

Nontraditional Biomarkers for Cardiovascular Disease in Patients With Chronic Kidney Disease

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Cardiovascular disease (CVD) is the leading cause of death among patients who have chronic kidney disease (CKD). Nowadays, CKD per se is considered one of the coronary heart disease (CHD) risk equivalents. Apart from traditional CVD risk factors, there are several possible determinants for CVD in patients with CKD, for example, uremic toxins, increased inflammatory stage, abnormal bone mineral metabolism, and positive calcium balance. In this narrative review, we offer a summary of the extensively studied biomarkers for CVD in patients with CKD, including uremic toxins (p-cresol, indoxyl sulfate, and advanced glycated end products), and a novel indicator of arterial stiffness, cardio-ankle vascular index (CAVI), which is an independent prognostic predictor for CVD. For the uremic toxins, we reviewed their metabolisms, particularly, how the reduced renal function in CKD patients affect their clearance and their clearance with dialysis. Also, we pay attention to the recent evidence on how those uremic toxins contribute to CVD and their clinical associations. We do not include the possible treatment targeting at those uremic toxins. As for the novel indicator of arterial stiffness, we reviewed the clinical application of CAVI in comparison to the standard indicator for arterial stiffness, pulse wave velocity.

Keywords: P-cresol, Indoxyl sulfate, Advanced glycated end products, Cardio-ankle vascular index, Chronic kidney disease, Dialysis

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Introduction

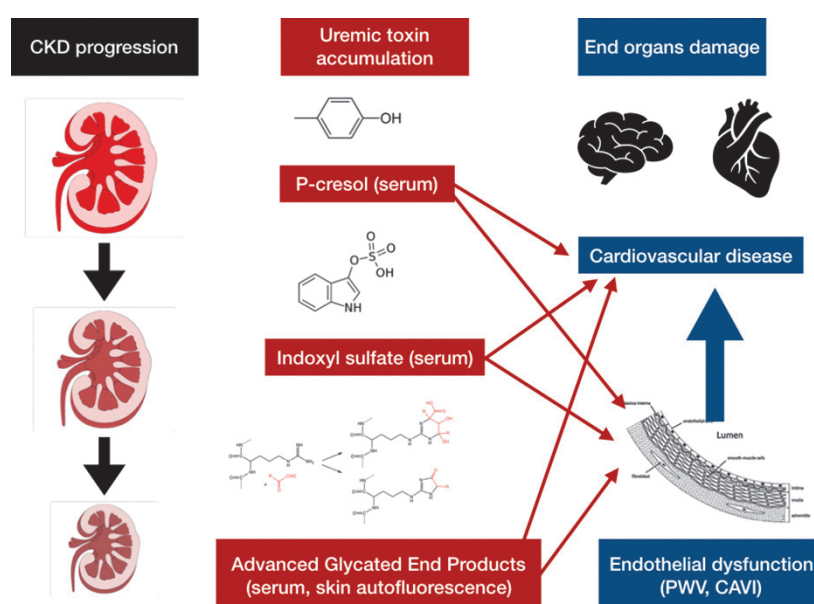
Cardiovascular disease (CVD) is a group of disorders that involves the heart and blood vessels. CVD is categorized in 4 areas, which are coronary heart disease (CHD), cerebrovascular disease, peripheral artery disease, and aortic atherosclerosis /thoracic or abdominal aneurysm.

CVD is common in the general population, and it is the leading cause of death globally. Based on data from the World Health Organization (WHO), an estimated 17.9 million people died from CVD in 2016, representing 31% of all global deaths. CHD accounts for approximately one-third to one-half of the total cases of CVD. Some people without known CHD have a risk of developing cardiovascular events equivalent to those with established CHD (a 10-year risk of developing cardiovascular events higher than 20%). Those high-risk patients include the noncoronary atherosclerotic arterial disease (carotid artery disease, peripheral artery disease, and abdominal aortic aneurysm), diabetes mellitus, and chronic kidney disease (CKD).

CKD is an independent risk factor for the development of CVD. Several studies have identified that a reduced glomerular filtration rate (GFR) and proteinuria are both independently associated with an increased risk of cardiovascular events in community-based populations. In patients with CKD, numerous risk factors are contributing to the development of CVD, which are divided into traditional and nontraditional risk factors. Tradition risk factors include age, hypertension, diabetes, dyslipidemia, smoking, and metabolic syndrome. As for nontraditional risk factors, possible determinants for CVD in patients with CKD include retention of uremic toxins, anemia, elevated certain cytokines, increased inflammatory stage, poor nutritional state, positive calcium balance, and abnormal bone mineral metabolism.

In this review, we focus on the clinical association of the extensively studied novel biomarkers for CVD, including uremic toxins (p-cresol, indoxyl sulfate, and advanced glycated end products), and a novel indicator of arterial stiffness, cardio-ankle vascular index (CAVI), which is an independent prognostic predictor for CVD (Figure 1).

Figure 1. Schematic Diagram Depicting the Chronic Kidney Disease Progression Leading to Uremic Toxins Accumulation and Endothelial Dysfunction and Cardiovascular Disease



Abbreviations: CAVI, cardio-ankle vascular index; CKD, chronic kidney disease; PVW, pulse wave velocity.

Uremic Toxins

P-Cresol

P-cresol, considered a prototype of protein-bound uremic toxin, is a small phenolic compound with a small molecular weight of 188.2 g/mol. P-cresol is produced by bacteria in the large intestine by catabolizing tyrosine and phenylalanine. It is detoxified in the intestinal wall and the liver by conjugation processes into p-cresyl sulfate and p-cresyl glucuronide. P-cresyl sulfate is the main conjugated p-cresol in the human body. This conjugated metabolite exerts various toxic effects in vivo. Toluene, cigarettes, and herbal medications are examples of environmental sources of p-cresol.

P-cresyl sulfate is primarily cleared by kidneys. Accordingly, as renal function declines, p-cresyl sulfate is gradually accumulated, as early detected as in CKD stage 2.¹ In chronic dialysis patients, it has been known that p-cresol is poorly removed with standard hemodialysis (HD) despite the small molecular weight. This limited clearance is contributed to its strong protein-bound affinity.² The study of intradialytic removal of protein-bound uremic toxin found that there is no beneficial effect in p-cresol removal with high-flux hemodialysis (HF-HD) when compared with low-flux hemodialysis (LF-HD).² However, p-cresol appears to be efficiently removed with a convective than a diffusive approach as hemofiltration (HF) and hemodiafiltration (HDF) have superior dialytic clearance of p-cresol than standard HD.³ The study of removing protein-bound p-cresol with fractionated plasma separation and adsorption, a nonbiologic detoxification system for treatment of liver failure, shows promising results. However, significant coagulation disturbance resulting in arteriovenous access thrombosis raises a concern. In the in vitro study, adding an adsorptive material, hollow fiber mixed matrix membrane, on a high-flux membrane markedly enhances the removal of protein-bound solutes, including p-cresyl sulfate.⁴ As for peritoneal dialysis (PD), p-cresol is less removed by PD when compared to HF-HD.⁵ However, serum p-cresol level has been reported to be lower in PD patients. This finding is likely due to the

residual renal function as the native kidneys can filter protein-bound solutes more effectively than dialysis.⁵

In regard to the clinical outcomes, several studies have reported that accumulation of serum p-cresol is implicated with uremic symptoms, increased hospitalization mainly related to infection, increased cardiovascular disease and increased overall mortality independently with traditional CVD risk factors.⁶ P-cresyl sulfate induces the shedding of endothelial microparticles, which might act as proinflammatory or prothrombotic mediators leading to increased susceptibility to vascular damage and cardiovascular disease.⁷ P-cresyl glucuronide, the second conjugated p-cresol, also has a role in the activation of an inflammatory response by exerting a synergistic effect with p-cresyl sulfate on leukocyte activation and direct vascular toxic effect as demonstrated in an animal model study. In addition to the activation of the immune system, p-cresyl sulfate also has direct renal toxicity through various mechanisms, including proximal tubular cell damage through increased inflammatory response, glomerulosclerosis, and fibrosis through activation renin-angiotensin-aldosterone system and suppression of Klotho gene expression as demonstrated in a rat model.

Indoxyl Sulfate

Indoxyl sulfate, another uremic toxin, is a hepatic metabolite of L-tryptophan from indole, which is produced by intestinal microbiota. Indoxyl sulfate is a highly protein-bound, small solute, with a molecular weight of 213.21 g/mol. As indoxyl sulfate is cleared by the kidneys through tubular secretion, a decline of renal function is primarily responsible for an accumulation of indoxyl sulfate.⁸ Also, diet plays an essential role in the production of indoxyl sulfate. The higher level of indoxyl sulfate has been observed with the consumption of the high protein diet, as indoxyl sulfate is a metabolite of tryptophan.

As indoxyl sulfate is at least 90% bound to plasma proteins, its clearance by HD is limited.² In standard HD, superflux HD is superior to LF-HD for the removal of indoxyl sulfate.⁹ Increasing convection with HDF can increase the clearance of indoxyl sulfate; however,

the effect may not be sustained in the long term as a re-elevation of predialysis indoxyl sulfate levels was observed several weeks later.¹⁰⁻¹¹ Increasing diffusion by either adding a dialysate absorbent (activated charcoal), increasing dialysate flow, or utilizing a dialyzer with a higher dialyzer mass transfer area coefficient, is another strategy to enhance the clearance of indoxyl sulfate. In the *in vitro* study of the mixed matrix membrane (activated charcoal coated outer membrane) to enhance absorption of protein-bound solutes, the application of this membrane can effectively remove a more significant portion of indoxyl sulfate.⁴

Regarding the clinical outcomes, an accumulation of indoxyl sulfate may contribute to kidney disease and vascular disease.¹² Oral administration of indoxyl sulfate can stimulate glomerular sclerosis in uremic rats. Indoxyl sulfate can induce kidney fibrosis through several mechanisms, including activation of nuclear factor- κ B (NF- κ B), upregulation of plasminogen activator inhibitor-1 (PAI-1) expression, increase in production of inflammatory cytokines, activation of the renin-angiotensin-aldosterone system,¹³ and suppression of Klotho gene expression. In prospective studies in humans, an increase in indoxyl sulfate has been shown to be associated with the progression of kidney disease.¹⁴ However, the association may have been influenced by p-cresol, which is a known predictor of kidney disease progression. Indoxyl sulfate is believed to cause vascular injury by inhibiting endothelial cell proliferation and repair and promoting vascular smooth muscle cell proliferation. This injury to blood vessels may lead to atherosclerosis. Moreover, in several clinical studies, indoxyl sulfate has been reported to be associated with other cardiovascular outcomes including coronary artery atherosclerosis, cardiac stent restenosis in patients receiving drug-eluting stent implantations, left ventricular diastolic dysfunction, hospitalization for heart failure in patients with dilated cardiomyopathy, and aortic calcification.⁸ The meta-analysis of the association of indoxyl sulfate with cardiovascular events shows that increased indoxyl sulfate was associated with overall mortality but not CVD events.¹⁵

Advanced Glycated End Products

The advanced glycation end product (AGE) is a heterogeneous group of compounds derived from the nonenzymatic glycation reactions between reducing sugars and proteins, lipids, or nucleic acids through a complex sequence of reactions. Among several types of AGEs, pentosidine, N-carboxymethyl lysine, methylglyoxal (MG), and hydroimidazolones are best characterized and serve as markers of AGE accumulation in several tissues.

AGEs can be generated endogenously in response to hyperglycemia or formed in conditions with high oxidative stress. Exogenous exposure of AGEs includes diet,¹⁶ particularly cooked under dry and high heat conditions, and cigarettes. In patients with CKD, markedly increased AGEs are not only due to their decreased clearance but also due to spontaneous production of AGEs by the endogenous formation in response to uremia. The elevation of the pentosidine level is independent of hyperglycemia in the uremic stage. Moreover, uremic patients have higher glycated low-density lipoprotein (LDL), which is more prone to oxidation than nonglycated LDL. Chronic dialysis patients are known to have elevated reactive oxygen species (ROS) and reduced antioxidant levels, which further results in increased formation of AGEs.¹⁷ Interestingly, dialysis membrane types per se may be associated with a different degree of AGE accumulation, as demonstrated in the study of different types of dialysis membranes with different degrees of predialysis pentosidine levels.¹⁸

Several pathways involving in AGE homeostasis include AGE homeostasis: degradation of AGEs by glyoxalase I (Glo-1) and glyoxalase II (Glo-2), modification of AGEs by lysozyme, which enhances their renal excretion, and receptor-dependent uptake and degradation. Advanced glycation end products receptor 1 (AGER1), a transmembrane receptor, plays a role in AGE degradation. AGER1 binds AGEs and leads to their sequestration and intracellular degradation. If these mechanisms are overwhelmed by elevated AGEs, AGEs can trigger inflammatory and oxidative pathways, which leads to activation of immune cascade resulting in endothelial dysfunction and tissue damage. Interestingly, AGER1,

which has antioxidant properties, is downregulated by elevated AGE levels leading to a decrease in negative regulation of inflammatory responses. In contrast to AGER1, another receptor that binds AGEs and initiates oxidative stress is the receptor for advanced glycation end product (RAGE), a transmembrane cell surface immunoglobulin (Ig) protein receptor. Interaction of AGEs and RAGE initiates a cascade of intracellular signaling leading to activation of inflammatory responses and eventually producing ROS. The elevated ROS results in the production of inflammatory cytokines, recruitment of inflammatory cells to the vessel wall, and formation of the extracellular matrix, which amplify the development of vascular inflammation and atherosclerosis. Besides, an increase in AGE levels, such as pentosidine, is associated with increased coronary artery calcification. In addition to transmembrane cell surface RAGE, the soluble form of RAGE (sRAGE), which is released into circulation and sequesters AGEs, may also be implicated with clinical outcomes. Recent data shows that high circulating sRAGE level was associated with an increased incidence of CKD and dialysis risk, but not after adjustment for baseline kidney function.¹⁹ Further studies are needed to elucidate the association between AGEs and sRAGE.

The methods of AGE measurement can be performed by directly measuring plasma pentosidine or utilizing skin autofluorescence (SAF) to detect AGEs deposited in the subcutaneous tissue. In dialysis patients, even though plasma AGE sampling is convenient and straightforward, the plasma AGE is influenced by HD as its level is reduced by 14% after HD, whereas SAF is not affected by HD.²⁰ It has been suggested that SAF can be performed during the whole HD period.²⁰ SAF, a novel technique of estimation of AGE accumulation, not only offers a less invasive technique, but it is also reliable and reproducible with low intraobserver variability. Moreover, it is cost-effective and may be useful for rapid assessment for AGE accumulation. To date, AGE SAF is produced in the Netherland (AGE Reader, Diagnostics) and China (DM Scan, Chinese Academy of Sciences). The Netherland model has been validated in Europe, the US, and Japan. However, skin complexion and pigmentation in the South-East Asian and African

populations may limit its use.¹⁶ The China model may be more applicable to the Asian population as the database of the SAF detection correlation model was studied in Chinese subjects. The study using this machine shows that elevated SAF was a significant risk factor for developing CKD in diabetic patients. In comparison to the Netherland model, the China model comes with a lower cost. However, its validation and reproducibility will need to be explored.

As a significant portion of AGEs, particularly pentosidine, are bound to plasma protein, even though the free form of pentosidine is effectively removed by HF-HD, the clearance of total pentosidine is marginal.²¹ When compared with HF-HD, HDF may prevent further accumulation of AGEs. The prospective study from the UK regarding the effect of on-line HDF shows that AGE levels continued to increase over time in the HF-HD group but not in the HDF group.²² As with HD, the AGE levels are also increased in chronic PD patients. Glucose-containing dialysate and heat sterilization of dialysate can contribute to increased AGE accumulation in the mesothelial layer of peritoneum, which may lead to peritoneal fibrosis. When compared with HD, PD has a higher clearance of AGEs, such as pentosidine. Higher albumin clearance in PD is likely contributed to the greater AGE clearance. Moreover, residual renal function plays an essential role in AGE clearance and may alleviate AGE accumulation in chronic dialysis patients. It has been reported that the residual urine volume greater than 250 mL/day is negatively associated with AGE levels.²²

As for the clinical outcomes, an association between AGEs and cardiovascular outcomes has been extensively studied. Several studies of serum and skin AGEs show that accumulated AGEs were associated with increased carotid artery intima-media thickness (IMT), increased carotid artery pulsatility index, reduction in carotid distensibility, increased cardiovascular and overall mortality independently from traditional CVD risk factors.²³ Skin AGE has been reported as an independent determinant of serum C-reactive protein (CRP) levels, which is a well-established predictor of cardiovascular disease. Dysregulation of the immune system associated with AGEs can contribute to

atherosclerosis in dialysis patients. The formation and accumulation of AGEs could activate the immune system through monocyte activation and complement dysregulation leading to vascular inflammation. Moreover, AGEs may be implicated with dialysis-related amyloidosis. The AGE-modified β 2-microglobulin can initiate the inflammatory response by enhancing the migratory activity of monocytes and activate inflammatory cytokines. These can ultimately result in the development of CVD.

Cardio-Ankle Vascular Index

Arterial function and structural alterations are known to be associated with CVD. Recently, there has been a growing interest in arterial wall properties, particularly arterial stiffness, in predicting CVD outcomes. The arterial stiffness reflects the distensibility and contractility of the arterial wall in response to pressure changes. The arterial stiffness is responsible for pathologic processes and has been identified as an independent prognostic predictor for CVD.

The pulse wave velocity (PWV), the velocity at which the blood pressure pulse propagates along the arterial tree, is widely used to measure arterial stiffness. However, its accuracy is hindered by changes in blood pressure. Moreover, PWV does not reflect the pathological changes of atherosclerosis until its advanced stage when calcification develops in the atherosclerotic plaque.²⁴ Given the major limitation of PWV, the cardio-ankle vascular index (CAVI) has been proposed as a new method in the evaluation of atherosclerosis.²⁵ CAVI is obtained by recoding the distance from the level of the aortic valve (the brachial level) to the measuring point (the ankle) and the time delay from the closing of the aortic valve to the detected change in arterial pressure wave at the measuring point.²⁴ In theory, CAVI is independent of changes in blood pressure. According to the manufacture's instruction (Fukuda-Denshi Company L, Tokyo, Japan), a CAVI score equal to or greater than 9.0 is suspicious for arteriosclerosis, whereas CAVI scores less than 8.0 is considered normal.

CAVI has been used in several clinical studies, particularly those involving the assessment of arterial

stiffness to establish CVD in high-risk populations. CAVI has been reported to be correlated with other well-established vascular indices such as ankle-brachial PWV, increased carotid intima-media thickness, a presence of carotid arterial plaque.²⁶ CAVI has not only been found to reflect coronary artery plaque burden in patients with known coronary heart disease, but can be useful to evaluate the prognosis and the risk for subclinical coronary atherosclerosis in asymptomatic patients.²⁷ In hypertensive patients, CAVI is independently associated with elevated plasma BNP (an indicator of left ventricular afterload). Also, in chronic hemodialysis patients, CAVI has been identified as an independent determinant of left ventricular diastolic dysfunction.²⁸ In addition to the association between CAVI and atherosclerosis, CAVI is also implicated with small vessel diseases. CAVI is sensitive in the detection of early diabetes-associated microvascular complications such as diabetic polyneuropathy and microalbuminuria in diabetic nephropathy.²⁶ Several studies suggest that CAVI is an independent factor associated with cerebral arteriosclerosis, including white matter lesions, silent lacunar infarction, and cerebral microbleeds.¹¹ The recent study showed higher CAVI in diabetic CKD compared to control and higher CAVI was independently associated with traditional and nontraditional risk for CVD.²⁹

Homocysteine

Homocysteine is a sulfhydryl-containing amino acid produced by the demethylation of dietary methionine. The elevation of the homocysteine level is related to CVD through an increased inflammatory stage. Accumulation of homocysteine can lead to the stimulation of macrophages by activating NF- κ B, via superoxide anion generation, and increasing monocyte chemoattractant protein-1 expression.³⁰ Moreover, homocysteine can directly stimulate vascular smooth muscle cell proliferation. In CKD patients, the homocysteine level is 2 - 4 times higher than the general population and possibly contributes to accelerated atherosclerosis.³¹

Guanidine

Guanidine is a small uremic toxin with a molecular weight of 59.07 g/mol. Among guanidine compounds, asymmetric and symmetric dimethylarginine (ADMA and SDMA) have been increasingly recognized as toxic amino acids. Once a renal function declines, ADMA and SDMA start to accumulate. Also, like other protein-bound uremic toxins, they are difficult to be removed by conventional HD. In addition to the known neurotoxicity of ADMA and SDMA,³² they also have adverse cardiovascular effects. The proposed mechanisms are the reduction of the endothelial protective nitric oxide synthase and the production of tumor necrosis factor α (TNF- α), leading to increased free radical released from inflammatory cells.^{33,34}

Other Biomarkers

There are other potential novel biomarkers in association with CVD in patients with CKD, such as phenylacetic acid,³⁵ resistin,³⁶ and ischemic modified albumin.³⁷ However, the evidence of these biomarkers remains scarce, and their clinical application in everyday practice are still limited.

Conclusions

CKD is an independent risk factor for the development of the cardiovascular disease. In addition to the traditional CVD risk factors, there are substantial evidences to show the association between the development of cardiovascular disease and accumulated uremic toxins, such as P-cresol, indoxyl sulfate, and AGEs, in patients with renal failure. As their high protein-bound affinity, the removal of these solutes by dialysis is challenging. Further studies are required to improve their clearance and establish clinical outcomes.

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ตัวชี้วัดใหม่สำหรับโรคหัวใจและหลอดเลือดในผู้ป่วยโรคไตเรื้อรัง

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โรคหัวใจและหลอดเลือดเป็นสาเหตุการตายที่สำคัญในผู้ป่วยโรคไตเรื้อรัง ปัจจุบันโรคไตเรื้อรังนั้นถูกจัดเป็นหนึ่งในปัจจัยเทียบเท่าความเสี่ยงต่อโรคเส้นเลือดหัวใจ นอกเหนือจากปัจจัยดั้งเดิมต่อโรคหัวใจและหลอดเลือดแล้วยังมีหลายปัจจัยที่ส่งผลต่อการเกิดโรคหัวใจและหลอดเลือดในคนไข้ที่มีโรคไตเรื้อรัง เช่น สารพิษในเลือดสถานะที่มีการเพิ่มขึ้นของการอักเสบ และความผิดปกติของระบบการควบคุมเกลือแร่และกระดูก รายงานการทบทวนบทความนี้ได้สรุปดัชนีชี้วัดทางชีวภาพต่อการเกิดโรคหัวใจและหลอดเลือดที่ได้มีการศึกษาอย่างแพร่หลาย ได้แก่ สารพิษในเลือด (P-cresol, Indoxyl sulfate, และ Advanced glycated end products) และตัววัดความแข็งของหลอดเลือดแดง (Cardio-ankle vascular index, CAVI) ซึ่งเป็นปัจจัยพยากรณ์การเกิดโรคหัวใจและหลอดเลือด โดยบทความนี้มุ่งเน้นไปที่ระบบการขับออกทางไตของสารพิษในเลือดดังกล่าวในคนไข้โรคไตเรื้อรังและการกำจัดสารพิษด้วยการบำบัดไตทดแทน นอกจากนี้ บทความนี้ได้ทบทวนหลักฐานที่สารพิษในเลือดดังกล่าวสามารถส่งผลต่อการเกิดโรคหัวใจและหลอดเลือดและอาการทางคลินิก อย่างไรก็ตาม บทความนี้ไม่ได้ทบทวนการรักษาที่เกี่ยวข้องกับสารพิษในเลือด แต่เป็นการทบทวนการประยุกต์ใช้ทางคลินิกของตัววัดความแข็งของหลอดเลือดแดงเปรียบเทียบกับความเร็วคลื่นความดันหลอดเลือดแดง (Pulse wave velocity) ซึ่งเป็นตัววัดความแข็งของหลอดเลือดแดงมาตรฐาน

คำสำคัญ: สาร P-cresol สาร Indoxyl sulfate สาร Advanced glycated end products ตัววัดความแข็งของหลอดเลือดแดง โรคไตเรื้อรัง การฟอกเลือด

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