**Cardiovascular Aging in Patients with Chronic Kidney Disease: Pathogenesis and Potential Therapeutics**

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**Keywords: Cardiovascular, CKD, Aging, Vascular Calcification, Dialysis**

**Running Title: Cardiovascular Aging in CKD**

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**Declaration of Interest :**

**The authors declare no conflict of interest.**

**ABSTRACT**

Patients with chronic kidney dysfunction have an elevated risk for various cardiovascular diseases.

Even in the early stages of chronic kidney disease (CKD) the prevalence of cardiovascular events and mortalities is extremely high if compared with age-matched general population. With worsening of kidney function this risk is growing intensely. There are many traditional and non-traditional risk factors that can lead to cardiovascular disease in CKD. Cardiovascular rather than kidney failure, per se, is the main cause of mortality in CKD. The increase of calcification promoters and the decrease of inhibitors leads to the development of vascular calcification in the early stages of CKD. In this regard, CKD mimics cardiovascular system aging with a premature onset and an accelerated progression.

Various non-pharmacological and pharmacological interventions have been studied to retard premature cardiovascular aging in CKD. In this review article, we are summarizing the pathogenesis, risk factors, and possible management strategies of cardiovascular disease in CKD.

**INTRODUCTION**

CKD is characterized by abnormalities in kidney function or structure that persist for more than three months. The severity of CKD is determined by the level of glomerular filtration rate (GFR) and albuminuria [1]. Patients in advanced stages of CKD face a greater risk of cardiovascular events and death [2].

The incidence of chronic kidney disease (CKD) is estimated to be 13.4% of the worldwide population, and it is progressively recognized as a major public health issue that burdens societies and healthcare systems with significant medical and financial costs [3, 4]. CKD could be described as a clinical model of premature aging. The aging process can either be pathogenic, often known as premature aging, or physiological. The slowly declining functional capacity leads to physiological aging [5, 6]. Contrarily, premature aging is marked by an accelerated functional decline that causes aging to occur earlier than anticipated given chronological age [7]. Cardiovascular disease (CVD), persistent uremic inflammation, osteoporosis, muscular atrophy, and frailty are all characteristics of CKD.

CKD is associated with CVD, such as heart failure, arrhythmias, ischemic heart disease, and cardiac death. Patients with advanced CKD stages demonstrate a noticeably augmented risk. The occurrence of cardiovascular events is already higher in patients with mild kidney dysfunction compared to the general population. Cardiovascular disease—rather than kidney disease —is the major cause of death in CKD. Long-lasting proinflammatory conditions induced by kidney disease enhance arterial calcification and cardiac remodeling [8].

Vascular calcification (VC) is a sign of aging and a reliable predictor of cardiovascular morbidity and mortality in the population with CKD. There is evidence that VC are predominant even in early CKD stages [9]. VC was once thought to be a passive process, but it is now understood that VC is an invertible and highly controlled pathological process and that the response to circulating calcification inhibitors, genetic factors, and hormones involves numerous cellular signaling channels [10]. VC which is a cell-based process largely drived by vascular smooth muscle cells (VSMCs), mediates the accelerated early vascular aging (EVA) [11]. Patients with CKD die prematurely due to CVD even before many of them developed end-stage kidney disease (ESKD) [12].

In this review article, we are discussing risk factors, pathophysiology, and management of CVD in patients with CKD.

**PATHOPHYSIOLOGY OF PREMATURE VASCULAR AGING**

There are traditional and non-traditional risk factors for premature vascular aging and calcification in CKD. Traditional risk factors for CKD include diabetes mellitus, dyslipidemia, hypertension, and obesity. On the other hand, non-traditional factors, include vascular calcification, phosphate imbalance, inflammation, oxidative stress, and cellular senescence. Figure (1) illustrates the non-traditional and traditional risk factors for cardiovascular aging in CKD.

**NON-TRADITIONAL RISK FACTOR**

1. **VASCULAR CALCIFICATION**

Vascular calcification is highly prevalent in patients with CKD and is closely associated with cardiovascular (CV) morbidity and mortality [13]. Vascular calcification can occur in tunica intima and/or tunica media. The calcification of the intimal layer will form atherosclerotic plaques and patchy crystals as a result of lipid and cholesterol deposits. It has been linked to smoking, dyslipidemia, and hypertension. In contrast, medial calcification occurs usually in the absence of lipid and cholesterol deposits and results in a sheet-like calcification and concentric thickening. Even in its early stages, patients with CKD are more likely to have medial calcification. It leads to decrease vessel compliance causing more arterial stiffness, which results in impaired cardiac perfusion and progression of CVD. Medial calcification leads to an early vascular aging process (senescence) in patients with CKD. This premature aging is accompanied by chronic inflammation, continuous oxidative stress, DNA mutilation, and unbalanced pro- and anti-aging factors [14].

There is accumulating evidence that VC is a cell-mediated pathological process that resembles the physiological bone formation by vascular smooth muscle cells (VSMCs) [15]. VSMCs are derived from the mesenchymal origin and under stress they can go through osteogenic differentiation to another mesenchymal-derived cell type. VSMCs are present in the medial layer of vessels and play a fundamental role to regulate arterial tone and to maintain the vascular wall integrity [16].

In the patient with CKD, several factors can trigger calcification, including hypercalcemia, hyperphosphatemia, elevated levels of parathyroid hormone (PTH), inflammatory cytokines, oxidative stress, uremic toxins, advanced glycation end products [17]. In normal circumstances, blood vessels are protected from excessively high levels of serum calcium and phosphorus by various active inhibitors that prevent abnormal mineral accumulation in soft tissues. These inhibitors are pyrophosphate, adenosine, matrix Gla protein, osteopontin, fetuin-A, osteoprotegerin (OPG), and Bone morphogenetic protein 2 (BMP-2) [18-21]. The increase of calcification inducers and the decrease of active inhibitors may explain the exceptionally high incidence of VC in CKD [22-24]. CKD's uremic environment also encourages DNA damage, a major factor in cellular senescence, and stimulates osteogenic pathways in VSMCs, which leads to progression of VC [25]. There is increasing evidence that VC starts early and is predominant even in patients with mild renal impairment [9]. Figure (2) shows the frequently studied calcification promoters and inhibitors.

1. **PHOSPHATE IMBALANCE**

Phosphate (Pi) levels are maintained mainly by the actions of three main players: the parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (Vit D), as well as fibroblast growth factor 23 (FGF-23) and, its co-receptor, Klotho [26]. PTH and Vit D, the two major hormones, have antagonizing effects: PTH reduces the reabsorption of Pi in the kidney, whereas Vit D promotes this reabsorption and enhances intestinal absorption [27].

In CKD, Pi absorption and excretion are impaired resulting in elevated Pi levels. FGF-23 and PTH are increased to keep Pi within the normal range by inducing hyperphosphaturia, but as the disease progresses, these systems are unable to maintain proper homeostasis, resulting in hyperphosphatemia [28]. Hyperphosphatemia is a key driver of VSMC differentiation into osteoblast-like cells [29]. Therefore, a wealth of data has shown that hyperphosphatemia negatively affects the cardiovascular system in CKD patients. High phosphate levels were linked to heart failure and an enlarged left ventricular mass even in the general population. However, a 2022 systematic review of 7 randomized clinical trials found no evidence of a reduction in cardiovascular risk in non-dialysis-CKD patients with phosphate-lowering treatment [30]. Elevated FGF23 may induce cardiac damage and increase left ventricular hypertrophy (LVH) [31]. Additionally, epidemiological research has shown that FGF23 is linked to a higher risk of negative cardiovascular outcomes, including heart failure [32]. Low expression of Klotho, a cofactor of FGF receptors that was identified as an anti-aging hormone, may play a role in this association. The precise molecular relationship between high FGF23 and CVD is still unknown [33]. When compared to healthy people, soluble -klotho expression is lower in CKD patients, and they have a premature CV aging [34].

When the concentration of calcium and phosphate ions rises above the blood saturation level, amorphous calcium phosphate precipitates. This precipitate is then quickly absorbed by the serum protein fetuin-A to form calcium calciprotein monomers (CPMs), which then spontaneously aggregate to form primary calciprotein particles (CPPs). Secondary CPPs are created when primary CPPs aggregate and go through a transition phase from the amorphous to the crystalline state of the calcium-phosphate form. In cultured VSMC, secondary CPPs cause calcification, which is followed by inflammatory reactions [35].

1. **OXIDATIVE STRESS**

Excessive Oxidative Stress (OS) has been linked to the pathogenesis of VC [36]. Endoplasmic reticulum (ER) stress, can be activated by OS, leads to VSMCs differentiation into osteoblast-like cells. Endoplasmic reticulum stress boosted XBP-1 expression, which has been demonstrated to bind to the Runx2 promoter, start VSMC differentiation, and accelerate VSMC calcification [37]. In VSMCs and calcified aortas from experimental models, investigations discovered an increase in ER stress protein-activating transcription factor 4 (ATF4). Reduced ER stress, apoptosis, and VSMC calcification were seen with ATF4 RNA knockdown [38]. Simvastatin and ezetimibe may reduce ER stress and slow down VC in patients with kidney dysfunction who had high OS [39].

1. **INFLAMMATION**

Clinical and epidemiological research has revealed a strong correlation between the risk of CV events and markers of inflammation in patients with CKD [40]. Traditional cardiovascular risk factors, such as HTN and hyperlipidemia, are linked to the inflammatory process in patients with CKD [41]. Moreover, several factors contribute to inflammation in CKD, including post-translational alteration of lipoproteins, infection, uremia, oxidative stress, insulin resistance, and buildup of pro-inflammatory cytokines due to poor renal clearance [42]. Additionally, severe intestinal edema from CKD can cause overhydration, which can lead to bacterial or endotoxin translocation and systemic inflammation [43]. Indoxyl sulfate (IS) and p-cresyl sulfate, two protein-bound uremic toxins that are not eliminated by conventional dialysis, promote inflammation and OS, leading to damage to vascular endothelial cell injury [44]. C reactive protein (CRP) and cytokines like IL-6 and TNF-a levels in the plasma can be used to identify low-grade inflammation. In a long-term analysis, CRP, which was assessed at baseline during the Modification of Diet in Renal Disease (MDRD) research, was a reliable indicator of mortality from all causes and CVD [45, 46]. In dialysis patients, the lower the CRP level, the lower the risk of mortality [47].

1. **CELLULAR SENESCENCE**

Cellular senescence may play a crucial role in EVA and VSMC osteogenesis and calcification in CKD [48]. The accumulation and persistence of DNA damage is the primary factor causing cellular senescence. Senescent cells exhibit several pro-inflammatory and pro-fibrotic alterations in gene expression and cell metabolism while losing their ability to divide but maintaining their metabolic activity. The senescence-associated secretory phenotype (SASP) is the name given to this novel trait. Growth factors, cytokines, proteases, and chemokines are more abundantly expressed and secreted in SASPs [49]. After an acute kidney injury, SASPs can help with tissue regeneration; however, long-term exposure to SASPs might promote sterile inflammation and speed up the development of CKD by encouraging renal fibrosis [50, 51]. Senescence and immune system dysfunction are two terms that are jointly referred to as immunosenescence [52]. Because immunosenescence is linked to low-grade sterile inflammation and diminished cellular defenses against infections and vaccinations, it is considered as hazardous [53]. BMP-2 and OPG, which are essential molecules in modulating calcification processes, were found to be secreted by aging VSMCs and may have activated osteogenic differentiation. This suggests a direct relationship between senescence and VC [54].

**TRADITIONAL RISK FACTOR**

In addition to the non-traditional risk factors, patients with CKD have many traditional risk factors which predispose to early vascular aging among these patients.

Diabetes mellitus and hypertension are the two main causes of CKD worldwide [55], and they are also major risk factors in CVD progression.

The kidney has a significant role in regulating blood pressure, and HTN can predict the presence of underlying kidney disease. Inadequately managed hypertension can lead to a rapid decline in kidney function, eventually resulting in ESKD. This could lead to a vicious cycle [56]. CKD leads to the development of HTN by various causes, among them sympathetic nervous system, sodium retention, and activation of the renin–angiotensin–aldosterone system (RAAS) [57-60]. HTN can both cause CKD and serve as a clinical indicator of the disease. According to USRDS 2020, 72% of patients with CKD have hypertension [61].

There is strong evidence of the link between CVD and hypertension in patients with CKD. Patients with CKD who have hypertension had a 68% higher chance of developing CVD [62]. The link between hypertension and CVD in patients with CKD has been explained by several different mechanisms include changes in RAAS, oxidative stress, inflammation, and endothelial dysfunction [63]. The RAAS is known to be a noteworthy pathogenic component in VSMC proliferation, differentiation, and it likely contributes to VC [64]. To lower the risk of CVD, the American Heart Association advises vigorous blood pressure control in patients with CKD [65].

Compared to non-diabetic patients, people with diabetes had more calcification. These patients had higher levels of osteopontin, type I collagen, and alkaline phosphatase in the medial layer of the arteries, which are bone matrix proteins [66]. It has been hypothesized that the advanced glycation end-products (AGE) and their receptors for AGE (RAGE) facilitate the phenotypic transformation of VSMCs into osteoblast-like cells and trigger diabetes-related VC [67, 68].

Obesity is a major precursor to diabetes and HTN. Moreover, it raises the risk of CKD and CVD [69, 70]. Obesity can have a direct impact on the heart, both pathologically and hemodynamically via increase myocardial fibrosis and volume excess [71]. In addition, obesity raises the risk of CVD through augmenting renal hyperfiltration and low-grade systemic inflammation [72].

Hypercholesterolemia is also a significant factor in the increased CVD risk [73]. Additionally, it was found that oxidized LDL induced phenotypic shifts in VSMCs toward osteoblast-like cells and may be crucial to the development of hypercholesterolemia-related VC [74, 75].

**NON-PHARMACOLOGICAL** **INTERVENTIONS OF CARDIOVASCULAR DISEASE IN CKD**

Non-pharmacological interventions are often overlooked; however, they are proved to be effective in slowing the progression of cardiovascular aging, generally without side effects. Advising patients for quitting smoking, regular muscle activity, dietary salt reduction, and weight loss are useful therapies at all CKD stages [8]. There is a mutual association between CKD and aging. Elderly people with ESKD should be treated using a multifaceted treatment strategy that includes active rehabilitation as well [76]. Figure (3) illustrates the possible non-pharmacological interventions in patients with CKD.

**PHARMACOLOGICAL TREATMENT OF CARDIOVASCULAR DISEASE IN CKD**

Controlling DM and HTN are cornerstones of lowering cardiovascular risk in general population and in patients with CKD. Therefore, current recommendations call for strict control of blood pressure in patients with diabetic or nondiabetic CKD with RAAS blockers as the first-line medications [77].

Using SGLT2 inhibitors or GLP-1 receptor agonists, patients with type 2 diabetes have demonstrated a significant decrease in cardiovascular events. Guidelines therefore recommend using these medications to treat individuals with CKD and those without CKD who have CVD or many cardiovascular risk factors [78].

There is a shortage of data available to support management plans for cardiovascular risk in patients with CKD. Many approved and off-labeled drugs have been studied to decrease the vascular calcification in CKD.

1. **Statin and aspirin**

Dyslipidemia frequently occurs in CKD patients. KDOQI advises all adult patients with diabetic CKD and hypercholesterolemic non-diabetic CKD patients to receive treatment with a reductase inhibitor, or statin, to decrease LDL cholesterol. Statins help lessen a variety of cardiovascular complications brought on by atherosclerosis. According to recommendations, statins are advised for all CKD patients over 50 years old and by people who are 18 to 49 years old and at high risk for atherosclerotic cardiovascular disease (CVD) [79].

The severity of CKD appears to have an impact on how well lipid-lowering therapies reduce CV risk in people with CKD. In patients with advanced CKD who had no prior history of myocardial infarction or coronary revascularization, the SHARP study discovered a significant relative decrease in the primary end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization after using statins and ezetimibe [80].

In contrast, neither the 4D nor the AURORA investigations could demonstrate a meaningful decrease in CVD in ESKD patients taking HD when compared to placebo [81]. According to these data, the cardiovascular benefits of lipid-lowering treatments are reduced with significant reduction of glomerular filtration rates and are only minimally effective in people with ESKD who are receiving hemodialysis [82] .

Antiplatelet medication is well established to lower cardiovascular risk in people without CKD who have coronary artery disease, however the prognostic advantage is less obvious in CKD patients. Additionally, these medications raise the risk of bleeding incidents in CKD patients, thus may outweigh any potential advantages [78].

1. **Phosphate binders**

When dietary restriction is insufficient, patients with advanced CKD and hyperphosphatemia frequently need to be treated with phosphate binders. Since phosphate and the rise in FGF-23 and PTH that occurs along with it have all been linked to VC, lowering or keeping stable phosphate levels close to normal may be associated with improved overall CV system [83].

Using either calcium-containing (acetate, carbonate) or calcium-free (sevelamer, lanthanum, iron compounds, magnesium) binders, serum phosphate can be reduced to normal levels [84]. As a result of their ability to significantly lower dietary phosphate absorption, phosphate binders are the cornerstone of the therapy of patients with CKD and hyperphosphatemia [85, 86]. Non-calcium-based phosphate binders are generally preferable due to the possible risk of increased VC with calcium-based binders.

Phosphate binders successfully reduce urine phosphate excretion in studies done on healthy volunteers while maintaining serum phosphate levels within the usual range [87]. Moreover, phosphate binders—but not a placebo—reduce 24-hour urine phosphate in normophosphatemic patients with CKD stages 3–4 [88, 89]. Calcium-based binders did not decrease urinary phosphorus, possibly because calcium only serves as a secondary stimulant for the synthesis of FGF23 [83].

1. **Calcimimetic**

Calcimimetics can activate the parathyroid gland's calcium sensing receptor (CaSR), which makes parathyroid cells more sensitive to extracellular calcium. Thus, inhibits the release of PTH and lowers serum calcium [90]. Patients with ESKD can effectively treat secondary hyperparathyroidism and by targeting CaSR which is found in a variety of organs but mainly in the parathyroid glands [91]. There is an evidence that VSMCs may include CaSR, based on that calcimimetics may directly influence the calcification process in these cells [92].

It appears that calcimimetics may slow down VC progression and decrease cardiovascular risk [93]. In one trial evaluating cinacalcet's impact on cardiovascular morbidity and mortality, participants receiving cinacalcet saw significantly lower hospitalization rates and a tendency towards lower mortality [94]. Etelcalcetide, an intravenous calcimimetic that acts at a different location on the CaSR, outperformed cinacalcet on biochemical endpoints and was highly effective at reducing PTH and FGF-23. Although neither VC nor clinical outcomes have not been studied in relation to Etelcalcetide effects [84].

1. **Vitamin D**

Vitamin D deficiency may have a major negative influence on CV risk. Vitamin D receptor activation has been associated to better blood pressure control and prevention of diabetic nephropathy [95].

On the other side, natural calcitriol, a non-selective activator of vitamin D receptors, raises calcium and phosphate levels which would exacerbate the CV risk in CKD. Recent research revealed that Paricalcitol, a selective VDRA, may have ameliorative effects on CV disease. Its potential benefit for diabetic nephropathy, cardiac illness, hypertension, and VC may pave the way for novel pathways in the treatment of CVD in patients with CKD [95].

PTH could be regulated in advanced CKD by active vitamin D. Retrospective studies have also revealed lower cardiovascular mortality in dialysis patients getting active vitamin D supplements [96].

Despite the limited number of clinical trials supporting the use of either native or active vitamin D analogues to stop the progression of VC, low doses of vitamin D or vitamin D analogues could be taken to prevent extremely high parathyroid hormone concentrations. On the other side, low parathyroid hormone concentrations (over suppression) are noticeable side effects of overzealous use of calcium and vitamin D [8, 97, 98]. Repleting vitamin D deficiency with nutritional vitamin D, in addition to controlling PTH in patients with advanced CKD and secondary hyperparathyroidism with non-high calcium and phosphorus could be beneficial for CVD management in patients with CKD.

1. **Vitamin K**

The protein matrix GIa protein (MGP), which depends on vitamin K for synthesis has an inhibitory role in VC as it prevents the development of calcium crystals [99-101]. To gain its calcification inhibitory capacity, vitamin K must decarboxylate MGP. Vitamin K antagonists use, vitamin K insufficiency, and, as a result, decreased uncarboxylated MGP level have been associated with VC [91, 102].

Schurgers et al. demonstrated in animal models that undercarboxylation of MGP—caused by 6 weeks of therapy with the vitamin K antagonist warfarin—was related with accelerated VC [103]. When compared to rats who received vitamin K supplements, the warfarin group showed quick VC, high atherogenic status, and notably higher levels of circulating undercarboxylated MGP, whereas high dosages of vitamin K led to a 37% regression of VC status. This was the first in vivo study to demonstrate that vitamin K treatment may be able to prevent and even reverse vascular calcification [104].

There are no recommendations for the use of vitamin K supplements in patients with CKD. Of note, their use has not been associated with toxicity or serious side effects in any interventional research to yet. It could be a potentially safe supplement with probable benefit for CVD management in selected patients.

1. **Magnesium**

Recent studies have emphasized magnesium's possible involvement in preventing vascular calcification [105, 106]. Few human clinical investigations have demonstrated that oral magnesium given to individuals with moderate to advanced CKD, in the form of a phosphate binder or as a supplement, may reduce VC progression or lowered the tendency for calcification [106].

1. **Renal transplantation and Renal Replacement Therapy**

As kidney function falls towards ESKD, important decisions regarding starting dialysis must be made. Regular or continuous dialysis treatments may be advantageous for CKD 5D patients with CHF [8, 97, 98].

Renal transplantation may reverse uremia, which is a major trigger to development of VC in people with ESKD [79]. Pre-emptive kidney transplantation is the best option for patients with advanced CKD [98]. Patients with CKD who undergo renal transplantation have some reduction in their cardiovascular risk [79].

1. **Potential Novel Medications:**
* **The silent information regulator sirtuin 1 (sIRT1)**

Through its control of fibrosis, apoptosis, and senescence, as well as oxidative stress, inflammation, VC, and ageing process, SIRT1, a NAD+-dependent deacetylase, may have a protective role in CKD and its consequences on cardiovascular system. It could be a potential target for CVD management in CKD as it suppresses VSMCs osteoblastic trans differentiation induced by hyperphosphatemia [107, 108].

* **SNF472:myo-inositol hexaphosphate**

SNF472, a hexasodium salt of the active component, myo-inositol hexaphosphate (IP6), or phytate, has shown encouraging benefits in experimental trials. By adhering to hydroxyapatite crystal growth sites, SNF472 prevents the onset and development of calcification. This mechanism appears to be independent of the underlying cause of calcification and may offer a chance to block the final common pathway of VC [91].

**CONCLUSION**

In summary, CKD is a state of accelerated aging. Cardiovascular disease (CVD) is the leading cause of death in patients with CKD. Slowing the progression of CVD in CKD depends greatly on early detection and management of possible risk factors. CKD patients should maintain blood sugar and blood pressure control. Calcimimetics, non-calcium phosphate binders, and vitamin D have been used to control CKD-mineral and bone disorders. Magnesium, vitamin K, and vitamin D could be potential therapies. New therapeutic agents and targets have been identified in the last years.

It is crucial to address the shortage of data from significant cardiovascular outcome studies in CKD with high-risk CVD. The most ideal strategy, till now, for advanced CKD may be kidney transplantation, which can improve ESKD-related cardiovascular outcomes.

**Figure Legend:**

**Figure (1) Non-traditional and traditional risk factors for cardiovascular aging in CKD.**

There are many traditional and non-traditional risk factors that promotes vascular calcification and premature cardiovascular aging in CKD. Diabetes mellitus, dyslipidemia, hypertension, and obesity are among the most common traditional risk factors among patient with CKD. On the other hand, non-traditional factors, include vascular calcification, phosphate imbalance, inflammation, oxidative stress, and cellular senescence. This figure was created with BioRender.com.

**Figure (2) Vascular Calcification Promoters and Inhibitors.**

In CKD there is an imbalance between calcification promoters and inhibitors leading to vascular calcification and premature cardiovascular aging. This figure was created with BioRender.com.

**Figure (3) Non-pharmacological Interventions of Cardiovascular Disease Management in CKD.**

Non-pharmacological interventions are often overlooked however they can retard the progression of cardiovascular aging in CKD if properly advised and monitored. Advising patients for quitting smoking, regular exercise, salt reduction, and weight loss is beneficial at all CKD stages. Early screening and regular close follow up can also help in early management of cardiovascular disease. This figure was created with BioRender.com.

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