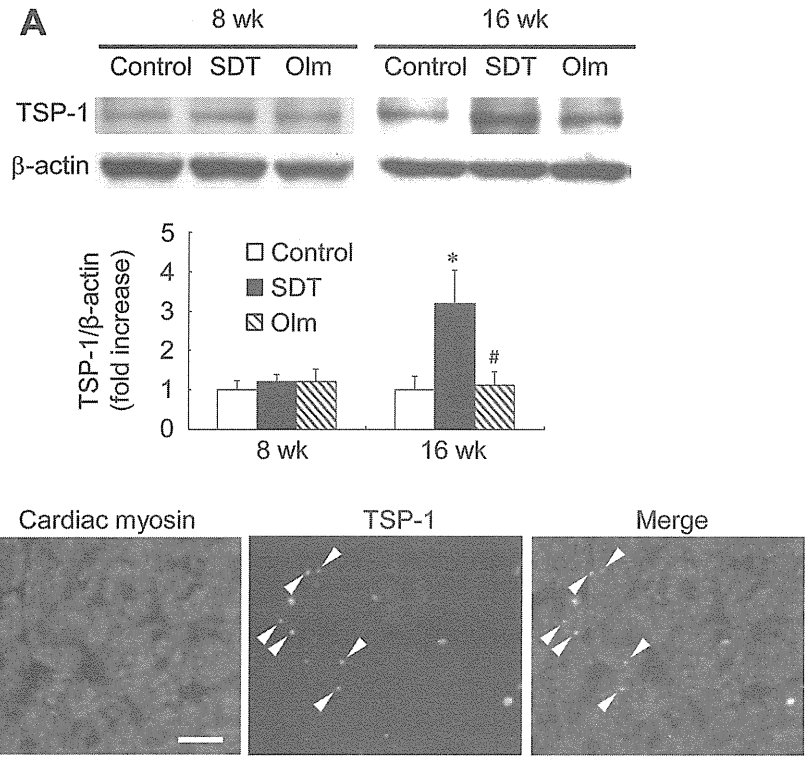

Fig. 9. Expression of thrombospondin (TSP)-1 in the three groups of rat LVs. *A*, *top*: Western blot analyses of TSP-1 in the three groups of rat LV tissues at 8 and 16 wk. *Bottom*, densitometric analyses of the expression of TSP-1 in the three groups of rats at 8 and 16 wk relative to that in the control group at 8 and 16 wk, respectively. Data are means ± SE of 4–6 rats/group. *B*: immunofluorescence double staining for cardiac myosin and TSP-1 in the LV tissue of the SDT group at 16 wk. Arrowheads show TSP-1 expressed in cardiomyocytes. Scale bar = 20 μm. *$P < 0.05$ vs. the control group at the same time point; #$P < 0.05$ vs. the SDT group at the same time point.

In SDT rats, both phases were characterized by ANG II overproduction in LV cardiomyocytes, without systolic blood pressure elevation. In contrast, at the onset of diabetes, there was no LV ANG II overproduction or LV functional or morphological alteration-only significant hyperglycemia. As reported in diabetic patients and animals (24, 35), circulating ANG II levels were also decreased in SDT rats at 8 and 16 wk only. Treatment of SDT rats with Olm for 8 and 16 wk after diabetes onset completely suppressed both LV ANG II overproduction and LV dysfunction and morphological abnormalities, without influencing hyperglycemia or systolic blood pressure. These findings are in good agreement with a report by Mazzolai et al. (23), in which mice overexpressing angiotensinogen specifically in the heart displayed increased heart ANG II levels and cardiac hypertrophy without an elevation of either plasma ANG II levels or blood pressure, and these were abolished by treatment with losartan, an ARB. Similarly, elevated ANG II levels have been demonstrated in cardiomyocytes of STZ diabetic rats, which were inhibited by treatment with ARBs (5, 46). Moreover, the SDT rat LV at 8 and 16 wk exhibited enhanced EGFR phosphorylation and NHE1 upregulation, both being downstream signals of ANG II-induced LVH (4, 49); these were completely suppressed by Olm treatment. Therefore, these findings indicate that during both phases under persistent hyperglycemic conditions, sustained LV cardiomyocyte ANG II overproduction, but not chronic pressure overload, induces prolonged LVH through its growth factor effect on cardiomyocytes, which respectively stimulates and suppresses coronary capillary angiogenesis in the early and late phases. It should be noted that the local ANG II overproduction by SDT rat LV cardiomyocytes continued in the late phase. In the late phase alone, we detected these events, including interstitial fibrosis, cardiomyocyte apoptosis, TGF-β_1 upregulation in LV tissues, decreased coronary capillary angiogenesis associated with cardiomyocyte hypertrophy, enhanced apoptosis and suppressed proliferation of capillary endothelial cells, and upregulation of TSP-1 in hypertrophied cardiomyocytes. However, it is presently unknown why these events, especially the TSP-1 upregulation, were limited to the late phase. The events observed in the late phase alone were accompanied by more persistent hyperglycemia and longer ANG II overproduction and more severe and longer hypoxia in the hypertrophied cardiomyocytes than in the early phase, all of which (except for hyperglycemia) were reversed by Olm. Thus, these Olm-sensitive events observed in the late phase alone must be closely linked to each other independently of hyperglycemia. It has been reported that ANG II upregulates TSP-1 protein expression in cultured rat cardiac fibroblasts independently of high-glucose media (55). It has been shown that hypoxia induced HIF-1α-dependent expression of TSP-1 mRNA and protein in cultured human coronary artery smooth muscle cells (34). Therefore, the longer ANG II production and/or more severe and longer hypoxia in hypertrophied cardiomyocytes at 16 wk may be involved in processes involving TSP-1 upregulation. TGF-β_1 is a known regulator of TSP-1 expression in a variety of cell types (29, 30, 32). It has been reported that TGF-β_1 production is significantly increased under hypoxic conditions in lymphatic endothelial cells (17). Alternatively, therefore, TGF-β_1 overproduced under more severe chronic hypoxia at 16 wk may contribute to the TSP-1 upregulation. These possibilities need further investigation. Taken together, in SDT rats after diabetes onset, sustained local ANG II overproduction actually contributes to all the events observed in both phases of DCM in a time-dependent manner. Conversely, from a therapeutic point of view, our findings suggest that persistent inhibition of LV ANG II overproduction with

Olm may provide protective effects against the progression of DCM in diabetic patients, independently of hyperglycemia and systolic blood pressure.

Our study has several important limitations that deserve mention. First, although our findings indicate that Olm-sensitive processes, especially LV cardiomyocyte ANG II overproduction, correlate well with the events observed in both phases, we did not directly demonstrate that LV ANG II developed and progressed DCM. Second, we did not evaluate how persistent hyperglycemia induced the sustained LV cardiomyocyte ANG II overproduction or how the sustained LV cardiomyocyte ANG II overproduction was inhibited by the ARB Olm. These currently unresolved issues should be addressed in future studies.

In conclusion, the present findings suggest that LV ANG II in SDT rats at 8 and 16 wk after the onset of diabetes induces cardiomyocyte hypertrophy without affecting hyperglycemia or systolic blood pressure, which promotes and suppresses coronary angiogenesis, respectively, via VEGF and TSP-1 produced from hypertrophied cardiomyocytes under chronic hypoxia. TSP-1 may play an important role in DCM progression in this model. These findings reveal a novel mechanism for the pathogenesis of DCM, in terms of the cross-talk between cardiomyocytes and the coronary vasculature during diabetic heart ANG II-induced cardiac growth and suggest the clinical significance of long-term heart ANG II inhibition in patients with diabetes.

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DISCLOSURES

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REVIEW ARTICLE

Mechanism by which chronic kidney disease causes cardiovascular disease and the measures to manage this phenomenon

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Abstract In Japan, the number of chronic kidney disease (CKD) patients is thought to be 13,300,000, next in size after those with hypertension and diabetes. Although the number of patients with CKD seems large, it does not mean that all these patients require special treatment. Among them, nephrologists should pay special attention to patients with glomerular filtration rate below 50 mL/min/1.73 m^2 and progressive deterioration of renal function. Treatment of these CKD patients by a limited number of specialists is simply impossible; hence, it is essential to request treatment from physicians who are involved in general internal medicine and primary care. It is well known that not only does CKD cause end-stage renal failure, it also causes the onset of cardiovascular diseases (CVD) such as cardiac infarction and cerebral stroke; however, the question is how much significance does CKD have as a risk factor for CVD. It is understandable that hypertension and CVD are often complications of CKD; however, in addition to what is conventionally mentioned, there are three or four mechanisms that we would like to emphasize, and discuss herein. Among them, we would like to stress the role of klotho genes with special reference to the generation of CVD in CKD patients. When patients develop CKD, it is therefore necessary to remove as far as possible any factors that could represent a risk for CVD. Moreover, by taking appropriate measures against clinical conditions that often complicate CKD, such as hypertension, renal anemia, hyperuricemia, and hyperlipidaemia, the development of CVD can be prevented.

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Introduction

Attention is being paid to chronic kidney disease (CKD) as a new risk factor for cardiovascular disease (CVD). It is known that if CKD is not treated, the risk of end-stage renal failure increases, and it has become clear that not only does the disorder affect the kidneys, it also systemically affects the vascular system. It is already known that when renal function deteriorates, the risk of onset of CKD or death increases, and this has been identified as the correlation between the heart and the kidney. Generally, the risk factors for developing CVD in patients with CKD have been reported; however, it is believed that there are various other risk factors. In this review, those factors are outlined and measures for successfully managing them are also discussed.

CKD requiring active participation in medical care by primary care physicians

According to the CKD medical care guidelines published by the Japanese Society of Nephrology in September 2007, CKD is defined as cases in which a renal disorder is observed or cases in which deterioration of renal function, with a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2, continues for 3 months or more [1]. According to Imai et al. [2], in Japan, the number of patients to whom this definition applies is thought to be 13,300,000, next in size after 32,200,000 for hypertension and 16,000,000 for

diabetes. The estimated figure for CKD patients is based on the data from a large-scale medical examination performed in Japan, and hence the figure is believed to be quite accurate. However, because renal function deteriorates with age, in an aging society such as Japan the number of patients having a decreased GFR is correspondingly higher. For example, for people aged 40 or older, it is said that the GFR decreases by 1% each year. In other words, if the GFR is 100 mL/min/1.73 m^2 at age 40, when patients reach 70–80, physiologically their GFP falls to approximately 60–70 mL/min/1.73 m^2. In this way, although the GFR decreases with age, it is not solely responsible for causing CKD; when factors such as hypertension, diabetes, and chronic glomerulonephritis are added, renal function rapidly deteriorates, and the risk of renal failure increases. Although the number of patients having CKD, at 13,300,000, seems large, it does not mean that all these patients require special treatment. However, deterioration of renal function itself is a risk factor for renal disorders; therefore, when factors such as hypertension are added, the risk obviously increases. In that sense, this group includes patients with renal failure as well as patients who may potentially develop renal failure. For cases of CKD, when the GFR reaches 50 mL/min/1.73 m^2 or below, renal failure progresses rapidly, and this requires diagnosis and decision on the treatment plan by specialists; however, even for a mild renal disorder that does not progress rapidly, early detection and observation of the course are important. Treatment of this substantial number of CKD patients by a limited number of specialists is simply impossible; hence, it is essential to request treatment from physicians who are involved in general internal medicine and primary care. Although the measurement of blood pressure or blood sugar level and HbA1c is widely practiced in primary care, the intention of introducing the CKD medical care guidelines is to ask physicians to "pay attention to renal function, and measure the GFR on a regular basis". Fortunately, because a GFR quick reference chart or a calculator has been introduced and is used widely, the calculation itself is not difficult; however, if it can be calculated automatically based on the test data, it will greatly assist physicians. In addition, recently we are able see the eGFR data automatically in the hospital, and an inspection company has already shown the eGFR data to physicians.

CKD increases the risk of CVD

Not only does CKD cause end-stage renal failure, it also causes the onset of CVD such as cardiac infarction and cerebral stroke; however, the question is how much significance does CKD have as a risk factor for CVD? The fact that CKD increases the risk of CVD has been proven by a number of epidemiological studies. In the United States, the results of a study that was performed over approximately 2.8 years on approximately 1,100,000 people who subscribed to private health care services have been reported [3]. From the results of the study, it has become clear that compared to groups with a GFR $\geq$60 mL/min/1.73 m^2, the risk of developing CVD was higher in the groups with a lower GFR. The lower the GFR, the higher the risk, and compared to groups with a GFR $\geq$60 mL/min/1.73 m^2, the relative risk increases by as much as 1.4–3.4 times. In Japan, the results of a study performed at Hisayamacho Research in Fukuoka and the results of a study performed on residents who participated in general health examinations in Ibaraki have also been reported [4, 5], and according to the results of both studies, when the GFR of the subjects fell below 60 mL/min/1.73 m^2, which is the diagnostic criteria for CKD, the risk of CVD increased.

Reasons why CKD increases the risk of CVD

Renal disorders are known to increase blood pressure, and conversely hypertension is also known to lead to the development of renal disorders. In this way, because renal disorders and hypertension are closely related to each other, hypertension is believed to substantially affect the risk of CVD associated with CKD. Moreover, recently, diabetes, which is the primary causative disease of CKD, has come to be regarded as an important risk factor for arteriosclerotic disease. Furthermore, the activation of the sympathetic nervous system or renin–angiotensin (RA) system, which are associated with renal disorders, increased circulatory blood volume, deterioration of vascular endothelial function, etc., affects the clinical conditions related to CKD; however, these are also believed to accelerate cardiovascular system disorders. As a renal disorder progresses, these risks act additively and synergistically in establishing a foundation for developing CVD.

An exacerbation of the sympathetic nervous system or RA system, which is associated with renal disorders, increased blood pressure, and increased circulatory blood volume, causes a rise in blood pressure and an increase in cardiac strain. Therefore, it is understandable that hypertension and CVD are often complications of CKD; however, in addition to what is conventionally mentioned (Table 1), there are three or four mechanisms that we would like to emphasize, and present herein.

The first mechanism pertains to the deterioration of vascular endothelial function, which is described above. The vascular endothelium has various functions, such as producing a vasodepressor substance, namely nitric

Table 1 Known and our proposed risk factors by which CKD induces CVD

Known risk factors	Risk factors proposed by us
Albuminuria	Decrease in endothelial progenitor cells
Homocysteine	Indoxyl sulfate
Lipoprotein A	Klotho gene
Apolipoprotein A	
Remnant lipoprotein	
Anemia	
Calcium and phosphte metabolosm	
Overhydration	
Electrolyte disorder	
Oxidative stress	
Inflammtion	
Malnutrition	
Thrombotic factors	
Sleep disorder*	
Nitric oxide / endothelin imbalance	

* We also reported the risk of sleep disorder [15]

monoxide, that protects the blood vessels from oxidant stress or inflammation, and inhibits thrombosis. In addition, based on recent studies, it has become clear that the number of endothelial progenitor cells (EPCs), which are essential in forming the vascular endothelium, decreases and their functions deteriorate in CKD patients [6, 7]. Hence, when we measured the EPCs in the peripheral blood of dialysis patients and compared it to healthy individuals, not only did the EPCs decrease in number, but the functions also deteriorated substantially [8]. Therefore, it is believed that as CKD progresses, the vascular repair capacity decreases, making it easier to develop CVD.

The second mechanism has to do with the possibility that the accumulation of indoxyl sulfate, which is associated with deterioration of renal function, is related to the development of CVD. Indoxyl sulfate is a uremic substance and when it accumulates, the progress of any renal disorder will accelerate; however, we discovered that it also serves the function of promoting the proliferation of vascular smooth muscle cells [9]. Indoxyl sulfate stimulates a MAP kinase, which has the effect of accelerating the proliferation of cells, and this was shown in an in-vitro study. Clinically, although the effect of removing indoxyl sulfate is observed in activated carbon kremezin, it has been reported that when this medical drug is used for treatment, the thickening of the carotid or the pulse wave velocity is inhibited; hence, there is a possibility that indoxyl sulfate leads to arteriosclerosis [10]. Subsequently, it was reported that indoxyl sulfate is a risk factor for arteriosclerosis in dialysis patients, that there are data which relate it to the mortality of CKD patients attributed to CVD, and that calcification of arteries is also accelerated, according to animal tests. Moreover, activated carbon is reported to alleviate cardiomyopathy in CKD patients by inhibiting oxidant stress [11–14].

The third mechanism pertains to sleep-disordered breathing (SDB). Recently, we discovered that SDB is one of the risk factors in CVD events or mortality in dialysis patients [15]. Generally, SDB is known to be a CVD event or mortality risk [16]; however, it has not been studied in dialysis patients. A study was performed on 94 dialysis patients and a pulse oximeter was installed overnight on the day of dialysis. Based on the study, when SDB is defined to occur at a frequency in which the oxygen saturation is decreased 3% from the baseline of 5 times or more every hour, 44 patients (47%) fell into the defined category. The basal metabolic index, diabetes, and daytime sleepiness were also high in patients complicated with SDB. On the other hand, during the dialysis period, the Kt/V, protein catabolic rate, and Hb were low. During the follow-up period of 55 months on average, the incident rate of CVD and death resulting from all causes were significantly higher in the SDB group. In conclusion, SDB by itself is an independent predictive factor for a CVD event or mortality risk, and early detection and treatment are believed to be important for the prognosis of patients.

The fourth mechanism concerns the possibility that a decrease in aging control genes in CKD is related to the development of CVD. A decrease in anti-aging hormones, namely klotho genes [17], which have gained attention recently, is possibly related to a decrease in presenility for CKD patients, including dialysis patients [18]. Interestingly, the klotho genes are expressed primarily in the distal renal tubule of the kidney [19]. Therefore, when CKD progresses and causes renal failure, the expression of klotho gene mRNA also decreases. Aging progresses in animals in which the klotho genes are disabled; they develop CVD within a short period of time and die, and it is believed that similar conditions may occur in human CKD.

Recently, factors that lead to an increase or decrease in the expression of the klotho genes have been discovered [20]. The increasing factors include a low phosphorus diet, active vitamin D, statins, PPAR agonists, and triiodothyronine. The decreasing factors include factors related to lifestyle diseases such as aging, a high phosphorus diet, renal failure, hypertension, and diabetes. Moreover, when the klotho genes are expressed to excess, the progress of renal failure is inhibited, and a decrease in oxidant stress or apoptosis resulting from the klotho genes has thus been considered to occur as an underlying mechanism [21].

The klotho genes can be classified into a membranous form and a secretable form, and, in particular, the number of the secretable form genes is believed to produce a circulating klotho protein which was decreased in human renal failure. There are some reports that claim that this can be measured using a radioimmunoassay; however, it is necessary to study safety and reproducibility in the future. The klotho proteins in the secretable form act as an anti-aging protein by adjusting Ca [22] or K channels [23], or by inhibiting growth factors such as insulin or IGF-1 [24], and furthermore by inhibiting Wnt signaling [25]. Moreover, the klotho proteins are also reported to control renal fibrosis and the metastasis of cancer by inhibiting the signaling of TGF-β [26]. On the other hand, the membranous form of the klotho genes are known to inhibit the production of phosphorus and active vitamin D in combination with FGF23. In a mouse that lacks the klotho genes, if hyperphosphatemia is prevented, then aging can be controlled. Phosphorus toxicity is known to increase the sensitivity of insulin and/or to increase oxidant stress. Therefore, there are many cases in which hyperphosphatemia is observed in CKD patients, and this is believed to accelerate CVD or aging.

Phosphorus outside the cells is transported inside the cells by means of a sodium–phosphorus cotransporter; however, the phosphorus that is transported to the cytoplasm is transported to the mitochondria and is used in oxidative phosphorylation. The phosphorus concentration of the cytoplasm is correlated with the membrane potential of the mitochondria, and is also known to be correlated with the production of active oxygen [27].

Black-tails have a shorter animal life with a high serum phosphorus level, and a mouse that lacks the klotho genes or a mouse that lacks FGF23 has a high phosphorus blood level; however, when the phosphorus concentration is reduced, geromorphism is known to decrease [28, 29]. Moreover, as described above, phosphorus toxicity is known to increase the sensitivity of insulin and/or to increase oxidant stress. When the serum phosphorus level is high in humans, the mortality rate resulting from all causes is known to be high [30, 31].

Renin–angiotensin-based inhibitors improve the hemodynamics of the entire body and the kidney

There are many cases in which physicians involved in primary care and nephrologists jointly provide medical care to CKD patients, including those with diabetic nephropathy. When a non-nephrologist examines a CKD patient, according to the CKD medical care guidelines, if any of the 3 criteria are met, namely (1) the GFR is below 50 mL/min/1.73 m^2, (2) urinary protein is 0.5 g/day or 0.5 g/gCr or more, and (3) proteinuria and hematuria are 1+ or more, the patient must be referred to a nephrologist. For mild cases in which the GFR has not decreased to this extent, it is necessary to control the CVD risk factors by observing the course; however, it is especially necessary to provide treatment for hypertension. Based on the CKD medical care guidelines, the antihypertensive target for CKD patients is set to below 130/80 mmHg, and for cases in which proteinuria is 1 g or more daily, it is set to below 125/75 mmHg. This antihypertensive target is based on clinical results showing the usefulness of antihypertensive treatment for CKD patients, and the evidence is certain [32].

As an antihypertensive drug for hypertension complicated with renal disease, it is preferable to use RA-based inhibitors such as angiotensin II receptor blockers (ARBs) because RA-based inhibitors exhibit desirable effects on the hemodynamics of the entire body and the kidneys. Although decreased GFR is caused by the decreased renal glomeruli function, when this happens the kidney attempts to maintain the GFR by increasing the intraglomerular pressure. Although this is a compensatory action for the disorder, when the increase in the pressure load to the renal glomeruli continues, the vascular tissues cause disorders. Therefore, it is necessary to reduce the glomerular hypertension; one of the methods is to reduce the systemic blood pressure and the other is to reduce the local pressure load by expanding the efferent arterioles of the renal glomeruli. In particular, an exacerbation of the sympathetic nervous system or RA systems of the kidneys is strongly related to contraction of the efferent arterioles, and RA-based inhibitors are effective here. RA-based inhibitors reduce the systemic blood pressure and inhibit glomerular hypertension. Antihypertensive drugs that can improve the systemic and local hemodynamics include RA-based inhibitors and some calcium antagonists such as cilnidipine, efonidipine, and azelnidipine [33–35].

The RA-based inhibitors include ARBs and angiotensin-converting enzyme (ACE) inhibitors, and both demonstrate excellent antihypertensive effects; in CKD, both are often selected as the drug of first choice. Moreover, both drugs have been shown to inhibit renal disorders; hence, from a usefulness perspective, either drug can be used. However,

side effects such as dry coughs are frequently observed with ACE inhibitors, as one difference between the two drugs, and this is a disadvantage. Although the true mechanism of dry cough with ACE inhibitors is unknown, both kinins and substance P are metabolized by ACE; thus, their levels are increased by ACE inhibition [36]. Kinins, for example, may induce bronchial irritation and cough via enhanced production of prostaglandins. In addition, ACE inhibitors should be reduced in dosage depending on the degree of renal impairment, because many ACE inhibitors are excreted from the kidney. On the other hand, ABRs tend to be excreted from the liver. These differences may also be responsible for the production of dry cough by ACE inhibitors. Although CKD is a disease that occurs frequently in the elderly, it is understandable that not only elderly but also the young want to avoid using an antihypertensive drug that may induce respiratory symptoms. On the other hand, ARBs are useful because they exhibits fewer side effects, and because the incidence of side effects does not increase even if the amount is increased. Currently, in Japan, the prescription rate of ARBs exceeds that of ACE inhibitors, and such factors contribute to the current background.

Recently, we showed that a renin inhibitor, aliskiren, directly lowers the blood pressure of dialysis patients, that it lowers CVD biomarkers such as brain natriuretic hormone (BNP), high-sensitivity CRP, etc., and that it alleviates oxidant stress. No increase in the serum potassium concentration was observed [37]. Therefore, in the future, aliskiren may be a useful antihypertensive drug for treating hypertension in CKD patients, including dialysis patients; however, it requires further research.

ARBs improve the endothelial dysfunction that is associated with renal failure and diabetes

For treatment of hypertension complicated with CKD, an RA-based inhibitor should be used as the basal agent; however, if ARBs are to be used, it is preferable that drugs that exhibit high antihypertensive effects and high proteinuria reduction effects are used as much as possible. Recently, Weinberg et al. reported on the long-term safety of high-dose angiotensin receptor blocker therapy in hypertensive patients with chronic kidney disease. The average ARB dose of 48 CKD patients tended to increase over time and was 3.2 times greater at the end of the study than that at the start. The average estimated glomerular filtration rate was 53 mL/min, and they received treatment with high doses (1.5–5 times greater than the maximum approved dose) of ARBs, on average for 40 months. From the results, they concluded that high-dose ARB treatment in patients with CKD was not associated with any clinically significant long-term negative effects on serum creatinine or potassium and is thus a important therapeutic modality with which to achieve further reductions in urinary protein excretion [38]. For CKD that includes diabetic nephropathy, cases in which the target antihypertensive level is reached account for 20% or less; therefore, in that regard, ARBs, which can provide antihypertensive effects, are desirable. Moreover, increased dosages are acceptable, as long as the antihypertensive effects and proteinuria reduction effects can be obtained. There are interesting findings regarding olmesartan. Although EPCs have been indicated to decrease in patients with renal failure, olmesartan is reported to increase EPCs [39]. A study was performed on patients with type 2 diabetes, and the results indicated that the EPCs are significantly decreased in diabetic patients compared to healthy individuals, and when olmesartan was administered to the diabetic patients, the EPCs significantly increased. The results indicate that ARBs improve the endothelial dysfunction associated with diabetes, and that they inhibits systemic vascular disease in addition to demonstrating antihypertensive effects and renoprotective effects; this serves as one of the new items of evidence that support treatment using ARBs for hypertension that is associated with CKD. Recently, there have been a series of reports in which even other ARBs cause the EPCs to increase and in which the features of such ARBs are enhanced; therefore, this may be a common effect across ARBs. Therefore, ARBs are expected to increase the vascular endothelial function of patients who have hypertension and diabetes, including CKD, and to reduce angiopathy [40].

Conclusion

The kidney and cardiovascular systems, both parts of the body, affect each other. Therefore, when affected by kidney diseases, especially CKD, depending on the primary disease, severity, time period, etc., it is natural that the vascular systems are affected to a greater or lesser extent, and this gives rise to CVD. Recently, there have been many cases in which lifestyle diseases, such as diabetes, hypertension, hyperlipemia, and metabolic syndrome, cause renal disorders. When patients develop CKD, it is therefore necessary to remove as far as possible any factors that could represent a risk for CVD. Moreover, by taking appropriate measures against clinical conditions that often complicate CKD, such as hypertension, renal anemia, hyperuricemia, and hyperlipidaemia, the development of CVD can be prevented. From the viewpoint of hypertension, Ito et al. [41] reported a "strain vessel hypothesis" which may explain why hypertension and diabetes, unforeseen in the concept of evolution, preferentially affect

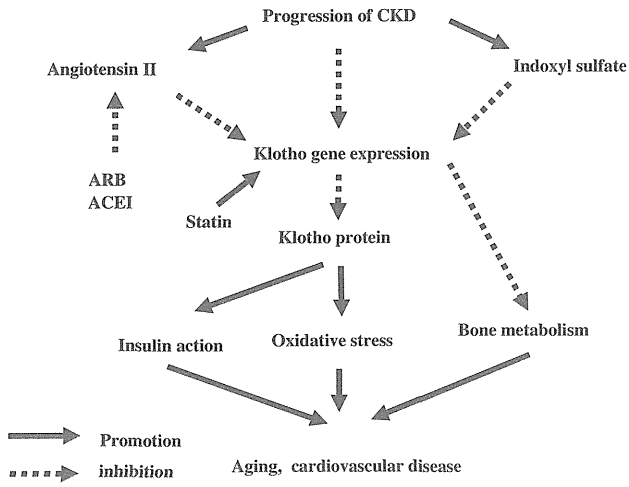

Fig. 1 Working hypothesis for the mechanism by which CKD causes CVD—contribution of klotho genes. *ACEI* angiotension-converting enzyme inhibitor

vital organs such as the brain, heart and kidney. It is worthwhile considering the association of CKD and CVD. Traditionally, with regard to CKD, it had been believed that metabolic products excreted from the kidney impaired the functions of cells and organs. However, recently it was discovered that aging control genes, namely the klotho genes, are expressed primarily in the kidneys, and as CKD progresses, the klotho genes and their product, namely proteins, decrease, thereby causing aging control to be reduced and CVD to be accelerated (Fig. 1). Gradually, as the effects of the klotho genes become clear, it is expected that the relationship between CKD and CVD will also thus be elucidated.

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Conflict of interest I state that there is no conflict of interest regarding the material discussed in the manuscript.

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Original Article

Association between Cystatin C and Arteriosclerosis in the Absence of Chronic Kidney Disease

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Aim: Chronic kidney disease (CKD) is a known risk factor for cardiovascular disease (CVD). Cystatin C was recently reported to be an endogenous surrogate of kidney function, and a high level of cystatin C is reported to be a strong predictor of CVD; however, the association between cystatin C and arteriosclerosis in a non-CKD population is unclear. This study aimed to clarify the association between cystatin C and arteriosclerosis in a non-CKD population.

Methods: Of the 637 Japanese adults (264 men, 373 women) enrolled, we analyzed 446 participants with an estimated glomerular filtration rate (eGFR) >60 mL/min and no proteinuria (177 men, 269 women) without a history of CVD. Kidney function was evaluated according to serum cystatin C levels and eGFR. Arteriosclerosis was evaluated on the basis of the cardio-ankle vascular index (CAVI) and carotid intima-media thickness (CIMT).

Results: The mean age of our subjects was 67.0±10.0 years. No variables showed any significant differences according to gender. The results of multiple linear regression analysis showed a significant correlation between serum cystatin C and CAVI only in women, but not CIMT.

Conclusion: We observed a significant correlation between cystatin C and CAVI, which is a marker of early-stage arteriosclerosis, in women in a non-CKD population with no proteinuria and eGFR >60 mL/min.

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Key words: Cystatin C, Cardiovascular disease, Cardio-ankle vascular index (CAVI), Carotid intima-media thickness (CIMT)

Introduction

Recently, chronic kidney disease (CKD) has become an important public health problem worldwide. In the United States, it is estimated that there are 25 million people with CKD[1]. In Japan, about 13% of the Japanese adult population (approximately 13.3 million people) was predicted to have CKD in 2005[2]. CKD has been recognized as a risk factor not only for end-stage renal disease but also for the development of cardiovascular disease (CVD)[3,4] and is a known predictor of cardiovascular mortality[5,6]. In fact, an independent and graded association has been observed in a community-based population between renal dysfunction and the risk of death, cardiovascular events, and hospitalization[7]. Therefore, it is necessary and important to detect CKD in its early stages to reduce cardiovascular disease events.

The glomerular filtration rate (GFR) is an important indicator of kidney function for detecting, evalu-

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ating, and managing CKD. The accurate and internationally accepted method of measuring GFR is by measuring inulin clearance; however, this is a complex procedure and is normally not used in clinical practice in Japan. Instead, creatinine clearance is often used as a surrogate marker of GFR. However, several factors other than GFR, such as muscle mass and dietary intake, affect the serum creatinine level. Recently, cystatin C has been proposed as an endogenous surrogate marker for GFR, because it can easily pass through the glomerular filtration barrier because of its size[8]. Cystatin C is a non-glycosylated 13-kDa basic protein that is a cysteine protease inhibitor; it is also a member of the human cysteine superfamily, functioning as a housekeeping gene protein that is stably produced by most nucleated cells[9]. Furthermore, cystatin C is filtered by the glomeruli and reabsorbed and catabolized by tubular epithelial cells, with only small amounts being excreted in the urine[10]. Further, in comparison to traditional markers of renal dysfunction, an advantage of cystatin C is that very small reductions in GFR cause a significant increase in cystatin C serum[11]; cystatin C is therefore gaining attention as a marker of early-stage renal impairment.

It is very important to establish effective and accurate screening methods for arteriosclerosis to prevent CVD. Several non-invasive parameters, such as the ankle brachial index (ABI), carotid intima-media thickness (CIMT), and pulse wave velocity (PWV), have been useful for evaluating arteriosclerotic lesions in the clinical setting. CIMT is an established measure of subclinical arteriosclerosis that holds prognostic significance for cardiovascular events in the general population[12-15]. Among the several methods available for the evaluation of arterial stiffness, PWV is easy, fairly reproducible, and correlates well with arterial stiffness determined by an invasive method[16]. However, since PWV is influenced by blood pressure, severe fluctuations in blood pressure values at the time of measurement of PWV can cause clinical difficulties. Therefore, a novel arterial stiffness parameter that reflects the stiffness of the aorta, the cardio-ankle vascular index (CAVI)[17, 18], has been recently developed; this index is independent of blood pressure[17].

To date, a large number of studies have demonstrated that CKD patients are at a high risk of arteriosclerosis-related CVD[7]. However, based on studies that have assessed the association between kidney function and arteriosclerosis in the non-CKD adult population, this relationship is considered controversial[19-26]. Currently, CKD is defined by either GFR <60 mL/minute per 1.73 m^2 of body-surface area or the presence of kidney damage, regardless of the cause, for 3 or more months[5]. Thus, in the present study, the "non-CKD population" included people with eGFR >60 mL/min and without proteinuria, and without an apparent past or present history of cerebral infarction or hemorrhage or ischemic heart disease. Thereafter, we measured cystatin C as an indicator of kidney function, and CIMT and CAVI as indicators of arteriosclerosis, and we investigated the association between cystatin C and arteriosclerosis in a Japanese non-CKD population.

Materials and Methods

Subjects

Ethics approval was obtained from the Special Committee of Nagasaki University (project registration number 08043068) before commencement of the study. The study population was chosen by using a medical screening program for individuals aged over 40 years living in Goto city (total population in 2007, 44,874), Nagasaki Prefecture, Japan. After obtaining informed consent, we enrolled 637 Japanese adults (264 men, 373 women) in the study. We excluded 164 participants based on eGFR <60 mL/min and proteinuria; patients with a urine albumin-to-creatinine ratio of 300 mg/gCr or higher were judged to be positive for proteinuria. In addition, we excluded 27 other participants because they had an apparent past or present history of cerebral infarction or hemorrhage or ischemic heart disease. Finally, 446 participants (177 men and 269 women) were included for further analysis. With regard to underlying diseases in the study participants, we adhered to the following definitions (based on values observed during physical examination or self-reported at an interview): hypertension was defined as blood pressure $\geq 140/90$ mmHg[27]; dyslipidemia, as low-density lipoprotein-cholesterol (LDL-C) ≥ 140 mg/dL or high-density lipoprotein-cholesterol (HDL-C) <40 mg/dL[28]; and diabetes mellitus (DM), as hemoglobin A1c (HbA1c) $\geq 6.4\%$ (HbA1c notation converted from the original Japan Diabetes Society (JDS) values to the National Glycohemoglobin Standardization Program (NGSP) values[29].

Data Collection and Laboratory Measurements

Sociodemographic characteristics, past medical history, and details regarding lifestyle behaviors (smoking) were obtained by means of a questionnaire. Height, weight, and waist circumference (WC) were measured, and body mass index (BMI: kg/m^2) was calculated as an index of obesity. Systolic and diastolic blood pressure (SBP and DBP) were recorded at rest,

Table 1. Characteristics of the study participants

	Men (n=177)	Women (n=269)	p value	All participants (n=446)
Age (years)	66.5±11.0	67.4±9.2	n.s.	67.0±10.0
BMI (kg/m^2)	23.5±3.1	23.0±3.5	n.s.	23.2±3.4
WC (cm)	84.5±9.3	82.1±10.2	n.s.	83.1±9.9
SBP (mmHg)	144±18	144±21	n.s.	144±20
TG (mg/dL)	99±71	94±53	n.s.	96±61
HDL-C (mg/dL)	57±14	60±13	n.s.	59±14
LDL-C (mg/dL)	118±27	126±25	n.s.	122±26
UA (mg/dL)	6.1±1.3	4.7±1.0	n.s.	5.2±1.3
HbA1c (%)	5.6±0.7	5.6±0.5	n.s.	5.6±0.6
U-Alb/Cre (mg/g·Cre)	18.7±32.4	25.7±36.7	n.s.	22.9±35.2
Cre (mg/dL)	0.78±0.09	0.59±0.07	n.s.	0.67±0.12
eGFR (mL/min/1.73 m^2)	78.0±12.0	76.8±11.6	n.s.	77.3±11.8
CysC (mg/L)	0.78±0.13	0.73±0.11	n.s.	0.75±0.12
CIMT (mm)	0.72±0.12	0.69±0.11	n.s.	0.70±0.12
CAVI	8.4±1.5	8.1±1.4	n.s.	8.2±1.4

with the simultaneous measurement of CAVI. Blood samples were collected from each participant after overnight fasting. Serum and plasma were separated and stored at −20℃ and −80℃, respectively, until the assay. Serum concentrations of total cholesterol (TC), triglyceride (TG), and HDL-C were measured by standard laboratory procedures, and LDL-C values were calculated by the Friedewald equation. In addition to fasting blood sugar and HbA1c, serum creatinine (Cre) and uric acid (UA) were measured by standard laboratory procedures. Serum cystatin C was measured in plasma specimens by the latex immunoturbidimetric method using OLYMPUS AU600 (Ikagaku Co. Ltd., Kyoto, Japan).

We also analyzed random urine samples from each patient to measure urinary albumin and creatinine excretions.

eGFR was calculated by the following formula[30]:

$$eGFR = 194 \times \text{standardized Scr}^{-1.094} \times \text{Age}^{-0.287} \ (\times 0.739 \text{ [if female]})$$

Measurement of CAVI and CIMT

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) with the participant resting in the supine position. The principles underlying CAVI have been described by Yambe *et al.*[18] ECG electrodes are placed on both wrists, a microphone for detecting heart sounds is placed on the sternum, and cuffs are wrapped around both the arms and ankles. After automatic measurements, the obtained data were analyzed using VSS-10 software (Fukuda Denshi), and the values for right and left CAVI were calculated. Averages of the right and left CAVI were used for analysis.

Measurement of CIMT by ultrasonography of the left and right carotid arteries was performed using a LOGIC Book XP with a 10-MHz linear array transducer (GE Medical Systems, Milwaukee, WI, USA).

Statistical Analysis

Results are expressed as the mean ± standard deviation. Differences between women and men in laboratory values were evaluated using the t-test. Simple linear regression analysis was conducted to determine the correlation between cystatin C and the other variables measured. Variables that showed a significant association were subjected to multiple linear regression analysis. Probability values <0.05 were considered significant. All statistical analyses were performed using SPSS v. 11.0 software (SPSS Japan, Tokyo, Japan).

Results

The characteristics of the study participants are shown in **Table 1**. The mean age was 67.0±10.0 years. With regard to the presence of underlying diseases among the study participants, 30 (6.7%) had DM, 159 (35.7%) had dyslipidemia, and 291 (65.2%) suffered from hypertension. Further, 49 participants (11.0%) had a positive history of smoking.

No variables showed any significant differences according to gender. Simple linear regression analysis revealed that cystatin C was significantly correlated with CAVI in all the participants (men: r=0.24, $p<$ 0.01; women: r=0.247, $p<0.01$; total population:

$r=0.256$, $p<0.01$). Furthermore, cystatin C was significantly correlated with CIMT in men and with BMI, SBP, and LDL-C in women. In all the participants, cystatin C was significantly correlated with age, WC, TG, HDL-C, UA, Cre, eGFR, and CAVI as well as CIMT according to the results of simple linear regression analysis (**Table 2**).

By multiple linear regression analysis adjusted for confounding factors associated with arteriosclerosis, cystatin C was found to be significantly correlated with CAVI in women, but not in men (**Table 3A**); however, cystatin C was not correlated with CIMT in any participants, unrelated to gender (**Table 3B**). In addition, we analyzed the association between eGFR, which is routinely used as a surrogate marker of kidney function, and CAVI or CIMT using multivariate analysis, but did not find any association between eGFR, and CAVI or CIMT in any participants (**Table 4A** and **4B**).

Table 2. Simple correlation analysis of CysC and other variables

	Men	Women	All participants
Age	0.374**	0.347**	0.343**
BMI	0.145	0.287**	0.239**
WC	0.212**	0.320**	0.291**
SBP	0.092	0.160**	0.134**
TG	0.226**	0.199**	0.209**
HDL-C	−0.190*	−0.208**	−0.222**
LDL-C	0.098	0.129*	0.085
UA	0.244**	0.312**	0.332**
HbA1c	0.042	0.106	0.076
U-Alb/Cre	−0.009	0.086	0.005
Cre	0.420**	0.426**	0.426**
eGFR	−0.516**	−0.513**	−0.495**
CIMT	0.228**	0.108	0.181**
CAVI	0.240**	0.247**	0.256**

*$p<0.05$ and **$p<0.01$

Discussion

In this study, we investigated the association between cystatin C and arteriosclerosis in adult Japanese subjects who underwent a physical examination, who were determined not to have CKD based on the absence of proteinuria and eGFR >60 mL/min. In consideration of the effects of age, BMI, diabetes mellitus, dyslipidemia, hypertension, and smoking, we found a significant correlation between cystatin C and CAVI in women.

The association between progressive impairment of kidney function and arteriosclerosis with CVD has been previously demonstrated[3, 4]; however, in people without CKD, the association between cystatin C and arteriosclerosis has been unclear. Although a few studies have investigated the association between arteriosclerosis and serum cystatin C, which is considered more sensitive in detecting early-stage renal impairment as compared to serum creatinine[31-33], their results have differed due to variations in the targets and indicators used for arteriosclerosis. Thus, in the present study, we simultaneously measured CAVI, CIMT, and serum cystatin C levels in a non-CKD population; to the best of our knowledge, this is the first report to demonstrate that cystatin C was associated with CAVI in female non-CKD subjects with no proteinuria and eGFR >60 mL/min.

These findings indicate that a slight decrease in kidney function even within the normal range may promote arteriosclerosis, similar to the report by Verhave *et al.* that arteriosclerotic risk factors, such as increasing diastolic blood pressure and serum triglycerides, were associated with a decrease in kidney function in the population who had normal kidney function[34]. On the other hand, our results also showed that very mild dysfunction caused by arteriosclerosis might be detected by cystatin C.

After adjustment for cofounding factors, we could not find a significant association between cystatin C and CIMT. A number of studies have investigated the association between cystatin C and CIMT as a marker of arteriosclerosis; these studies targeted a healthy Chinese population[20], middle-aged adults in the Seychelles[23], and cardiovascular disease-free people[22]; however, no relationship was observed between cystatin C and CIMT in these studies, as in our study. On the other hand, a study that targeted hypertensive patients reported a positive correlation between cystatin C and CIMT[24, 26]. One reason for this result might be the insufficient number of participants. Furthermore, our results can be explained by a report that CAVI could detect arterial stiffness prior to evident carotid arteriosclerosis and high CAVI might imply the progression of carotid arteriosclerosis[35]; that is, CAVI may be more sensitive than CIMT for detecting arteriosclerosis.

Furthermore, the difference between men and women in the smoking rate might explain why a significant association between cystatin C and CAVI was not observed in men. In our subjects, the smoking rates were 23.2% in men and 3.0% in women. Previously, it was reported that elevated cystatin C was independently associated with smoking[36]. Cystatin C is the most widespread and potent inhibitor of cathepsins B and L and it has been considered that a cathep-

Table 3A. Multiple linear regression analysis of CysC with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	0.319	<0.001	0.404	<0.001	0.306	<0.001
UA	0.116	0.018	0.134	0.051	0.154	0.005
BMI	0.169	<0.001	0.136	0.042	0.194	<0.001
Diabetes mellitus	−0.006	0.886	0.012	0.847	0.016	0.748
Dyslipidemia	0.033	0.417	0.029	0.661	−0.029	0.573
Hypertension	−0.042	0.336	−0.031	0.635	−0.070	0.245
Smoking	0.052	0.205	0.202	0.002	−0.030	0.559
Cre	0.349	<0.001	0.397	<0.001	0.392	<0.001
CAVI	0.075	0.101	0.042	0.569	0.117	0.049

β: regression coefficient; CI: confidence interval.

Table 3B. Multiple linear regression analysis of CysC with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	0.363	<0.001	0.394	<0.001	0.384	<0.001
UA	0.129	0.008	0.150	0.030	0.182	0.001
BMI	0.162	<0.001	0.145	0.029	0.164	0.003
Diabetes mellitus	−0.001	0.987	0.010	0.874	0.027	0.586
Dyslipidemia	0.038	0.341	0.027	0.675	−0.032	0.541
Hypertension	−0.032	0.456	−0.033	0.611	−0.039	0.510
Smoking	0.060	0.144	0.202	0.002	−0.003	0.961
Cre	0.353	<0.001	0.394	<0.001	0.395	<0.001
CIMT	0.015	0.736	0.089	0.206	−0.062	0.280

β: regression coefficient; CI: confidence interval.

sin-cystatin C imbalance causes tissue destruction; therefore, elevated cystatin C influences the state of lung tissue destruction, such as emphysema. We consider that cystatin C in smokers might be possibly elevated not only as a result of early renal dysfunction but also as a direct response to smoking. In our study, smoking might have influenced our results since cystatin C was significantly related to smoking in men. In addition, our subjects were comparatively older. It is well known that kidney function is correlated negatively with age. In fact, a strong correlation has been reported between cystatin C and age, regardless of the presence of impaired renal function[37-40]. Since the average age of our subjects was 67.0 years, there is a possibility that age influenced the serum cystatin C values. Moreover, it is known that women develop arteriosclerosis and cardiovascular disease typically after the menopause. As the mean age of women in our study was 67.4 years, ovarian hormone deprivation might also have affected our result that cystatin C was related to CAVI only in women.

In this study, we adopted cystatin C and eGFR as surrogate markers of renal function. Currently, eGFR is accepted as a surrogate marker of kidney function worldwide; however, Coll *et al.* reported that serum cystatin C levels began to increase beyond the normal limit when the GFR was 88 mL/min/1.73 m^2, whereas serum creatinine levels began to increase when the GFR was 75 mL/min/1.73 m^2 [41]. These data suggest that the measurement of serum cystatin C may be useful for estimating GFR, especially for detecting mild reductions in GFR, and may therefore be important in the detection of early renal insufficiency in a variety of renal diseases for which early treatment is critical.

In this study the subjects had eGFR >60 mL/min and relatively intact renal function; therefore, we considered that cystatin C was a more sensitive marker than eGFR for detecting slight decreases in GFR. We subsequently focused upon the correlations of cystatin

Table 4A. Multiple linear regression analysis of eGFR with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	−0.010	0.841	−0.099	0.229	0.037	0.586
UA	−0.090	0.052	−0.199	0.003	−0.126	0.333
BMI	0.066	0.147	0.110	0.105	0.036	0.565
Diabetes mellitus	0.027	0.513	0.015	0.864	0.016	0.762
Dyslipidemia	−0.114	0.006	−0.136	0.037	−0.062	0.264
Hypertension	−0.049	0.278	−0.034	0.600	−0.066	0.301
Smoking	0.154	<0.001	0.203	0.002	−0.041	0.451
CysC	−0.462	<0.001	−0.444	<0.001	−0.462	<0.001
CAVI	−0.030	0.529	0.016	0.829	−0.060	0.343

β: regression coefficient; CI: confidence interval.

Table 4B. Multiple linear regression analysis of eGFR with relevant factors

	All		Men		Women	
	β	*p* value	β	*p* value	β	*p* value
Age	−0.008	0.876	−0.067	0.398	0.032	0.635
UA	−0.097	0.036	−0.200	0.004	−0.133	0.025
BMI	0.066	0.145	0.116	0.087	0.038	0.531
Diabetes mellitus	0.026	0.523	0.019	0.766	0.013	0.813
Dyslipidemia	−0.117	0.005	−0.129	0.047	−0.065	0.238
Hypertension	−0.044	0.322	−0.029	0.658	−0.063	0.314
Smoking	0.157	<0.001	0.212	0.001	−0.043	0.432
CysC	−0.464	<0.001	−0.445	<0.001	−0.469	<0.001
CIMT	−0.035	0.456	−0.032	0.653	−0.059	0.330

β: regression coefficient; CI: confidence interval.

C with CAVI and CIMT, although it is unfortunate that our results only led to the conclusion that cystatin C is superior to eGFR with regard to the association with arteriosclerosis. In contrast, although the urinary albumin-to-creatinine ratio (UACR) is also known to be a sensitive marker of kidney injury, no significant association was observed between UACR and cystatin C or eGFR in our study. UACR mainly reflects glomerular injury or increased intra-glomerular pressure, but not GFR, while cystatin C is a sensitive marker that reflects GFR[42]. In other words, while cystatin C and UACR are both markers of kidney dysfunction, we consider that they reflect fundamentally different conditions. One such example is nephrosclerosis, which is an underlying disease of chronic kidney failure; even when proteinuria is not observed, this entity leads to decreased kidney function, wherein cystatin C or eGFR and UACR do not necessarily display identical changes. Therefore, although no correlation was observed between cystatin C and UACR, we consider that our result is helpful for subjects whose eGFR is >60 mL/min with no evident proteinuria.

Apart from renal function, classical risk factors for arteriosclerosis, such as hypertension, DM, dyslipidemia, and smoking, may also affect the level of CAVI or CIMT; this may have affected our results. The relationship of DM and LDL-C with kidney function and arteriosclerosis has been previously demonstrated[43, 44]; however, no association between DM and cystatin C was observed in our study and we believe that this was because the overall proportion of DM patients was only 6.7%. With regard to the association between cystatin C and dyslipidemia, although univariate analysis found no correlation between LDL-C and cystatin C, a significant negative correlation was observed between cystatin C and HDL-C. Low HDL-C is also defined as dyslipidemia and is believed to be a risk factor for arteriosclerosis[45]; therefore, we consider that our results are consistent with previous studies. In this study, the mean LDL-C (143

mg/dL) was relatively low, which may have influenced the lack of a significant association between cystatin C and LDL-C.

There were some limitations of our study. First, our subjects were selected within a confined geographical area. Thus, our results might have been affected by this selection bias. We therefore hope for future large-scale studies. Second, there is no standard assay system or cutoff value for cystatin C[46]. The possibility that the lack of such standards affected the results of not only our study but also previous research cannot be ruled out. It is therefore necessary to define a cutoff value for cystatin C and to establish a universal assay system for cystatin C.

In conclusion, we observed a significant correlation between cystatin C and CAVI in women in a non-CKD population with no proteinuria and eGFR >60 mL/min. This may imply that patients with a high level of cystatin C, even within the normal range, have the potential to develop CKD or CVD. Therefore, patients with high levels of cystatin C or CAVI in medical screening studies should be carefully monitored for kidney function and arteriosclerosis severity in order to prevent CKD or CVD.

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Conflicts of Interest

None.

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I. 血栓と腎の病態

4. 腎臓病と血管炎

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§論文のポイント

[1] 血管炎とは液性免疫・細胞性免疫の異常などによって血管壁に炎症が生じる病態であり，全身性の炎症性疾患である．

[2] 罹患する血管のサイズに基づいて分類する Chapel Hill 分類が用いられてきたが，2013 年に新分類である CHCC2012 が発表された．

[3] 炎症に伴う全身症状と多臓器の虚血や出血による多彩な症状を呈するが，特に腎臓は血管に富み血管炎の好発臓器である．

[4] 近年，小血管を主体とした壊死性血管炎である ANCA 関連血管炎が増加しているが，急速進行性糸球体腎炎を呈し，病理学的には半月体形成性の糸球体腎炎が認められることが多い．

[5] ANCA 関連血管炎については，日米欧での前向き試験などから診断基準や標準治療法が確立されつつある．

§キーワード

Chapel Hill 分類／CHCC2012／ANCA 関連血管炎／急速進行性糸球体腎炎／半月体形成性糸球体腎炎