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Vascular dysfunction and atherosclerosis in chronic kidney disease; A distinct entity

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ABSTRACT

Cardiovascular disease (CVD) is prevalent among patients with chronic kidney disease (CKD) and its occurrence and severity cannot be fully defined by the conventional cardiovascular risk factors namely age, hypertension, dyslipidaemia, diabetes mellitus and obesity. Contemporary studies have examined the role of non-conventional risk factors such as anemia, hyperhomocysteinemia, calcium and phosphate metabolism, vascular stiffness due to endothelial dysfunction (ED), oxidative injury, and inflammation in the causation of CVD in CKD. Therapeutic interventions used in non-CKD patients are found to be less effective on patients with CKD. The purpose of this review was to gather available evidence on the CVD risk among CKD patients. Numerous mechanisms have been postulated to describe the increased atherogenicity in CKD patients. We discuss these mechanisms especially arterial stiffness, ED and inflammation in detail. In conclusion, CVD in CKD is still an unexplored area which needs further studies to uncover the possible mechanisms. Identifying newer therapies to improve health among this group of patients is of paramount importance.

Review

Implication for health policy/practice/research/medical education:
Summarizing the available literature on the increased cardiovascular risk and postulated mechanisms among patients with chronic kidney disease guides the future researchers. Revealing new mechanisms or risk factors may have a significant impact on the healthcare management and policy.

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1. Background

Chronic kidney disease (CKD) is a serious global health problem. Despite optimum treatment, growing number of patients, progress to end stage renal failure (ESRF) requiring regular dialysis and kidney transplant (KT). Currently more than one million patients worldwide are on dialysis with the numbers increasing every year (1). There are 30 dialysis centres in state hospitals in Sri Lanka equipped with 284 dialysis machines providing dialysis to patients with ESRF, free of charge (2). This is a considerable financial burden to the healthcare expenditure in the country. The probability of cardiovascular disease (CVD) is increased in patients with CKD and results in premature death due to CVD than other causes (3-5). Decline in gromerular filtration rate (GFR) is associated with increased CVD risk (6) and patients with ESRF have increased cardiovascular morbidity and mortality (7).

Increased risk of CVD in CKD cannot be solely described by the conventional cardiovascular risk factors like hypertension, diabetes mellitus, obesity and dyslipidemia (8). This raises the possibility that vasculopathy leading to CVD in CKD is a distinct yet uncertain entity.

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Numbers of studies in the recent past have discussed the role played by the non-traditional CVD risk factors in CKD (9,10). Non-conventional risk factors identified include anemia, hyperhomocysteinemia, calcium and phosphate metabolism, vascular stiffness, oxidative injury, and inflammation (11,12). Furthermore, therapeutic interventions used in patients with CVD without renal dysfunction are found to be less protective in patients with CVD complicated by CKD. Drugs such as statins are less effective in declining CV mortality in patients with CKD or ESRF (13-17). A study on atherosclerotic animal models has shown that statins are less effective in reducing the degree of atherosclerosis in the uremic background (18). Furthermore, dialysis did not reduce the CV mortality in a group of patients (19). In addition, these would support the assumption that CVD in CKD is a distinct entity.

Despite optimum preventive measures, the CV mortality in ESRF was consistent over the last 20 years while there is an urgent need to understand the underlying mechanisms of CVD mortality in CKD especially in ESRF (20). This will enable identifying specific therapies which are efficient in managing CVD events in patients with renal impairment (12).

The objective of this review was to gather the existing evidence on the CVD risk in patients with CKD.

2. Atherosclerosis and CKD

Number of mechanisms has been suggested to explain the high level of atherogenicity in CKD patients. D'Apolito et al found that increased urea concentration in CKD leads to greater production of mitochondrial reactive oxygen species (ROS) by the arterial endothelial cells triggering pro-atherosclerotic pathways. Further, ROS inactivate the endothelial specific anti-atherosclerotic enzyme, PGI_2 synthase. Therapeutics which directly target urea mediated ROS production may improve the overall health of ESRF patients (10).

Studies have shown an impaired one-carbon metabolism leading to DNA hypomethylation in patients with CKD (21-23). However, Nanayakkara et al did not find an impairment of global DNA methylation in initial stages of CKD, in the absence of diabetes or clinical signs of atherosclerosis. They concluded that DNA hypomethylation is not a probable benefactor of hastened atherosclerosis in patients with kidney disease (8). However, that study only included mild to moderate CKD patients and the possibility of DNA hypomethylation and accelerated atherosclerosis in advanced CKD cannot be ruled out.

Reffelmann et al found a link between eGFR and flow mediated vasodilation (FMD) of the brachial artery in CKD patients. The association remained unchanged in women after controlling for conventional risk factors and markers of inflammation, but became non-significant in males after adjusting for confounders (24). Flow mediated vasodilation of the brachial artery is associated with carotid intima media thickness (CIMT) and is weighed a forerunner of atherosclerosis and a predictor of CV risk (25-28).

Dursun et al explored the relationship between endothelial micro-particles, arterial sclerosis (using pulse wave velocity) and atherosclerosis (using CIMT) in children with CKD (29). Endothelial dysfunction (ED) in CKD results in apoptosis. Endothelial micro-particles are tiny vesicular fragments of the endothelial cell membrane liberated during apoptosis or activation and it is contemplated a marker of ED. Cardiovascular risk factors namely high parathyroid hormone (PTH), blood pressure and C-reactive protein (CRP) and decreased albumin, haemoglobin and GFR increase the endothelial micro-particles level. Dursun et al concluded that CIMT and pulse wave velocity are increased in children with CKD. Mean arterial blood pressure (MBP) is found to be the major risk factor for atherosclerosis and endothelial micro-particles and MBP is the ultimate risk factor for arterial stiffness (29). Long-term activation of endothelium by uremic toxins leads to ED and endothelial micro-particles release from the vessels (30).

Carbamylation refers to a non-enzymatic process of chemical reformation of proteins. Accumulation of blood urea in CKD gives rise to high amounts of isocyanic acid in circulation leading to the stimulation of carbamylation of proteins. Carbamylated LDL (cLDL) level is high in uremic patients compared to normal individuals. Carbamylated LDL affects the endothelial cell damage and vascular smooth muscle cell propagation which results in atherosclerosis (31). The fundamental mechanism by which cLDL induces cell damage is unexplored. Autophagy denotes to a process of breakdown of proteins, organelles and other molecules by the lysosomes (32). Researchers in their latest studies have suggested that cLDL mediated oxidative stress may responsible for autophagy (33). It is evident that autophagy is a key player in cLDL-mediated endothelial cell damage that may partially describe the fundamental processes leading to the generation of atherosclerosis (34).

3. Risk factors for vascular dysfunction in CKD

3.1. Arterial stiffness

Arterial stiffness (AS) is used in assessing CV risk and detection of emerging vascular diseases. It is an indication of vascular aging. Amplified AS in kidney patients may result mainly from ED, vascular calcification, oxidative stress, chronic volume overload and inflammation (35). According to previous studies, AS is identified as an

independent predictor of CV morbidity and mortality in patients with diabetes mellitus, hypertension, and CKD (36-39). CIMT, ankle-brachial pressure index and AS measurements together are used in risk stratification of macrovascular lesions (40). Microvascular damage can be evaluated by the study of arterial current. Doppler sonography is used to measure the resistive index which provides information on impedance and renal vascular resistance (41). Renal resistive index (RRI) is useful in measuring the renal impairment in CKD patients (42). For the early revelation of vascular injury and for the prevention of cardiovascular diseases, analysis of microvascular and macrovascular circulation is useful. Calabia et al assessed the association between RRI and the markers of macrovascular damage and the role played by the ED in micro and macrovascular damage (43). It was revealed that RRI is an indirect measure of AS and atherosclerosis. It gives satisfactory information on the microvascular and macrovascular impairment. The relationship between ED and RRI could reveal the early damage to the renal microvasculature (43).

3.2 Hyperphosphatemia and secondary hyperparathyroidism

Hyperphosphatemia and secondary hyperparathyroidism leading to vascular calcification are recognized CV risk factors in CKD patients (44,45). Fibroblast growth factor-23 (FGF23) is a bone-originated factor that is responsible for phosphate and vitamin D metabolism (46,47). Hyperphosphatemia, in CKD results in high FGF23 levels (48). According to a Sweden community-based study, higher circulating serum FGF23 is independently associated with vascular dysfunction (49).

3.3. Endothelial dysfunction

Endothelium acts as the barrier between the blood flow and the tissue. ED is an early indicator of the advancement of atherosclerosis (50). Therefore, ED is considered as the best predictor of future CVD events in CKD patients (51). ED begins at the early stages of renal impairment, where GFR begins to decrease and blood pressure increases (50). Increased endothelial triggering by inducements like pro-inflammatory cytokines, growth factors, infectious agents, lipoproteins and oxidative stress, results in ED. ED leads to cell detachment, apoptosis and necrosis (30). Several biomolecules such as asymmetric dimethylarginine, (43) and sonographic methods like FMD of the brachial artery (52) were used by different researches to measure ED.

However, the exact cause of ED in CKD is unidentified. Conventional risk factors are unable to describe the ED in CKD patients as unconventional risk factors are dominant in this group of patients. Unconventional risk factors potentially work through inflammation as an eventual common pathway (52).

Vitamin D deficiency, a non-conventional risk factor responsible for CVD risk in CKD is found to be independently related with ED in early stages of CKD (53). Experiments done on animal models have revealed the ability of vitamin D therapy to downregulate the inflammation and renin angiotensin system. However, immunomodulatory effects of vitamin D on humans are still undiscovered (54).

3.4. Inflammation

Inflammation is a key factor that contributes to ED seen in CKD patients. The worsening ED with declining eGFR suggests that the building up of uremic factors of inflammation may be the reason for increased CV events with progressing CKD. Recio-Mayoral et al found a relationship between CRP, FMD and intima-media thickness which shows the association between inflammation, ED and atherosclerosis. However, that association is not adequate to determine a cause and impact relationship as many pathways of inflammation could relate to ED (52).

4. Distinction between the vascular dysfunction in CKD and conventional coronary artery disease

4.1. Possible mechanisms for the difference?

D'apolito et al have suggested a mechanism accountable for the hastened atherosclerosis in CKD patients. They postulated that increased blood urea and amplified ROS production in adipocytes might escalate the mitochondrial ROS origination in endothelial cells, thereby injuring the cells and triggering pro-inflammatory pathways and deactivating the anti-atherosclerotic enzymes. Experiments carried out using human aortic endothelial cell cultures discovered that, urea induces mitochondrial ROS production results in activation of pro-inflammatory pathways and the deactivation of the anti-atherosclerotic enzyme PGI_2 synthase. This would partially explain the mechanism of accelerated CVD risk in CKD patients (10).

Recio-Mayoral et al studied three patient groups; pre-dialysis, hemodialysis and kidney transplanted patients. They found an improvement in FMD in transplanted patients. They postulated that the improvement seen in this group might be due to the retrieval from urea linked non-conventional risk factors. Transplanted patients, however, showed a higher CVD risk compared to general population due to residual damage caused by uremia, immunosuppression and renal function abnormality (52).

5. Conclusions

Accelerated atherosclerosis in CKD is a growing concern but the exact mechanism of the pathophysiology remains unknown. It appears to be distinctly different from

conventional CVD. Currently there is a paucity of research and data in this subject, while, more studies are needed to clarify this issue**.** Studies should be focused on finding the inflammatory mechanism which is responsible for ED in CKD patients. Once the mechanisms are identified, studies should focus on finding newer drugs which can reduce the CVD risk in CKD patients. Randomized control trials should be planned to explore treatment modalities in this group of patients.

Authors' contribution

EHS contributed to data gathering. EHS, CMW and SL contributed to the preparation of manuscript and final revision. All authors read and approved the paper.

Conflicts of interest

All authors declare no potential conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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