖化反

[1]Nobuo Kajitani: Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science　岡山大学大学院医歯薬学総合研究科 腎・免疫・内分泌代謝内科学　[2]Kenichi Shikata: Center for Innovative Clinical Medicine, Okayama University Hospital　岡山大学病院 新医療研究開発センター

0047-1852/10/¥40/頁/JCOPY

応（グリケーション）や酸化ストレスの亢進，レニン・アンジオテンシン系の活性化などが考えられている．VEGFは血管内皮細胞増殖作用と血管透過性亢進作用の両者を併せもつ唯一の増殖因子であることから，増殖網膜症や糖尿病黄斑浮腫の病態と深く関係していると考えられている．

2. 腎症におけるmicroinflammation

糖尿病性腎症患者の腎生検組織では糸球体や間質におけるマクロファージの数が増加しており，炎症性サイトカインの放出などを介して糸球体硬化や間質の線維化に関与していることが示唆される[3]．一般に，炎症巣への白血球の浸潤は細胞接着分子とケモカインにより誘導される．糖尿病性腎症患者の腎組織では糸球体や間質の小静脈にICAM-1とE-セレクチン，P-セレクチンの発現が亢進しており[3]，これらの接着分子が糸球体と間質へのマクロファージの浸潤を誘導していると考えられる．内皮細胞に発現する接着分子の多くは，細胞膜から外れて血液中に放出される性質をもっている（shedding）．炎症性疾患では，血管内皮細胞における発現亢進の結果としてICAM-1やVCAM-1の血液中濃度が上昇することが知られているが，糖尿病患者においても血中可溶性ICAM-1およびVCAM-1濃度が増加しており，腎症を有する患者では更に高値となる[4,5]．

ストレプトゾトシンで糖尿病を誘発したラットの腎臓では糖尿病誘発後に1週間以内にICAM-1の発現とマクロファージの浸潤の増加を認め，インスリン投与による血糖正常化によりICAM-1の発現とマクロファージの浸潤が抑制される．また抗ICAM-1抗体を投与することにより腎糸球体へのマクロファージの浸潤が抑制されることから，高血糖によるICAM-1の発現増加がマクロファージの浸潤を誘導していると考えられた[6]．

糖尿病性腎症の成因におけるマクロファージの関与を直接的に証明した研究は少ない．しかし，放射線照射で白血球を減少させたラットでは糖尿病発症後の腎症の進展が抑制されること[7]，免疫抑制薬でマクロファージの浸潤を減少させることにより腎症を抑制できる[8]などの報告があり，糖尿病性腎症の発症進展にマクロファージが重要な役割を果たしていることが強く示唆された．

著者らは糖尿病性腎症の成因におけるマクロファージの役割を明らかにするために，ICAM-1ノックアウト（KO）マウスにストレプトゾトシンで糖尿病を誘発し，6カ月後の腎症の変化を検討した．ICAM-1 KOマウスではアルブミン尿の増加の抑制，糸球体肥大やメサンギウム基質の増加，間質の線維化の抑制が認められ，腎臓におけるTGF-βとIV型コラーゲンの発現も低下していた[9]．著者らは1型糖尿病モデルを用いて上記の検討を行ったが，その後Chowらにより2型糖尿病モデルであるdb/dbマウスにおいてもICAM-1欠損により腎障害の進展が著しく抑制されることが明らかとなり[10]，2型糖尿病モデルにおいても著者らの結果が裏付けられた．

糖尿病性腎症の成因に関しては，これまでに多くのメカニズムが明らかにされてきた．上述してきたように，著者らは糖尿病性腎症の進展因子としてマクロファージを中心としたmicroinflammationが重要な役割を果たしていることを明らかにしてきた．糖尿病性腎症の成因におけるmicroinflammationの関与について，著者らは**図1**に示すような機序を考えている[11]．腎症の成因の最上流に位置するものは高血糖であるが，高血糖から腎組織障害に至る過程には様々な経路が想定されている．これらの因子が複合的に関与して血管内皮細胞機能障害を惹起し，ICAM-1をはじめとする接着分子やケモカインの発現が誘導すると考えられる．腎組織に浸潤したマクロファージはTGF-βなどのサイトカインを介してIV型コラーゲンなどの細胞外基質の産生を亢進させ，糖尿病性腎症の病変を形成するものと考えられる．

近年，糖尿病性腎症の重要な臨床的特徴であるアルブミン尿が心血管死と関連していることが報告され[12]，アルブミン尿は全身の血管内皮障害の指標となりうることが示された．著者ら

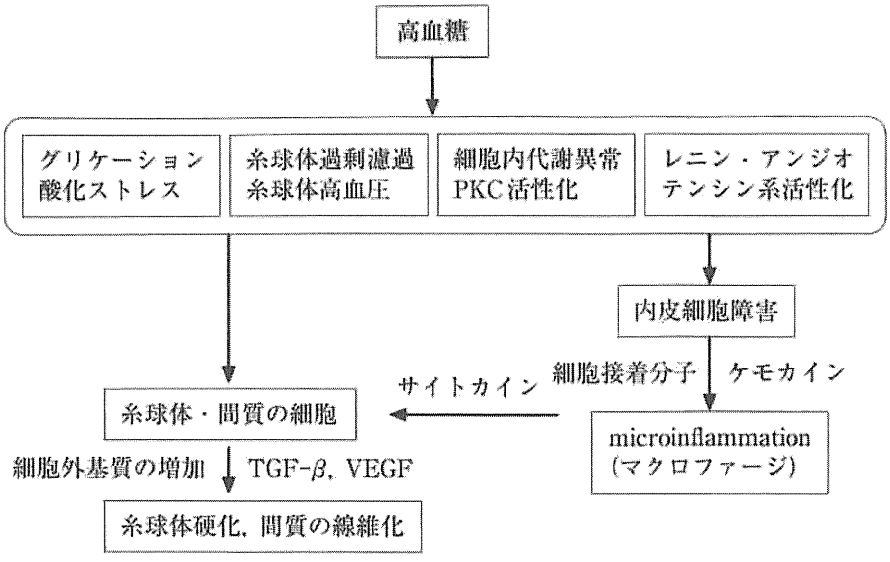


図1 糖尿病性腎症の成因における microinflammation の関与
(文献[11]より改変)

は2型糖尿病患者において炎症性サイトカインである IL-18 の血清濃度がアルブミン尿および動脈硬化の指標である脈波伝播速度(PWV)と相関し，更に血中および尿中の IL-18 濃度が腎症の進展予測因子となりうることを見いだした[13]．また，腎症を有する2型糖尿病患者において種々の血清中炎症性サイトカイン，ケモカイン，細胞接着分子濃度がアルブミン尿や，PWV・頸動脈内膜中膜複合体厚(IMT)と相関することを報告した[14]．microinflammation は細小血管障害のみならず大血管障害の成因とも関連していることが示唆される．

3. 糖尿病性神経障害における microinflammation

糖尿病性神経障害における microinflammation の関与については網膜症や腎症ほどの報告はないものの，末梢神経の虚血・再灌流障害に伴う microinflammation の関与が報告されている．

高血糖に伴う血管内皮機能障害により神経栄養血管の循環障害が生じると，好中球・単球の浸潤を伴い急性炎症反応が生じる．糖尿病状態では神経細胞は虚血・再灌流による形態学的な脆弱性を認めており，正常神経では形態学的な変化を呈さない程度の虚血によっても病理学的な異常を呈することが報告されている[15]．その原因として，糖尿病状態では慢性高血糖に伴うポリオール代謝異常，グリケーション，PKC 経路の活性化などにより神経細胞は既に酸化ストレスにさらされており，そこに虚血・再灌流による更なる酸化ストレスが加わることで炎症の増悪をきたすものと考えられている．

おわりに

糖尿病性細小血管症における microinflammation の役割について概説した．microinflammation は糖尿病性細小血管症の発症・進展に関与しており，microinflammation の制御は細小血管障害の治療ターゲットとなる可能性がある．糖尿病性腎症においては，免疫抑制薬であるメトトレキサートやミゾリビン，抗炎症作用を有するマクロライド系抗生物質(エリスロマイシン)などは，糖尿病ラットの腎臓における microinflammation を抑制することによって腎障害の進展を抑制することが報告されている．血管における炎症を制御する治療は，糖尿病性細小血管症に対する新しい治療戦略となることが期待される．

■文　献

1) van Hecke MV, et al: Inflammation and endothelial dysfunction are associated with retinopathy: the Hoorn Study. Diabetologia **48**: 1300-1306, 2005.
2) Miyahara S, et al: Simvastatin inhibits leukocyte accumulation and vascular permeability in the retinas of rats with streptozotocin-induced diabetes. Am J Pathol **164**: 1697-1706, 2004.
3) Hirata K, et al: Increased expression of selectins in kidneys of patients with diabetic nephropathy. Diabetologia **41**: 185-192, 1998.
4) Güler S, et al: Plasma soluble intercellular adhesion molecule 1 levels are increased in type 2 diabetic patients with nephropathy. Horm Res **58**: 67-70, 2002.
5) Clausen P, et al: Plasma concentrations of VCAM-1 and ICAM-1 are elevated in patients with type 1 diabetes mellitus with microalbuminuria and overt nephropathy. Diabet Med **17**: 644-649, 2000.
6) Sugimoto H, et al: Increased expression of intercellular adhesion molecule-1(ICAM-1) in diabetic rat glomeruli: glomerular hyperfiltration is a potential mechanism of ICAM-1 upregulation. Diabetes **46**: 2075-2081, 1997.
7) Sassy-Prigent C, et al: Early glomerular macrophage recruitment in streptozotocin-induced diabetic rats. Diabetes **49**: 466-475, 2000.
8) Utimura R, et al: Mycophenolate mofetil prevents the development of glomerular injury in experimental diabetes. Kidney Int **63**: 209-216, 2003.
9) Okada S, et al: Intercellular adhesion molecule-1-deficient mice are resistant against renal injury after induction of diabetes. Diabetes **52**: 2586-2593, 2003.
10) Chow FY, et al: Intercellular adhesion molecule-1 deficiency is protective against nephropathy in type 2 diabetic db/db mice. J Am Soc Nephrol **16**: 1711-1722, 2005.
11) 羽田勝計，槇野博史(編)：糖尿病性腎症．基礎と臨床の最前線，p48，中外医学社，2007.
12) Hillege HL, et al: Prevention of Renal and Vascular End Stage Disease(PREVEND) Study Group: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation **106**: 1777-1782, 2002.
13) Nakamura A, et al: Serum interleukin-18 levels are associated with nephropathy and atherosclerosis in Japanese patients with type 2 diabetes. Diabetes Care **28**: 2890-2895, 2005.
14) Kajitani N, et al: Microinflammation is a common risk factor for progression of nephropathy and atherosclerosis in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract **88**: 171-176, 2010.
15) Nukada H: Mild ischemia causes severe pathological changes in experimental diabetic nerve. Muscle Nerve **15**: 1116-1122, 1992.

Evidence for remission of diabetic nephropathy

腎症の寛解は可能か？：最近のエビデンスより

廣田　大昌・四方　賢一

Key Words：①糖尿病性腎症　②寛解　③集約的治療　④DNETT-Japan

□はじめに

糖尿病性腎症の自然経過では，微量アルブミン尿から顕性蛋白尿へと進展し，腎機能の低下を経て血液透析療法へと至る．この経過は慢性に進行し，治療により可逆性となるか否かについての十分なエビデンスは得られていなかったため，これまでの治療目的は主に腎症の発症・進展の抑制であった．しかし，最近になって，早期腎症は寛解(remission)あるいは退縮(regression)するということが明らかとなってきた．その結果，これまでの進展抑制を目的とする治療戦略から，寛解や退縮を目的とした治療戦略への転換・対策が求められている．

糖尿病性腎症の進展抑制から寛解への転換

糖尿病性腎症の進展抑制を証明した臨床研究としては，1型糖尿病では1993年のDCCT(Diabetes Control and Complications Trial)[1]，2型糖尿病では1995年のKumamoto Study[2]，1998年のUKPDS(United Kingdom Prospective Diabetes Study)[3]が有名であり，これらのエビデンスのもと，糖尿病性腎症進展抑制の治療が行われていた．

アルブミン尿を伴う1型糖尿病患者に膵移植を行った後，5年ごとに腎生検を行った1998年のFiorettoらの報告によると，血糖値が正常化した5年後には明らかな改善を認めないものの，10年後には腎組織の改善とアルブミン尿の減少を認めている[4]．その後，1型糖尿病における早期腎症(アルブミン尿期の腎症)が，血圧，血糖および脂質の管理によって高率にアルブミン尿が陰性化するという報告が，2001年および2003年にそれぞれHovind[5]とPerkins[6]から報告された．

2005年には，Arakiらが216例のアルブミン尿を伴う日本人2型糖尿病患者を6年間追跡し，その51%が正常アルブミン尿へ移行したと報告している[7]．このなかで，アルブミン尿の陰性化に寄与する独立した因子として，アルブミン尿が出現してからの期間が短いこと，HbA1c(JDS)<6.95%，アンジオテンシン変換酵素(ACE)阻害薬またはアンジオテンシン受容体拮抗薬(ARB)を使用していること，収縮期血圧<129 mmHgが挙げられている．さらに，糖尿病治療ガイドラインで推奨される治療目標である血糖〔HbA1c(JDS)6.5%未満〕，血圧(130/80 mmHg未満)，脂質(総コレステロール200 mg/dL未満，中性脂肪150 mg/dL未満，HDLコレステロール40 mg/dL以上)の3項目のうち，1つでも達成でき

ていた場合には，1つも到達できていない場合に比べて寛解が得られやすく，3つすべて達成できた場合には約6倍も寛解が得られていたと報告されている．

一方，2002年，赤井らによってネフローゼ症候群が寛解した糖尿病性腎症の2症例が報告されている[8]．この症例では，インスリン治療による良好な血糖コントロール，およびACE阻害薬を中心とした多剤による血圧コントロールにて尿蛋白が消失している．

このように2000年前後から2005年にかけて，血糖，血圧，脂質の管理を厳格に行うことで，アルブミン尿期の早期腎症のみならず，ネフローゼ症候群を呈しているような顕性腎症期であっても寛解が報告されるようになった．

寛解が報告されて以後の経過

Arakiらは216例の検討をさらに2年間延長した報告のなかで，微量アルブミン尿の減少が腎・心血管イベントに与える影響を検討している[9]．このなかで，非寛解群と比較して，寛解群では，血液浄化療法の導入および入院を必要とした心血管イベントの発症率が有意に抑制され，糸球体濾過率(GFR)を用いた腎機能低下率の検討でも，腎機能低下率が抑制されていたことが明らかとなった．また，50%以上の尿中アルブミン排泄率減少が得られたかどうかで検討したところ，50%以上の減少群では同様にイベントの発生率が有意に抑制されていたことも明らかとなった．

2007年には，SMART研究[10]およびINNOVATION研究[11]が報告されている．両研究とも，早期腎症を伴う日本人の2型糖尿病患者を対象としており，SMART研究ではARBのバルサルタンとカルシウム拮抗薬のアムロジピンによる効果比較検討を，INNOVATION研究ではARBのテルミサルタンとプラセボによる効果比較検討を行っている．

SMART研究では，アムロジピン投与群で11%，バルサルタン投与群で32%の症例が寛解に至っている．さらに，バルサルタン投与群では血圧に関係なくアルブミン尿の減少効果が認められたことに対して，アムロジピン投与群では血圧が130/80 mmHg未満ではアルブミン尿の減少効果を認めたものの130/80 mmHg以上ではむしろアルブミン尿が増加する傾向を認めた．このことから，カルシウム拮抗薬は血圧依存性に，ARBは血圧非依存性に寛解を導く可能性を示唆している．

INNOVATION研究では，プラセボ群に対してテルミサルタン投与群では，早期腎症から顕性腎症への進展は有意に抑制され，寛解率も高値であったと報告されている．

赤井らは報告した2例をさらに追跡し，寛解後それぞれ8年後と5年後の腎生検組織について検討したところ，ともに腎糸球体の硬化病変改善を認めており，腎症は治癒したといってもよいほどであると報告している[12]．

2009年，Haraguchiらは1日2.9 gの蛋白尿を認める17年の罹病期間がある1型糖尿病患者に対して，強化インスリン療法，低蛋白減塩食，ACE阻害薬と利尿剤を用いた多角的治療を行い治療前と治療開始5年後で比較検討したところ，腎機能とともに組織変化も改善していたと報告している[13]．

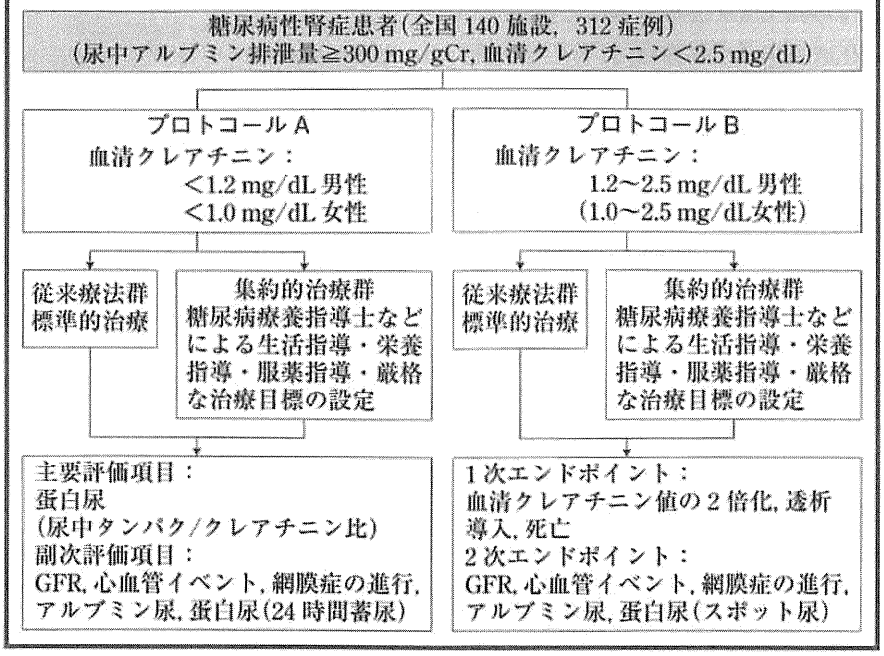
今後の展望

このように早期腎症と顕性腎症ともに寛解の報告は増加しているが，顕性腎症の症例での大規模臨床試験によるエビデンスは存在していない．寛解にいたる確率や蛋白尿はどれくらい軽減させられるのか，あるいは透析導入はどれくらい延ばせるのかといった疑問に対する明確な答えは残念ながら見つかっていない．

このエビデンスを得るべく，2004年度より厚生労働省研究事業としてDNETT-Japan(Diabetic Nephropathy Remission and Regression

腎症の寛解は可能か？：最近のエビデンスより

Box 1 DNETT-Japan：プロトコール概要



Team Trial in Japan)が開始されている[14]．この研究は，3 期～4 期の顕性腎症を伴う 2 型糖尿病患者を対象に，医師および糖尿病療養指導士(CDEJ)を中心としたコメディカルスタッフによるチーム医療によって強力に治療介入(集約的治療)を行うことで，腎症の進展を抑制できるか否か，さらに寛解させることが可能かどうかを検証する多施設共同無作為化臨床試験である．

A，B の 2 つのプロトコールに分かれており，プロトコール A では腎機能が比較的保たれている第 3 期を対象として蛋白尿の減少効果を主要評価項目としている．一方，プロトコール B では腎機能の低下した症例を対象として血清クレアチニン値の 2 倍化，透析療法への導入または腎移植，死亡を複合エンドポイントとして，集約的治療による腎症の進展抑制効果を検討する．両プロトコールとも，集約的治療群と従来療法群の 2 群に無作為に割り付けして 5 年間観察する(Box 1)．

従来療法群では，日本糖尿病学会，日本高血圧学会，日本動脈硬化学会が提唱している治療ガイドラインに準拠した治療目標値が設定され，集約的治療群ではこれよりもさらに厳しい治療目標が設定されている(Box 2)．

Box 2 DNETT-Japan：従来療法群と集約的治療群の治療目標

	従来療法群	集約的治療群
血糖管理	HbA_{1c}(JDS)<6.5%	HbA_{1c}(JDS)<5.8%
血圧管理	<130/80 mmHg	<125/75 mmHg ACE 阻害薬，ARB を使用 家庭血圧測定
脂質管理	T.cho<200 LDL.cho<120 HDL.cho>40	T.cho<180 LDL.cho<100 HDL.cho>40
食事：エネルギー	25～30 kcal/kg/日	30 kcal/kg/日
蛋白質	1.0 g/kg/日	0.8 g/kg/日
食塩	6 g/日	5 g/日
その他		服薬指導・禁煙指導・生活指導

治療の際，薬物療法においては，従来療法群では現在の標準的な治療を継続し，集約的治療群で

は降圧薬としてACE阻害薬とARB，脂質異常症治療薬としてHMG-CoA還元酵素阻害薬(スタチン)を，サプリメントとしてマルチビタミンを必ず使用することとなっている．

食事療法は，デジタルカメラを用いた食事記録などを参考に，管理栄養士が栄養指導を行う．

また，集約的治療群では，家庭血圧計による早朝血圧の測定，禁煙指導，服薬状況の厳格なチェックなどにて治療効果の向上をはかるよう設定されている．

本研究は，2009年5月31日に登録が締め切られ，全国65施設から312症例が登録されて現在観察期間に入り進行中である．

この研究を含め多数の臨床研究により，腎症の寛解をめざした集約的治療法が確立されることに期待が高まる．M

文　献

1) The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive therapy of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329 : 977-986
2) Ohkubo Y, Kishikawa H, Araki E, et al (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus ; a randomized prospective 6-year study. Diabetes Res Clin Pract 28 : 103-117
3) UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with convention treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352 : 837-853
4) Fioretto P, Steffes MW, Sutherland DE, et al (1998) Reversal of lesion of diabetes nephropathy after pancreas transplantation. N Engl J Med 339 : 69-75
5) Hovind P, Rossing P, Tarnow L, et al (2001) Remission and regression in the nephropathy on type 1 diabetes when blood pressure is controlled aggressively. Kidney Int 60 : 378-379
6) Perkins BA, Ficociello LH, Silva KH, et al (2003) Regression of microalbuminuria in type 1 diabetes. N Engl J Med 348 : 2285-2293
7) Araki S, Haneda M, Sugimoto T, et al (2005) Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. Diabetes 54 : 2983-2987
8) 赤井裕輝(2002)糖尿病性腎症は軽快するか．腎臓 24 : 70-77
9) Araki S, Haneda M, Koya D, et al (2007) Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. Diabetes 56 : 1727-1730
10) The Shiga Microalbuminuria Reduction Trial (SMART) Group (2007) Reduction of Microalbuminuria in Patients With Type 2 Diabetes. Diabetes Care 30 : 1581-1583
11) Makino H, Haneda M, Babazono T, et al (2007) Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes. Diabetes Care 30 : 1577-1578
12) 赤井裕輝(2010)糖尿病性腎症のレミッション(寛解)例．治療学 44 : 342-347
13) Haraguchi K, Hara S, Ubara Y, et al (2009) Complete remission of diabetic nephropathy in a type 1 diabetic patient with near-nephrotic range proteinuria and reduced renal function. Diabetes Res Clin Pract 83 : 295-299
14) Shikata K, Haneda M, Koya D, et al (2010) Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan) : Rationale and study design. Diabetes Res Clin Pract 87 : 228-232

ひろた　だいしょう
岡山大学大学院医歯薬学総合研究科　腎・免疫・内分泌代謝内科
しかた　けんいち
岡山大学病院　新医療研究開発センター
(〒700-8558　岡山市北区鹿田町2-5-1)