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# Activated Platelets, the Booster of Chronic Kidney Disease and Cardiovascular Complications

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**Keywords**
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**Abstract**
***Background:*** Chronic kidney disease (CKD) has become a global public health problem nowadays. As cardiovascular diseases (CVDs) are the primary cause of death in advanced CKD patients, much attention has been paid to resolving their cardiovascular complications. However, managing CKD and cardiovascular complications is still a big challenge for nephrologists, as satisfactory treatments are still lacking. Platelets, the second most abundant cells in the blood, are the major participants of hemostasis, thrombosis, and wound healing. In recent years, platelets have been reported in various physiological and pathological processes, including CKD and CKD-related CVDs.



## Introduction

Chronic kidney disease (CKD) is a kind of disease in which kidney damage or decreased glomerular filtration rate (<60 mL/min per 1.73 $m^2$) exists for more than 3 months. It has become a global health problem, as the morbidity achieved approximately 10–13% [1]. A large proportion of CKD patients will gradually progress to end-stage kidney disease and eventually need replacement therapy with dialysis for life and even kidney transplantation [2]. Although extensive studies indicate that CKD progression is characterized by tubular atrophy, glomerular sclerosis, interstitial fibrosis, and peritubular capillary rarefaction, the pathological mechanisms of CKD have not been fully elucidated.

Dramatically, in CKD patients, the most common complications and major causes of death are cardiovascular diseases (CVDs) [3]. Thus, the type 4 cardio-renal syndrome was defined as the CVDs induced by CKD. However, it remains largely unknown how CKD facilitates the development of CVDs. Therefore, exploring the

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mechanisms of CKD and its cardiovascular complications is either beneficial for finding preventive and therapeutic targets or reducing the morbidity and mortality of CKD patients.

During the past decades, platelets have been found with extensive and versatile functions. As we all know, platelets are essential participants in acute coronary syndromes and are involved in atherosclerosis and thrombosis [4]. Besides, accumulating evidence suggests that platelets are involved in the pathogenesis of CKD, as they are hyperactivated and can participate in the processes of chronic inflammation, oxidative stress, immunoreaction, and fibrosis associated with CKD progression [5]. Therefore, understanding the functions and mechanisms of platelets in CKD and identifying effective intervention targets of platelets provide broad prospects for CKD patients, with an ultimate aim to reduce cardiovascular morbidity and mortality. In this review, we mainly focus on the roles and mechanisms of activated platelets in CKD and CKD-related CVDs.

## Platelet and Its Vesicles

Platelets are anucleate blood cells with a 2–4 μm diameter. Platelets originate from proplatelets derived from megakaryocytes predominantly situated at bone marrow sinusoids [5] and a recent study also provided evidence for megakaryocytes and platelet production in the lung [6]. The traditional functions of platelets are hemostasis, thrombosis, and wound healing [7].

Platelets contain a great variety of cell surface receptors and adhesion molecules, which make them respond quickly to stimuli such as injury or infection [5]. As they are highly sensitive to environmental changes and are present in high numbers in the circulation, they are the first cells to arrive at sites of acute injury, where they interact with endothelial cells and leukocytes. In response to different stimuli, resting platelets become active and differentiate into different subtypes according to the activation of different surface receptors and signaling integrin molecules. Once activated, platelets begin to change shape, degranulate, and release microvesicles to recruit additional platelets and other immune cells [5].

Platelets carry three different types of microvesicles: α-granules, dense granules, and lysosomes. These microvesicles contain various biomolecules, including over 300 kinds of different proteins and other bioactive mediators, such as P-selectin, thrombospondin, platelet-derived growth factor (PDGF), thromboxane, and platelet-activating factor. In addition, platelet microvesicles contain mRNAs and miRNAs that can be transferred to other cells, modulating their gene transcription and protein synthesis. Through the release of microvesicles, platelets can rapidly modulate molecular processes that regulate coagulation, inflammation, fibrosis, and redox, all of which are associated with CKD and CKD-related CVDs [8].

## Hyperactivated Platelets Contribute to the Progress of CKD

Platelets are hyperactivated in CKD patients. This can be detected by the increased expression of P-selectin, thromboxane A2, CC-chemokine ligand 5(CCL5), CD154, platelet factor 4(PF4), etc. [9, 10]. Clinically, it was also detected that mean platelet volume was obviously increased with the progression of CKD. Many substances lead to platelet activation in CKD patients. On the other hand, hyperactivated platelets contribute to the progress of CKD in turn.

### *Platelets Release Proinflammatory Factors and Interact with Inflammatory Cells to Accelerate Renal Inflammation and Fibrosis in CKD*

Chronic, systemic, and low-grade inflammation is a long and generalized process, which can be usually observed in CKD patients [11]. Renal inflammation plays a central role in the initiation and progression of renal fibrosis and CKD-induced complications. Multiple pieces of evidence show there are bidirectional relationships between platelets and inflammation.

On the one hand, inflammation can induce platelet activation, evidenced by the increase in platelet aggregation and the interaction of platelets with monocyte [12]. On the other hand, platelets can release multiple proinflammatory factors such as PF4, stromal cell-derived factor-1, epithelial neutrophil-activating protein 78, IL-1β, CD40 Ligand (CD40L), and CCL5, all of which further accelerate the development of CKD [13, 14]. Platelet-derived proinflammatory factors can trigger a switch of endothelial cells to a more inflammatory phenotype [15], which will subsequently release inflammatory cytokines such as IL-8, CCL2, etc. Therefore, activated platelets in CKD contribute to leukocyte recruitment.

In CKD, the interactions between platelets, monocytes, and endothelial cells are enhanced, facilitated by the increases in inflammatory cytokine levels and cell adhesion molecules in these cell types [16]. Platelet-derived

extracellular vesicles (EVs) activate endothelial cells and leukocytes by surface molecules CD41 and CD62P. Additionally, platelet EVs can induce the migration and proliferation of vascular smooth muscle cells (VSMCs), as prolonged incubation of VSMCs with platelet EVs results in increased adhesiveness for THP1 monocytic cells and an increase in IL-6 production [17]. These findings indicate that platelet EVs have proinflammatory effects and promote endothelial dysfunction. Besides, incubating VSMCs with platelet-derived EVs led to a phenotypic transition towards a synthetic phenotype, as evidenced by the morphological changes and the reduced expression of contractile marker calponin [17]. Therefore, platelets can amplify the inflammation by releasing EVs under CKD conditions.

Particularly, activated platelets can express CD40 and CD154, the latter of which is also termed CD40L. CD40 is a transmembrane glycoprotein receptor expressed in platelets and endothelial cells. However, CD40L in platelets is only expressed upon activation and always in a soluble form [18]. In CKD patients, the level of CD40L from platelet microparticles was obviously increased, especially in CKD 4–5 stages [19]. According to the binding of CD40 and CD40L, CD40L on platelets induces endothelial cells to secrete chemokines and express adhesion molecules, thereby generating signals for the recruitment and extravasation of leukocytes at the site of injury [20]. This study revealed that platelets could directly initiate an inflammatory response of the vessel wall. Under this condition, endothelial cells upregulate the surface adhesion molecules E-selectin, VCAM1, and ICAM1, release CCL2, and further boost the recruitment of leukocytes, such as macrophages and neutrophils [21]. All these actions above promote the creation of a constantly inflammatory environment in CKD patients.

Some inflammatory factors are reported to be associated with renal fibrosis. After activation, platelets can increase the release of inflammatory factors in CKD [13]. The profibrotic inflammatory factors such as CCL5, TNF-a, TGF-β, and PDGF are reported to be up-regulated, while the antifibrotic factors, such as AMPK and IL-10, are down-regulated in the kidneys of CKD patients. Among them, TGF-β drives renal fibrosis by activating lots of signaling molecules and plays a central role in renal fibrosis [11]. It is reasonable to infer platelet can contribute to systemic inflammation and promote renal fibrosis in CKD patients, which is a characteristic process connecting inflammatory factors, recruitment of leukocytes, and activated fibrotic signal pathways.

Moreover, platelets are also involved in the phenotypic change of macrophages to promote fibrosis of CKD. Macrophages belong to the mononuclear phagocytic system [22]. Based on their functions and anatomical location, macrophages are divided into different subpopulations [23]. In the kidneys, macrophages can be broadly classified into two different subtypes: classically activated (M1) macrophages (which can release inflammatory factors) and alternatively activated (M2) macrophages (which can release TGF-β-promoting fibrosis) [24, 25]. With the development of CKD, M1 macrophages can switch to fibrotic-M2 macrophages [24]. A study illustrated that by incubating platelet-derived EVs with monocytes, platelet EVs can preferably bind to monocytes, and platelet EVs can be absorbed by phagocytic over time [26]. Thus, monocytes can harbor the platelet markers. Prolonged incubation of monocytes with platelet EVs results in a remarkable change of surface marker expression, indicating a polarization of the monocytes to M2-type macrophages [26]. Therefore, it is a novel thromboinflammatory pathway that platelets may mediate the monocytes to M2-type macrophages and probably contribute to the progress of CKD by M2 macrophages.

### *MiRNAs Released from Platelets Play a Vital Role in Fibrosis of CKD*

Although devoid of a nucleus and lacking genomic DNA, circulating human platelets retain as much as 45% of the Refseq genes in the form of mRNAs [27]. Platelets contain an abundant and diverse array of mRNAs and miRNAs. MiRNAs are noncoding RNAs with a length of 20–25 nucleotides. The binding of miRNAs to their respective target mRNAs promotes degradation of the mRNAs [28]. Clinical research investigated the circulating platelets of 10 CKD patients and five age- and sex-matched healthy subjects. They found that platelet mRNA and miRNA transcriptome was altered in CKD patients and could be restored partially upon dialysis [29]. Platelet-derived miRNAs can be internalized by recipient cells including endothelial cells, macrophages, and VSMCs, where the altered miRNAs may take part in the molecular processes of oxidative stress, inflammation, and fibrosis of CKD [30]. Therefore, some circulating miRNAs have been suggested as promising noninvasive biomarkers in CKD patients. Microarray screening revealed miRNAs from activated platelets or platelet microparticles mainly include miRNA-223, miRNA-126, miRNA-21, miRNA-191, miRNA-150, miRNA-24, and miRNA-197 [30–32].

The miRNA-21 is an evolutionarily conservative miRNA and almost exists in all types of cells, among which platelets are the major sources [33, 34]. MiRNA-21 is very stable in the blood and performs vital regulatory roles in health and disease [33]. A study in 2015 found a strong up-regulation of miRNA-21 in the kidneys of mice with unilateral ureteral obstruction and also in the kidneys of patients with severe kidney fibrosis. In addition, their data also indicated that circulating miR-21 levels were associated with renal fibrosis [35]. Another study reported miRNA-21 could contribute to fibrogenesis and epithelial injury by suppressing the expression of peroxisome proliferator-activated receptor (PPAR)-α, which is a major regulator of the mitochondrial β-oxidation pathways [36]. Genetic deletion of miRNA-21 in mice dramatically reduced interstitial fibrosis, glomerulosclerosis, tubular injury, and inflammation and prevented CKD progression. Inhibition of miRNA-21 was protective against TGF-β-induced fibrogenesis and inflammation in glomerular and interstitial cells, likely as the result of enhanced PPARα/RXR activity and improved mitochondrial function in CKD mice [37]. MiRNA-21 also upregulates extracellular signal-regulated kinase (ERK) signaling in the kidney. Both ERK1/2 and TGF-β/Smad signaling pathways seem to be emphasized in the development of kidney fibrosis in diabetic models [38]. Moreover, miRNA-21 and miRNA-124 also activate the profibrotic genes in human podocytes and tubular cells in a model of IgA nephropathy [39]. All these studies indicate that miRNA-21 plays an essential role in the fibrosis of CKD, and it can be a candidate target for antifibrotic therapies.

MiRNA-223 is the most abundant miRNA from platelet microvesicles. It is considered to be associated with several inflammatory disorders including diabetes-type 2, sepsis, and rheumatoid arthritis. MiRNA-223 can be delivered into vascular endothelial cells, where it participates in the process of inflammation in CKD [40]. Studies have revealed the close relationship between miRNA-223 and the NLRP3 gene in several disease models including IgA nephropathy, atherosclerosis, and diabetic cardiomyopathy [41, 42]. Thus, it is reasonable to predict that miRNA-223 may promote fibrosis of the kidneys by activating inflammation.

Although miRNAs have great potential and more and more research is exploring the functions of miRNAs, the studies regarding the detailed molecular mechanisms of platelet-derived miRNAs in CKD are quite limited. From existing data, we can infer that platelet-derived miRNAs can have extraordinary functions in regulating fibrosis in CKD, and targeting specific platelet-derived miRNAs could be a novel therapeutic approach to treating renal fibrosis. Therefore, further studies are needed to elucidate the molecular mechanism of miRNAs.

*Platelets Accelerate Glomerulosclerosis in CKD Progression*

Glomerulosclerosis is an important progressive pathological process that appears in almost all kinds of CKDs as well as the natural aging process. Glomerulosclerosis is defined as the obstruction of glomerular capillaries and loss of podocytes by extracellular matrix (ECM) deposition [43]. The glomerulus contains four different cell types including parietal epithelial cells, endothelial cells, podocytes, and mesangial cells [44], among which podocytes are the most important in maintaining the structure of the glomerular filtration. In recent years, platelets have been reported to influence the normal functions of glomeruli and participate in the process of glomerulosclerosis.

First of all, activated platelets may affect the functions of podocytes and the remodeling of GBM. As mentioned before, platelets are a primary blood reservoir for CD154. In the glomerulus, CD40 is synthesized by podocytes and can be detectable in kidney tissue sections. Activated platelet supernatants induced matrix metalloproteinases 9 (MMP-9) mRNA synthesis in podocytes, an effect reduced by anti-CD40 antibody [45]. This study uncovered the potential role of platelets through the CD40/CD154 signaling pathway in the control of GBM synthesis and degradation. In addition, there are still some studies that reported CD154 may contribute to the regulation of matrix remodeling proteins, particularly through the induction of MMP-9 in other disease models [46, 47]. In a word, the platelet-derived CD154 activates the CD40/CD154 signaling pathway to modulate matrix remodeling through the synthesis of MMPs in podocytes, further contributing to CKD progression.

Second, platelet secretory factors influence mesangial cell proliferation in glomerulosclerosis. Fibronectin, PF4, 12-hydroxyeicosatetraenoic acid, TGF-β, and PDGF, all can be released by platelets and almost all of them are related to mesangial cell proliferation [48–51]. A study reported that fibronectin could promote mesangial cell migration and proliferation in vitro and contribute to extracellular matrix formation and tissue remodeling during glomerular disease [48]. Moreover, this research also proposed a hypothesis that fibronectin derived from platelets and macrophages served as a provisional matrix involved with mesangial cell migration into glomerular lesions [48]. Platelets are also crucial in

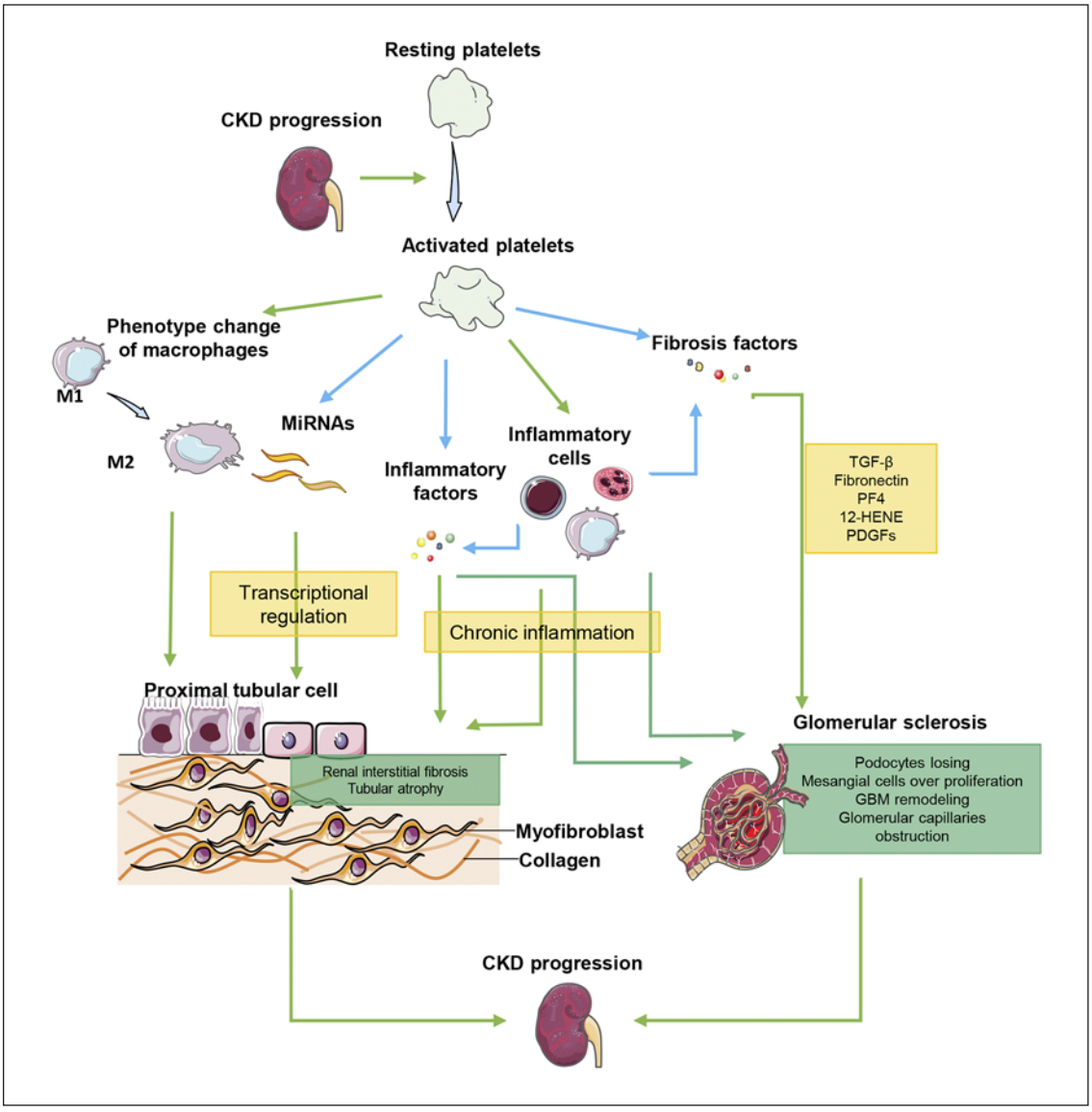


**Fig. 1.** The mechanisms of platelets in CKD progression. Platelets can not only release miRNAs, inflammatory factors, and fibrosis factors to directly promote renal fibrosis, but also interact with inflammatory cells to promote CKD progression indirectly.

mesangial cell injury to renal matrix expansion in an acute glomerular wound repair to chronic kidney injury animal model. Platelets inhibition significantly reduced TGF-β overexpression, fibrinogen deposition, and glomerular matrix expansion in this acute glomerular wound repair model [52].

In conclusion, platelets may involve in ECM remodeling, cell migration, and proliferation to stimulate glomerular remodeling. The mechanisms of platelets in CKD progression are shown in Figure 1.

## Involvement of Activated Platelets in Cardiovascular Complications of CKD

Cardiovascular complications of CKD mainly include cardiomyopathy, atherosclerosis, calcification, and subsequent result in heart failure, cerebrovascular, cardiovascular death, and so on [53]. CVD accounts for 40–50% of deaths among patients with end-stage kidney disease [54], which is much higher than that in age- and sex-matched people [55].

**Table 1.** Platelet inhibitors used in CKD and CKD related CVDs

| Medication | Dose | Comments |
|---|---|---|
| Acetylsalicylic acid | 100 mg/day | Reduced effect in CKD stages 4 and 5 |
| Clopidogrel | 75 mg/day | Reduced effect in CKD stages 4 and 5 |
| Prasugrel | 10 mg/day | More safety in bleeding events |
| Ticagrelor | 180 mg/day | A higher antiplatelets efficiency but a higher incidence of bleeding especially in CKD stages 4 and 5 |

A clinical study stated that for patients with CKD stage 5 or receiving dialysis treatment, higher platelet counts tend to be associated with a greater risk of CVD events [56]. It was also discovered that patients with CVDs had higher mean platelet volumes than those without CVDs in CKD [57]. Our group also reported that platelet counts, plateletcrit, and platelet distribution width were associated with CVD events in CKD patients without dialysis [58]. The changes in platelet indices in CKD patients indicate the vital role of platelets in CKD-related CVDs. To reduce the morbidity of cardiovascular complications in CKD, it has become a common therapy to use acetylsalicylic acid, clopidogrel, etc. as antiplatelet agents. A significant reduction in cardiovascular mortality was observed in CKD patients who received aspirin alone or in combination with a β-blocker compared to those who did not receive either medication [59]. What's more, although there is still a lack of evidence using acetylsalicylic acid as cardiovascular primary prevention in CKD patients, research has clearly shown aspirin administration resulted in an absolute risk reduction of major CVD events [60]. The information on antiplatelet agents in CKD and CVDs is listed in Table 1.

Under CKD conditions, many sera pathophysiological factors can lead to the activation of platelets. These factors, like accumulated uremic toxins and inflammatory cytokines, induce the overproduction of platelet microvesicles. They can be directly absorbed by vascular cells and even mediate platelet-monocyte aggregation, further leading to vascular calcification (VC), atherosclerosis, and heart fibrosis in CKD patients. In a word, platelets play a vital role in the cardiovascular complication progression of CKD patients. The functions of platelets in cardiovascular complications of CKD patients have been explored, which will be discussed below.

*Platelets Expedite VC of CKD*

Vascular calcification (VC) is defined as mineral deposition in the vasculature in a form of calcium-phosphate complexes [61]. VC often occurs with aging but is prevalent in patients with hypertension, CKD, or diabetes [61]. Different from other pathological types, CKD-induced VC often occurs in the medial layer. Even in the early stage of CKD, the rate of VC increases obviously. Many factors influence the progression of VC in CKD, such as oxidative stress, endothelial dysfunction, and the increased levels of proinflammatory cytokines.

As mentioned before, platelets can directly release many inflammatory factors that can contribute to the persistent inflammatory state in CKD and recruit more inflammatory cells, further enhancing the interactions between VSMCs and inflammatory cells [62]. These interactions result in phenotypic switching of VSMCs. The phenotype of osteochondrogenic VSMCs can enhance cell migration and proliferation and eventually facilitate VC [63]. This might be a general process that happened in the development of VC in CKD patients.

Furthermore, platelets can also express and release osteocalcin (OC). OC is one of the most abundant noncollagenous proteins in bone and is primarily generated by osteoblasts during bone formation. Recent data indicated OC was closely related to VC [64, 65]. OC exists in δ-granules of human platelets and is released upon platelet activation. In CKD patients, the total plasma OC concentration was higher when compared with that in the control group [66]. In the calcium-deposit area, there is an evident co-localization between OC and platelets, thus platelets probably secrete OC to promote the early stage of VC [64].

In conclusion, platelets can affect the inflammatory state either by releasing proinflammatory factors or releasing OC to promote VC in CKD. Further studies are needed to explore the detailed molecular mechanisms underlying the particular functions of OC and inflammatory factors from platelets in CKD-related VC.

*Platelets Facilitate Vascular Fibrosis and Atherosclerosis in CKD*

Both vascular fibrosis and atherosclerosis are momentous pathological processes in cardiovascular complications. Damage to vascular endothelial cells is the origin of vascular fibrosis and atherosclerosis and usually happens in CKD with a high frequency. The process of vascular endothelial cell damage often refers to premature senescence of endothelial cells, cell transition from an endothelial to a mesenchymal phenotype, endothelial cell dysfunction, and vascular fibrosis [67].

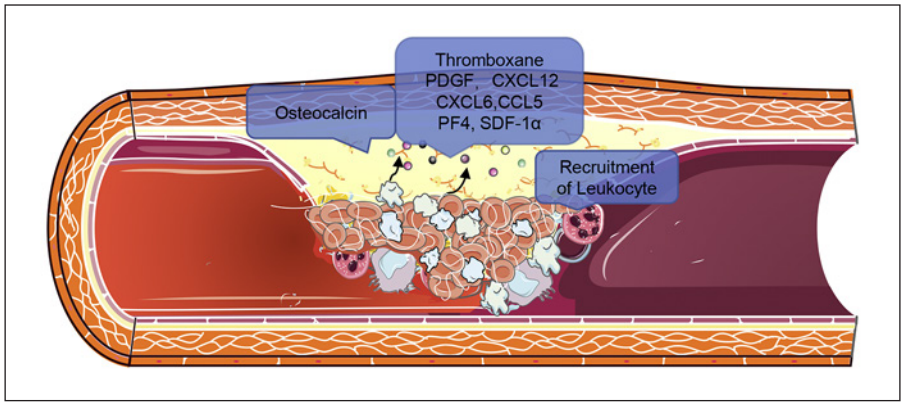


**Fig. 2.** Activated platelets can secret lots of chemokines to promote VC and atherosclerosis in CKD.

As we all know, platelets act essentially in vascular wound healing. At sites of vascular injury where endothelium is damaged or removed, clot formation and vessel contraction immediately occur, which is mediated largely by substances such as thromboxane and PDGF from activated platelets [5]. Then VSMCs are dedifferentiated and proliferated to repair the vascular injuries, with their phenotype shifting from a quiescent contractile phenotype to a highly synthetic and proliferating cell type. However, excessive repair of injuries by VSMCs can lead to intimal hyperplasia and fibrosis, which is engaged in the pathogenesis of atherosclerosis [7]. Current studies clearly show that platelets play an essential part in atherosclerotic lesions. Even more, activated platelets are present in the circulating blood of atherosclerotic individuals throughout the atherosclerotic process [5]. CKD, even at early stages, can increase the risk of atheromatous plaques [68].

From a general position, activated platelets can release a plethora of chemokines, including CXCL4 or PF4, CCL5, CXCL12 or stromal cell-derived factor-1α (SDF-1α), and CXCL16, all of which initiate or promote local inflammatory processes at sites of vascular injury and atherosclerosis. Moreover, genome-wide miRNA sequencing of VSMCs cocultured with activated platelets identified significant increases in platelet-derived miRNA-223. MiRNA-223 appears to directly target PDGFRβ (in VSMCs), reversing the injury-induced dedifferentiation and intimal hyperplasia [69]. Thus, platelets may have bidirectional functions in vascular fibrosis, including initiating an immediate repair process and excessive repair in a delayed manner. In CKD, the aggregation of the circulating activated platelets and platelet-leukocytes is enhanced, promoting the development of atherosclerosis. The chemokines released by platelets in VC, vascular fibrosis and atherosclerosis progression are shown in Figure 2.

There still exist some other functions of platelets in vascular fibrosis and atherosclerosis in CKD. Platelet-derived miRNAs are also proved to be implicated in the initiation and progression of atherosclerosis through the regulation of lipid metabolism, inflammatory response, oxidative stress, endothelial function, angiogenesis, and plaque formation [30]. MiRNA-126, mainly released by platelets, is thought to become a biomarker of CVDs because it was considerably elevated in vascular damage and endothelial dysfunction according to the detection in myocardial infarction patients. A positive association between circulating miRNA-126 and fatal myocardial infarction has been reported recently [70]. MiRNA-126 can control vascular inflammation by affecting the adhesion of white blood cells to the endothelium and has a positive function in CVDs. In addition, miRNA197, another miRNA shed mainly by platelets, is up-regulated in CKD patients. MiRNA-197 might facilitate dyslipidemia in metabolic syndrome, hence leading to the progression of CVDs [71]. Clinical research confirmed that an elevated level of miRNA-197 could be a predictor of cardiovascular death in a large patient cohort with coronary artery disease [72].

In a word, platelets are classic cells that participate in fibrosis and atherosclerosis. However, the particularity of CKD revealed some different roles of platelets. Thus, for one thing, platelets can secrete plenty of chemokines to enhance interactions between endothelial cells and leukocytes to enhance vascular fibrosis and atherosclerosis indirectly; for another thing, platelets can produce miRNAs to influence the transcription of key genes in the process of vascular fibrosis and atherosclerosis in CKD.

**Table 2.** Platelets-derived miRNAs in CKD and CKD related CVDs

| MiRNAs | Pathology | Effect | Mechanisms | References |
|---|---|---|---|---|
| MiRNAs in CKD | | | | |
| miRNA-223 | IgA nephropathy, atherosclerosis, diabetic cardiomyopathy | Inflammation, apoptosis of vascular endothelial cell | Insulin-like growth factor 1 receptor, NLRP3 inflammasome | [40–42] |
| miRNA-21 | CKD, cardiorenal syndrome type 4 | Glomerulosclerosis, interstitial fibrosis, tubular injury, and inflammation | ERK1/2, TGF-β/Smad signaling, left ventricular remodeling | [36–39] |
| MiRNAs in CVDs | | | | |
| miRNA-223 | Atherosclerosis | VSMCs dedifferentiation and intimal hyperplasia | PDGFRβ | [69] |
| miRNA-126 | Myocardial infarction | Vascular damage and endothelial dysfunction, vascular inflammation | – | [70] |
| miRNA-197 | Metabolic syndrome | Dyslipidemia | – | [71] |
| miRNA-21 | Type 2 cardiorenal syndrome | Left ventricular remodeling, cardiac hypertrophy | ERK-MAP, left ventricular remodeling | [78–80] |
| miRNA-24 | Heart failure | Cardiac remodeling | – | [81] |

*Platelets Deteriorate Cardiac Remodeling of CKD Both Directly and Indirectly*

Aberrant cardiac remodeling with hypertrophy and fibrosis is one of the major pathological changes of CKD-associated CVDs. In CKD patients, uremic cardiomyopathy is a specialized cardiac pathology characterized by aberrant cardiac remodeling [73].

Previous studies have illustrated that activated platelets can release some pathophysiological factors including serotonin, thromboxane A2, platelet-activating factor, PDGF, etc. to participate in cardiac remodeling by regulating endothelial and VSMCs [74]. For example, a study showed that platelets and platelet-released serotonin (5-HT) were directly involved in the functional regulation of neonatal rat cardiac fibroblasts by enhancing the secretion of TGF-β1 and promoting their migration and differentiation to promote cardiac remodeling [75]. A recent study also provided evidence that platelet-specific p38α contributed to cardiac remodeling via the MAPK/P38 signal pathway, and platelet-specific p38α-deficient mice had improved cardiac function, reduced infarct size, decreased inflammatory response, and microthrombus in a myocardial infarction model [76]. Furthermore, the P2y12 receptor, one of the predominant activating receptors for platelets, promoted pressure overload–induced cardiac remodeling via platelet-driven inflammation in mice [77]. These studies clearly indicated that platelets and their products participate in cardiac remodeling directly. In addition, platelets can interact with those inflammatory cells and lead to cardiac remodeling indirectly, which is similar to the inflammatory functions of platelets in other cardiac pathological processes of CKD complications such as atherosclerosis and VC.

Platelet-derived miRNAs are also deeply engaged in cardiac remodeling. A clinical study suggested miRNA-21 as a novel biomarker for elderly patients with type 2 cardiorenal syndrome, as obviously the elevated level of serum miRNA-21 was found in these patients [78]. Similarly, miRNA-21-5p is a mediator of left ventricular remodeling through its regulation of PPARα [79]. In addition, miRNA-21 can control cardiac hypertrophy and affect the overall structure and functions of the heart by regulating the signaling pathway of ERK-MAP kinase [80]. What's more, overexpression of miRNA-24 in cultured rat cardiomyocytes resulted in hypertrophic growth. This indicates that miRNA-24 may regulate the development of cardiac remodeling [81]. Last but not least, miRNA-223 can regulate the gene expression of NLRP3 and conduce to fibrosis and inflammation of myocardial tissues in diabetic cardiomyopathy [42, 82]. All these studies clearly showed that platelet-derived miRNAs were closely related to cardiac remodeling. The functions of platelet-derived miRNAs in CKD and CKD-related CVDs are listed in Table 2.

In CKD patients, the high frequency of cardiac remodeling is strongly linked to platelet activation, which causes a cascade of downstream reactions. In a recent study, Yang et al. [83] found that platelets were significantly activated in 5/6 nephrectomy-operated mice, while cardiac remodeling was significantly ameliorated when platelets were effectively depleted. They further found that activated platelets released PF4 and induced macrophages to polarize toward a specific phenotype intermediate be-

tween the previously characterized M1 and M4 phenotypes. Then activated macrophages secreted MMP7, which could cleave a wide range of ECM proteins including collagen I, thereby leading to the process of cardiac remodeling during uremia. This study provided a potential mechanism of cardiac remodeling in uremic mice [83].

In conclusion, inappropriate platelet activation can affect the cardiac remodeling of CKD. They can facilitate macrophage dysfunction in cardiac remodeling in uremic mice. What's more, platelets can also recruit proinflammatory cells or shed miRNAs to precipitate cardiac remodeling.

## Conclusion

Here, we review the pathogenic roles of platelets in CKD and its cardiovascular complications. Besides thrombosis, the hyperactivated platelets also release large amounts of cytokines and chemokines that directly or indirectly contribute to CKD progression and the development of cardiovascular complications. Meanwhile, the hyperactivated platelets can also be swallowed by other cells, wherein they shed miRNA to affect their activities. Given these pleiotropic roles of platelets, we anticipate that more pathogenic mechanisms of platelet hyperactivation in CKD need to be defined. What's more, the prolonged and persistent state of inflammation in CKD patients is closely linked to coagulation disorder. Inflammation results in activation of coagulation, and coagulation also affects inflammatory activity. Proinflammatory cytokines and other mediators are capable of activating the coagulation system and leading to thrombin generation. As a result of the central role of platelets in the process of thrombosis, there exists an upward tendency in thrombotic risk in CKD patients. So oral anticoagulants are commonly used drugs in patients with CKD. Of note, both thrombosis and hemorrhage are prevalent in CKD; it remains unclear how CKD affects hemostasis via regulating platelet activity. Further studies focusing on the distinctive regulation of platelet activity by different stages of CKD or the special treatment during CKD may reconcile this contradiction. We believe that deeply resolving these questions will help explain the intrinsic mechanism of the high morbidity and mortality of CVD in CKD as well as provide new therapeutic targets for CKD-associated CVD.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.


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## Author Contributions

Shuiqin Gong: writing the draft of the review; Chenyu Wang: graphic drawing of the figures; Jiachuan Xiong, Ke Yang, and Jinghong Zhao: revising the review; Ke Yang and Jinghong Zhao: designing and approving this work.

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