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Atherosclerosis in chronic kidney disease: the role of macrophages

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Abstract

Patients with chronic kidney disease (CKD) are at increased risk of atherosclerotic cardiovascular disease and loss of renal parenchyma accelerates atherosclerosis in animal models. Macrophages are central to atherogenesis because they regulate cholesterol traffic and inflammation in the arterial wall. CKD influences macrophage behavior at multiple levels, rendering them proatherogenic. Even at normal creatinine levels, macrophages from uninephrectomized *Apoe*^{-/-} mice are enriched in cholesterol owing to downregulation of cholesterol transporter ATP-binding cassette subfamily A member 1 levels and activation of nuclear factor κ B, which leads to impaired cholesterol efflux. Interestingly, treatment with an angiotensin-II-receptor blocker (ARB) improves these effects. Moreover, atherosclerotic aortas from *Apoe*^{-/-} mice transplanted into renal-ablated normocholesterolemic recipients show plaque progression and increased macrophage content instead of the substantial regression seen in recipient mice with intact kidneys. ARBs reduce atherosclerosis development in mice with partial renal ablation. These results, combined with the clinical benefits of angiotensin-converting-enzyme (ACE) inhibitors and ARBs in patients with CKD, suggest an important role for the angiotensin system in the enhanced susceptibility to atherosclerosis seen across the spectrum of CKD. The role of macrophages could explain why these therapies may be effective in end-stage renal disease, one of the few conditions in which statins show no clinical benefit.

Introduction

More than 50% of deaths in patients with chronic kidney disease (CKD) on dialysis are attributable to cardiovascular disease.¹ even modest renal dysfunction, including isolated albuminuria, results in a dramatic increase in the risk of cardiovascular disease.²⁻⁵ the relationship between decreasing renal function and increasing rates of cardiovascular disease and mortality is due to multiple mechanisms, including abnormal myocardial remodeling, ventricular hypertrophy, arrhythmia and cardiac arrest; the influence of these factors depends on the level of CKD. Compared with the prevalence of atherosclerotic disease in individuals with intact kidney function, however, atherosclerotic disease is over-represented across the entire spectrum of patients with CKD. macrophages have critical roles in all stages of atherosclerotic lesion formation and mounting experimental evidence implicates their importance in the vascular complications of renal disease.

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Competing interests

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Macrophages contribute to all stages of atherosclerosis through their role in inflammation and lipid homeostasis.⁶ retention of atherogenic lipoproteins in the arterial intima prompts the production of leukocyte chemo-attractant molecules. these molecules activate receptors on rolling monocytes, which leads to their initial adhesion mediated by selectins, followed by their integrin-dependent adhesion to the endothelium and their, subsequent diapedesis into the intima.⁷ Chemokines (chemotactic cytokines) and their receptors have been implicated in the migration of monocytes and t cells into the arterial intima.⁸ the critical role for macrophages in the development of atherosclerosis is illustrated by the observation that osteopetrotic mice, which lack macro-phage colony-stimulating factor, have low numbers of macrophages in their atherosclerotic lesions and a small lesion area, even in the presence of severe hyper-lipidemia.⁹ macrophages also have a central role in innate immunity.¹⁰ the interaction between antigen-presenting dendritic cells and T cells activates the adaptive immune response and defines the inflammatory processes of early atherogenesis. ligation of CD40 on activated Tt cells leads to enhanced production of T helper (T_H) 1 cell cytokines, including interferon γ ,¹¹ which is proatherogenic.¹² this T_H1 cytokine cascade is counterbalanced by the presence of antiatherogenic T_H2 cytokines, including interleukin (il)-10.¹³ this review focuses on the mechanisms of CKD-induced atherosclerosis, with particular emphasis on the role of macrophages, as demonstrated by experimental studies and data from clinical studies.

Macrophages and atherosclerosis

The accumulation of macrophages laden with cholesterol ester in the arterial intima is the hallmark of fatty streak formation in humans and experimental models. macrophages internalize atherogenic lipoproteins (such as oxidized LDL) via scavenger receptors, including CD36¹⁴ and class a scavenger receptors (SR-A).^{15,16} native lipoprotein receptors, such as the LDL receptor-related protein 1,¹⁷ are also expressed by macrophages and contribute to atherogenesis. Cholesterol entry into macrophages is counterbalanced by the efflux of free cholesterol into acceptor particles (such as HDL).¹⁸ Free cholesterol efflux is mediated by active trans porters, such as ATP-binding cassette sub family a member 1 (ABCA1), ATP-binding cassette subfamily G member 1 (ABCG1) and scavenger receptor class B member i (SR-BI), or by passive diffusion.¹⁹ an *in vitro* study of isolated mouse macrophages demonstrated that abca1 mediates the efflux of free cholesterol and phospholipids to both apo-lipoprotein A-1 (Apoa1) and apolipoprotein E (ApoE).²⁰ ApoE is abundantly expressed by macrophages in atherosclerotic lesions,²¹ might represent the physiological acceptor of cholesterol in atherosclerotic plaques,²⁰ and is strongly antiatherogenic.^{21,22} macrophages and/or dendritic cells are also capable of leaving the atherosclerotic plaque, thus promoting regression of atherosclerosis in murine models. Gene expression profiles of regressing atherosclerotic plaques have linked CC-chemokine receptor (CCR) 7 with dendritic cell emigration, and antibody-blocking experiments in *ApoE*^{-/-} mice have confirmed that CCR7 causes macrophage emigration and plaque regression.²³

Macrophages also influence atherogenesis through their susceptibility to death. endoplasmic reticulum stress is a major inducer of macrophage apoptosis^{24,25} and, whereas macrophage apoptosis in the early stages of atherogenesis might result in reduced lesion cell-ularity,²⁶ apoptosis in advanced lesions expands the necrotic core owing to impaired phagocytosis of apoptotic bodies.²⁷ *In vitro* and *in vivo* experiments from our laboratory revealed a critical cooperative role for LDL receptor-related protein 1 and ApoE in a functional axis that regulates efferocytosis of apoptotic macrophages in atherosclerotic lesions.²⁸

CKD modulates macrophage function

Macrophage infiltration

Anatomical and radiological analyses document that CKD dramatically accelerates growth of atherosclerotic lesions.^{29–32} atherosclerotic plaques of patients with CKD are more complex than those of individuals with normal renal function, and have features that suggest greater instability. these features include increased lipid content, widespread necrosis, disruption of the extracellular matrix, and enhanced inflammation.³⁰ macrophages, the largest cell contingent of the atheroma, are involved in all of these processes.

Experimental studies in atherosclerosis-prone *Apoe*^{−/−} mice reveal that a reduction in the renal parenchyma, ranging from uninephrectomy to subtotal renal ablation, significantly expands macrophage-positive areas within the intima (Figure 1).^{33–35} Peritoneal macrophages harvested from uninephrectomized *Apoe*^{−/−} mice show 50% greater migratory activity in response to chemo attraction with CC-chemokine ligand (CCL) 2 (also known as monocyte chemoattractant protein 1) than macrophages obtained from *Apoe*^{−/−} mice with intact kidneys.³⁵ experimental renal ablation activates numerous vascular chemotactic cytokines and chemokine receptors, including vascular cell adhesion molecule 1 (vCam1), intercellular cell adhesion molecule 1 (ICAM1), E-selectin, il-6, tumor necrosis factor and CCL2, to promote macrophage adhesion to the endothelium and trans migration into the subendothelial space.^{36–38} increased vascular expression of some of these factors precedes both the elevation in their plasma levels and the development of arterial plaques in renal-ablated *Apoe*^{−/−} mice, findings that support a role for early macrophage recruitment into the vessel wall in renal-injury-induced atherogenesis.³⁴

Plasma levels of adhesion molecules and markers of inflammation and oxidation are increased in patients with CKD and correlate with the degree of renal impairment.^{39–43} indeed, high plasma levels of iCam1 and VCAM1 are strong independent predictors of poor outcome in patients with CKD.⁴³ uremic serum increases the expression and shedding of adhesion molecules by vascular endothelial cells.⁴⁴ the coronary plaques of patients with CKD (particularly calcified plaques) have increased expression of the inflammatory markers CD40–CD154 and of C-reactive protein.⁴⁵ notably, peripheral leukocytes of patients with CKD have greater responses to inflammatory and oxidative stimuli than those of healthy controls.^{46–48} even without stimulation, circulating granulocytes and monocytes of patients on dialysis produce elevated levels of super oxide and hydrogen peroxide, and have greater expression of CD11b/ CD18 integrins than those of healthy individuals.⁴⁷ in addition, monocytes from patients with end-stage renal disease (ESRD) have suppressed levels of anti-inflammatory cytokines and seem to be more susceptible to macrophage transformation than cells from normal controls.⁴⁶ such observations support the idea that CKD increases systemic inflammation, vascular micro-inflammation and macrophage priming, all of which can amplify the expression of cytokines by macrophages and their recruitment into the subendothelial space.

A major contributor to heightened inflammation is the enhanced oxidative stress that develops early in CKD, persists as renal function declines, and is not improved by dialysis treatment.^{47–52} Urea, at disease-relevant concentrations, stimulates the generation of reactive oxygen species *in vitro* and *in vivo*.⁵³ Factors that promote oxidative stress in the setting of CKD include NADPH oxidase, uncoupled endothelial nitric oxide synthase and myeloperoxidase.^{49,54,55} myeloperoxidase is a predictor of cardiovascular disease risk and is abundantly expressed by neutrophils and macrophages within atherosclerotic lesions in patients with CKD.^{56,57} Compared with healthy controls, leukocyte lysate from patients with CKD has increased myeloperoxidase activity, which is not improved by dialysis.⁴⁶ a single nucleotide polymorphism in the promoter region of the myeloperoxidase gene has

been associated with reduced expression of myelo peroxidase and linked to reduced prevalence of cardio vascular disease in patients with CKD and ESRD.^{58,59} treatments that decrease oxidative stress and inflammation, such as *N*-acetylcysteine or neutralizing antibodies against the receptor for advanced glycation end products, significantly reduce experimental atherosclerosis caused by renal dysfunction.^{60,61} moreover, and in contrast with results in the general population, anti-oxidative therapy substantially reduces cardio vascular morbidity in patients with CKD.^{62,63} For example, *N*-acetylcysteine has been shown to decrease concentrations of oxidized LDL cholesterol by 76% and the composite end points of nonfatal myocardial infarction, cardiovascular death, revascularization and ischemic stroke by 40% in patients with stage 5 CKD.^{62,63} in these same small studies, antioxidant therapy with vitamin E reduced the rate of cardiovascular end points by >50% and the rate of myocardial infarction by 70% in patients on hemodialysis.^{62,63} although antioxidant therapies decrease levels of electronegative LDL and biomarkers of oxidative stress in patients with mild to moderate CKD and patients with ESRD on hemo dialysis,^{64–66} no large clinical trials have been conducted to evaluate the efficacy of such interventions on the risk of cardiovascular events or death in these populations. indeed, large-scale, long-term follow-up studies of vitamin E supplementation in individuals with normal renal function have been disappointing.^{67,68} nonetheless, CKD increases oxidative stress, thus creating an optimal set up for antioxidant therapies to target macrophage infiltration and function. However, currently available antioxidant therapies might not be sufficiently effective to influence the complexities that underlie the increased mortality rates in patients with CKD.

Macrophage egress

In addition to increased cellular infiltration, the vascular accumulation of macrophages in CKD might be caused by their increased survival or decreased egress from the vascular wall (Figure 1). transplantation of atherosclerotic aorta from hyperlipidemic *Apoe*^{-/-} mice into normolipemic wild-type mice results in plaque regression and the loss of foam cells into the local lymphatic system and circulation.^{23,69,70} substantial foam-cell exit is observed within 3 days of transplantation. the resolution of the atheroma under these conditions also includes abatement in areas of necrosis, extracellular accumulation of cholesterol, and fibrosis.⁷¹ in a 2010 study, renal ablation has been shown to inhibit macrophage emigration out of the vessel wall.⁷² transplantation of atheromatous aortic segments from *Apoe*^{-/-} mice into normolipemic mice after renal ablation did not cause plaque regression as seen after transplantation of atheromatous aortic segments from *Apoe*^{-/-} mice into normolipemic recipient mice with intact kidneys. on the contrary, the plaques of renal-ablated normolipemic recipients actually expanded and contained more macrophages than those of recipients with intact kidneys. the increased macrophage content was not linked to changes in cellular survival and macrophages within the plaques of renal-ablated mice showed downregulation of serum response factor target genes and upregulation of the migration factor CCR7. in view of the dynamic nature of the atherosclerotic plaque, impaired plaque regression and decreased macrophage emigration in the setting of renal damage might contribute not only to accelerated atherosclerosis, but also to the lack of vascular benefits from treatments that lower plasma lipids in advanced CKD.

Macrophage trapping

CKD-induced changes within the local vascular milieu and modulation of macrophage function may cause sub-endothelial trapping of macrophages (Figure 1). CKD increases the oxidation and glycosylation of matrix molecules including proteoglycans, collagen, and elastin.^{73,74} modifications of extracellular matrix promote lipoprotein retention and oxidation and lead to increased cholesterol accumulation by the macrophage, resulting in

increased cholesterol content in the cellular membrane, which causes stiffness and impaired cellular mobility.^{75,76}

Macrophage migration and trapping are also affected by the scavenger receptor CD36, which is upregulated in monocytes of patients with CKD and uremia.^{77,78} one study showed that CD36-mediated uptake of oxidized LDL induced actin polymerization and cell spreading via activation of focal adhesion kinase and inactivation of src homology 2-containing phosphotyrosine phosphatase, which inhibited cellular migration.⁷⁹ other investigators, however, have reported that upregulation of CD36 actually enhances macrophage migration.^{80,81} since CD36 regulates several specific intracellular signaling pathways related not only to cellular migration but also to inflammation and cholesterol efflux, CD36 activation might induce several diverse functions depending on the activating trigger in each particular biological setting.⁸²

CKD and macrophage lipid homeostasis

Macrophage foam-cell formation results from an imbalance between lipoprotein uptake and cholesterol efflux (Figure 2). scavenger receptors are upregulated in macro phages from patients with CKD as well as in tissues such as the aorta and kidneys of animals with renal injury.^{77,78,83–86} monocytes from patients on hemo-dialysis or peritoneal dialysis have higher levels of CD36 than monocytes from patients with CKD who are not on dialysis or individuals without renal disease.^{77,78} increased expression of SR-A has also been documented in macro phages from patients on hemodialysis.^{83,87,88} uremic serum enhanced SR-A expression and activity in the human monocytic cell line U937.^{83,87,88} such changes predict increased lipid uptake, inflammation, migration and trapping of macrophages.^{75,76,79–81} once upregulated, macrophages do not downregulate scavenger receptors or alter the influx of cholesterol by this pathway and prevention of foam-cell formation becomes critically dependent on lipid efflux.

Cholesterol efflux involves the mobilization of excess lipids from intracellular pools to the plasma membrane as well as the transfer of excess lipids to external cholesterol acceptors.^{89,90} a 2009 experimental study showed that even subtle renal perturbation resulting from uni-nephrectomy disrupted the mobilization of macrophage cholesterol and potentiated foam-cell formation. indeed, macrophages from uninephrectomized *Apoe*^{−/−} mice show a massive accumulation of cellular cholesterol that is independent of plasma cholesterol levels.⁹¹ these findings complement clinical observations demonstrating that the development of atherosclerotic complications in CKD does not necessarily follow plasma lipid levels and emphasize the importance of altered local dynamics in macrophage lipid handling under conditions of impaired renal function.

The key pathways for the movement of cholesterol out of macrophages involve an energy-dependent efflux that involves the cholesterol transporters ABCA1 and ABCG1, and the scavenger receptor SR-BI, which is driven by the cholesterol gradient (Figure 2). using the *Apoe*^{−/−} mouse model, we showed that uni nephrectomy downregulates the expression of both macrophage *Abca1* and the protein it encodes, but does not have significant effects on *abcg1* or *sr-b1* expression.⁹¹ notably, the repression of *abca1* in macrophages of uni-nephrectomized mice occurred despite very high levels of cellular cholesterol, the physiological stimulus that increases cholesterol efflux via membrane transporters. interestingly, uremic plasma downregulates levels of ABCA1 in cultured human coronary artery endothelial cells.⁹² Downregulation of ABCA1 expression in experimental and human CKD might be caused by activation of the nuclear factor κ B (NF κ B) signaling pathway.^{93–95} In support of this hypothesis, we showed that specific antagonism of NF κ B activation pathways in macrophages of uninephrectomized *Apoe*^{−/−} mice restored *abca1* levels.⁹¹

modulation of ATP-binding cassette transporters has also been reported for other chronic diseases, particularly diabetes mellitus, in which metabolic factors including reactive carbonyls and free fatty acids impair abca1-dependent cholesterol export by destabilizing abca1.^{96,97} these metabolites are also elevated in patients with CKD.⁹⁸ these findings indicate that repression of aBCa1 owing to renal dysfunction might contribute to the impaired clearance of excess cholesterol from arterial macrophages and suggest a potential target for intervention in CKD-induced atherosclerosis. Of note, treatment with human APOAI did not reduce the atherosclerotic burden of nephrectomized *ApoE*^{-/-} mice.⁹⁹ However, this intervention did lessen the lipid and collagen content of the atherosclerotic plaques and increased the area occupied by smooth muscle cells—changes that could be indicative of plaque stabilization.⁹⁹

In addition to modulating cholesterol homeostasis, ABCA1 has major anti-inflammatory and antiapoptotic functions.⁹⁰ macrophages from abca1-deficient mice have increased toll-like receptor (TLR) signaling, which enhances their inflammatory response to lipopolysaccharide and other TLR ligands.^{100,101} upregulation of TLR2 and TLR4 has been reported in monocytes of dialysis patients with systemic inflammation,¹⁰² whereas expression of these receptors was reportedly decreased in dialysis patients with low levels of C-reactive protein.¹⁰³ ABCA1 also directly suppresses lipopolysaccharide-induced inflammatory cytokine production by macrophages through a pathway that involves signal transducer and activator of transcription 3 and is independent of cholesterol export.⁹⁶ in view of the chronic systemic and vascular inflammation that prevails in CKD, repressed ABCA1 function in macrophages might be especially detrimental through suppression of lipid export and activation of the inflammatory response.

CKD and lipoproteins

CKD influences lipoproteins that are involved in macrophage function. CKD generates both atherogenic LDL and dysfunctional HDL particles. Plasma levels of modified and oxidized LDL, which correlate with cardiovascular event rates in the general population,¹⁰⁴ are elevated at all stages of CKD.¹⁰⁵ myeloperoxidase-generated reactive nitrogen species facilitate lipid peroxidation and protein nitration, which enables LDL to be avidly taken up by CD36.^{55,106} Furthermore, the catalysis of LDL carbamylation by myeloperoxidase reduces the affinity of LDL for the LDL receptor and increases its affinity for scavenger receptors.^{55,107} such findings suggest that CKD might be associated with modifications in the composition and function of LDL that promotes atherosclerosis, but is not affected by lipid-lowering therapy.^{108,109}

CKD also affects HDL levels and function. low levels of HDL cholesterol are a powerful negative risk factor for cardiovascular disease, prevail at all stages of CKD and, as in the general population, are associated with increased mortality.¹¹⁰ experimental and clinical studies demonstrate that several factors contribute to the low level of HDL in CKD, including reduced levels of APOAI, enriched levels of serum amyloid a, and decreased lecithin-cholesterol acyltransferase function.^{84,85,110–112} CKD also impairs HDL maturation, which can profoundly compromise many of its protective functions. For example, under normal conditions HDL fractions contain antioxidant enzymes such as paroxonase and glutathione peroxidase.^{113,114} However, the accumulation of advanced glycation end products and acrolein in CKD reduces the levels of these enzymes, compromising HDL function. indeed, HDL from patients with ESRD has markedly reduced antioxidant and anti-inflammatory activity, which is not altered by dialysis.^{85,112,115–118} Furthermore, HDL from patients on hemodialysis does not protect LDL from oxidation,¹¹⁸ whereas the addition of an APOAI mimetic peptide to LDL obtained from patients on dialysis reduces its capacity to increase monocyte chemotactic activity in cultured

endothelial cells.¹¹⁸ taken together, these observations suggest that severe CKD influences the composition and function of LDL and HDL, as well as macrophage gene expression, to cause perturbations that are not necessarily targeted by current lipid-lowering interventions. whether extreme reductions in LDL level have cardiovascular benefits in patients with ESRD remains unknown, but the answer to this question might come from studying the direct cellular effects of statin therapy. statins suppress cholesterol synthesis and reduce intracellular concentrations of oxysterols and isoprenoids, intermediaries that influence nuclear receptors and G proteins to modulate signaling pathways and gene expression. the effect of statins on these pathways is influenced by cholesterol content and by cellular activation and differentiation.^{119–125} For example, the downregulation of ABCA1 level induced by statins is more pronounced with increased macrophage differentiation and less pronounced with increased cholesterol loading of the cell.¹¹⁹ it is therefore possible that the activated macrophages of patients with advanced CKD do not respond normally to statin stimulation owing to their abnormal content and distribution of cellular lipids.

CKD activation of angiotensin II

CKD activates the renin–angiotensin system (RAS), which leads to heightening of its principal effector peptide, angiotensin II, and ultimately modulation of macrophage function. antagonism of the RAS by angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-II-receptor blockers (ARBs) is the cornerstone of treatment of progressive renal failure.^{126,127} angiotensin II is also a major driving force in atherosclerosis. Numerous epidemiological studies document fewer cardiovascular events and increased survival in individuals treated with antagonists or inhibitors of angiotensin II.^{128,129} notably, these benefits are independent of hemodynamic effects and underscore a more direct role for angiotensin II in cardiovascular and renal diseases. the levels, duration, and localization of angiotensin II activation that are necessary to activate these disease pathways are unknown. activated angiotensin II in CKD can potentiate macrophage infiltration of the arterial intima in every stage of atherogenesis. experimentally, a sustained increase in circulating levels of angiotensin II through exogenous infusion causes recruitment of macrophages along with vascular inflammation, lesional neovascularization, hemorrhage and elastolysis in hyperlipidemic mice and rabbits.^{130–135} in clinical settings, short-term elevations in angiotensin II activity, such as hypotension, volume depletion, and cardiac ischemia, might have delayed consequences on atherosclerosis. we examined whether transient elevations in levels of angiotensin II can affect future plaque development, and found that atherosclerosis was dramatically increased in *Apoe*-knockout mice 3 months after a 2-week infusion of a nonhypertensive dose of angiotensin II.¹³⁰ as the amplification of atherosclerosis did not occur during angiotensin II infusion, these results confirm that angiotensin II activates mechanisms that promote and amplify atherogenic processes. indeed, angiotensin II exposure caused an immediate increase in the vascular messenger RNA expression of several chemoattractants (including CCL2 and its receptor CCR2) and a subsequent accumulation of macrophages in the aorta of angiotensin-II-infused mice.¹³⁰ interestingly, our *ex vivo* study found that macrophages harvested from angiotensin-II-infused mice had substantially increased migration across the cell membrane in response to CCL2 chemotaxis.¹³⁶ moreover, angiotensin II amplifies atherosclerosis and increases macrophage content in the aorta of mice carrying *Apoe*^{−/−} macrophages.¹³⁶ Conversely, inhibition of angiotensin II reduces macrophage infiltration and promotes compositional changes such as increased collagen content that might stabilize the atherosclerotic plaque.^{137,138}

The modulation of macrophage-specific functions by angiotensin II is supported by observations that monocytes and macrophages express all components of the RAS, including type-1 (AT₁) and type-2 (AT₂) angiotensin II receptors.^{139–141} *In vitro*, angiotensin II increases the macrophage-mediated modification and uptake of LDL,

cholesterol synthesis in macrophages, differentiation of monocytes to macrophages, activation of macrophage-generated oxidative stress, and levels of proinflammatory cytokines.¹⁴² monocytes from patients with hypertension have high numbers of AT₁ receptor in dimer form, which correlates with increased angiotensin-II-dependent adhesion to endothelial cells.^{143,144}

The functional importance of the macrophage AT₁ receptor in modulating atherosclerosis *in vivo* is illustrated by studies using chimeric mice in which the AT₁ receptor (Atgr1) is either ablated or expressed exclusively in hematopoietic cells.^{145–148} Transplantation of bone marrow from *Atgr1*-knockout mice into atherosclerosis-prone mice lacking either Apoe or the LDL receptor did not markedly alter their atherosclerotic lesions.^{145,147} infusion of angiotensin II increased atherosclerosis and macrophage infiltration in *Apoe*^{−/−} mice that had received bone marrow from *Atgr1*^{+/+} mice but not in *Apoe*^{−/−} mice that had received bone marrow from *Atgr1*-knockout mice. likewise, reconstitution of *Ldlr*-knockout mice with bone marrow from *Atgr1*^{+/+} mice or *Atgr1*-knockout mice produced the same results.^{145,147} By contrast, *Atgr1*-knockout mice reconstituted with bone marrow from *Atgr1*^{+/+} mice had increased atherosclerosis and decreased collagen content after exposure to angiotensin II, consistent with the phenotype of a more unstable lesion. these findings suggest that in an angiotensin-II- heightened state, such as CKD, the macrophage AT₁ receptor is responsible for acceleration and destabilization of plaques.³⁵ in this way, increased expression of ACE by circulating monocytes correlates with cardiovascular events and mortality in patients on hemodialysis.¹⁴⁹

Inhibition of the action of angiotensin II with ACE inhibitors or ARBs reduces the risk of cardiovascular events in individuals with normal renal function. experimental findings suggest similar benefits in patients with CKD. we showed that atherosclerosis after uninephrectomy in *Apoe*^{−/−} mice is dramatically lessened by antagonism of angiotensin II with losartan but not with the nonspecific antihypertensive agent, hydralazine.³⁵ the reduction in the atherosclerotic burden with losartan treatment was accompanied by changes in plaque composition that included fewer macrophages. moreover, *in vitro* macrophage migration was reduced by ARB treatment. these effects on macrophage infiltration were accompanied by the preservation of extracellular matrix components, especially elastin, and decreased levels of the proteolytic enzyme, cathepsin S. none of these benefits were observed in hydralazine-treated mice.

As discussed above, a reduction in renal mass by uninephrectomy decreases cholesterol efflux in macrophages via repression of the macrophage ABCA1 transporter.⁹¹ *In vivo* treatment with an ARB restored macrophage Abca1 expression in the macrophages of uninephrectomized *Apoe*^{−/−} mice. these results complement previous *in vivo* and *in vitro* findings demonstrating that exogenous angiotensin II downregulates ABCA1.^{150,151} Furthermore, incubation of human and mouse macrophages with ARBs, especially, telmisartan, increased cholesterol efflux via a peroxisome proliferator-activated receptor - dependent pathway, which caused an upregulation of ABCA1 level.^{150–153} taken together, these observations suggest a pivotal importance of angiotensin II–ABCA1 interaction for cholesterol homeostasis in macrophages in the setting of renal dysfunction, which provides a basis for possible modulation of excess risk of cardiovascular disease in patients with CKD. interestingly, *in vivo* treatment of *Apoe*^{−/−} mice with the ARB losartan substantially attenuated upregulation of NF- κ B subfamily proteins REIA and p50, suggesting a potential key regulatory step in this pathway in cholesterol efflux.⁹¹ ARB treatment was also found to have suppressive effects on NF- κ B in other tissues.^{95,154}

CKD-induced activation of angiotensin II can also derange lipoprotein composition and function. angiotensin II promotes LDL oxidation and impairs maturation of HDL, whereas

inhibition of angiotensin II action has opposite effects.^{138,142,153–156} indeed, ACE inhibitors substantially reduced lipid myeloperoxidase-mediated oxidation of LDL,¹⁵⁷ oxidized-LDL-mediated transformation of cultured macrophages into foam cells,¹⁵⁸ and levels of oxidized lipoproteins in the serum and arteries of hypercholesterolemic rabbits and mice.¹⁵⁹ although experimental findings suggest that antagonism of angiotensin II might benefit patients with CKD, clinical studies remain sparse. Post hoc analysis of ACE inhibitor treatment in patients with mild to moderate renal impairment found an increased reduction in risk of cardiovascular events in these individuals than in those without compromised renal function.^{2,160} However, an inclusive evaluation of studies of ACE inhibitor or ARB treatment on cardiovascular outcomes in patients with CKD, including ESRD, did not allow a clear and definitive interpretation of the findings. some studies did not find a benefit of angiotensin II inhibition,^{161–163} while many others, including a large meta-analysis,¹⁶⁴ report that patients with advanced CKD treated with ACE inhibitors or ARBs have fewer cardiovascular events and reduced mortality.^{165–171}

Conclusions

CKD affects macrophage function both directly and indirectly. Direct effects include upregulation of scavenger receptors, decreased cholesterol efflux via activation of NF- κ B and repression of ABCA1. indirect effects include the modification of lipoproteins that renders these particles more susceptible to scavenging by macrophages and inflammatory and oxidative insults to the endothelium that cause increased recruitment, trapping and decreased egress of arterial macrophages. many of these macrophage changes are linked to the activation of the RAS and are responsive to treatment with agents that reduce vascular exposure to angiotensin II. interventions that modulate macrophage behavior via antagonism of angiotensin might produce vascular benefits across the spectrum of CKD.

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Key points

- Even subtle chronic kidney disease (CKD) increases the risk of cardiovascular events in humans and worsens atherosclerosis in experimental models
- CKD-associated inflammatory and oxidant stress promotes the infiltration and trapping of circulating monocytes in the arterial intima
- CKD promotes the formation of foam cells by downregulating cholesterol efflux through activation of nuclear factor κ B and repression of cholesterol transporter ATP-binding cassette subfamily A member 1
- CKD modifies lipoproteins and makes them more susceptible to scavenging by macrophages and less capable of acting as acceptors of cellular cholesterol
- Systemic and macrophage angiotensin II actions contribute to the enhanced susceptibility of patients with CKD to atherosclerosis
- Treatment with antagonists and inhibitors of angiotensin II might be of particular value in the prevention of cardiovascular disease in patients with CKD

Review criteria

Original articles, review articles and abstracts for this Review were obtained by searching PubMed and MEDLINE for full-length articles in English published up until 2010 using the search terms: “atherosclerosis”, “plaque”, “myocardial infarction”, “cardiovascular disease”, “CVD”, “vascular calcification”, “intima-media thickness” “apolipoprotein E”, “statin”, “chronic kidney disease”, “CKD”, “kidney”, “renal”, “uninephrectomy”, “dialysis”, “macrophage”, “monocyte”, “foam cell”, “cholesterol”, “lipid”, “lipid metabolism”, “LDL”, “HDL”, “cholesterol efflux”, “scavenger receptor”, “CD36”, “ABCA1”, “ABCG1”, “ApoAI”, “NF B”, “PPAR” and “angiotensin”.

Figure 1.

Potential pathways by which CKD modulates the accumulation of arterial macrophages. CKD potentiates macrophage infiltration into the vessel wall by increasing the expression of vascular adhesion molecules (VCAM1, ICAM1 and selectins) and chemoattractants (CCL2 and MCSF). CKD modifies extracellular matrix components of the vasculature (for example, the oxidation or glycation of glycoproteins, collagen, and elastin), thereby increasing lipoprotein retention and the migratory capacity of macrophages. CKD impairment of macrophage egress from the vessel wall might involve disruption of the CCR7 pathway. Abbreviations: CCL2, CC-chemokine ligand 2; CCR7, CC-chemokine receptor 7; CKD, chronic kidney disease; ICAM1, intercellular adhesion molecule 1; MCSF, macrophage colony-stimulating factor; VCAM1, vascular cell adhesion molecule 1.

Figure 2.

Potential mechanisms by which CKD modulates macrophage lipid handling. CKD promotes the modification (oxidation, carbamylation) of lipids and lipoproteins as well as the upregulation of scavenger receptors (CD36 and SR-A), leading to increased macrophage lipid uptake and foam-cell formation. CKD also dysregulates lipid efflux, by downregulating the expression of the ABCA1 transporter (but not ABCG1 or SR-BI) via upregulated NF- κ B activity. Retained metabolites, oxidative stress and inflammatory cytokines prevailing in CKD are likely key modulators of these macrophage receptors and transporters.

Abbreviations: ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; APOAI, apolipoprotein A-I; CKD, chronic kidney disease; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LXR/RXR, liver X receptor and retinoid X receptor heterodimer; mLDL, modified low-density lipoprotein; NF- κ B, nuclear factor- κ B; PPAR, peroxisome proliferator-activated receptor; SR-A, scavenger receptor class A member 1; SRBI, scavenger receptor class B member I; VLDL, very-low-density lipoprotein.