Narrative Review of Carotid disease and the kidney

Luca Zanoli[1]^, Dimitri P. Mikhailidis[2]

[1]Nephrology, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [2]Department of Clinical Biochemistry, Royal Free Hospital campus, University College London, London, UK

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Correspondence to: Luca Zanoli, MD, PhD, FASN. Nephrology, Department of Clinical and Experimental Medicine, Policlinico Universitario, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy. Email: luca.zanoli@unict.it.

Abstract: Patients with chronic kidney disease (CKD) have an increased cardiovascular (CV) risk that is only in part explained by established risk factors. Carotid arteriosclerosis and atherosclerosis are increased in CKD, play a role in the causation of CV disease in these patients and can affect the progression of renal disease. The arterial stiffening process is evident even in CKD patients with a very mild reduction of glomerular filtration rate (GFR) whereas arterial thickening is evident in more advanced stages. Possible mechanisms include functional and structural alterations of the arterial wall. Arterial stiffness can mediate the effect of CKD on target organs (i.e., brain, kidney and heart). In this review we discuss the arterial phenotype of patients with CKD. This is characterized by increased common carotid artery stiffness and outward remodeling (enlargement and thickening of the arterial wall) and a normal/reduced stiffness paired with an inward remodeling (narrowing of the arterial wall) of muscular arteries. We also discuss the consequences of carotid dysfunction, including the involvement of large elastic arteries stiffness on ventricular-vascular coupling, the mechanisms linking carotid stiffening and increased cardio- and cerebrovascular risk in CKD patients, and the therapeutic options to improve carotid function.

Keywords: Arterial stiffness; carotid artery; chronic kidney disease (CKD); inflammation; pulse wave velocity

Introduction

Cardiovascular (CV) risk is higher in patients with chronic kidney disease (CKD) compared with the general population (1) and, among patients at high CV risk, in those with a reduction of glomerular filtration rate (GFR) (2). This risk may be evident even with a mild reduction in renal function (2-4) or in the presence of microalbuminuria (5) and is 10–100-fold higher in patients with end stage kidney disease (ESKD) (6). In fact, patients in the early stages CKD are more likely to die from CV diseases than to progress to ESKD (7). These findings suggest that a reduced GFR is an independent CV risk factor. Since the prevalence of CKD in the general population is high and rising (8), this condition is a major public health problem.

Established CV risk factors, such as hypertension and diabetes mellitus, only explain part of the excessive CV risk reported in CKD patients (9). Therefore, other factors are likely to be involved. Carotid arteriosclerosis and atherosclerosis are increased in CKD, play a role in the causation of CV disease in CKD patients (10-12) and can also affect the progression of kidney disease (13-15). Possible mechanisms include functional and structural alterations of the arterial wall, including endothelial

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^ ORCID: 0000-0003-1678-3778.

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dysfunction, extracellular matrix stiffening, mesangial cell proliferation, low density lipoprotein (LDL)-dependent stimulation of fibronectin, mesangial matrix production and recruitment of inflammatory cells (16-19). Considering that myocardial disease [left ventricular hypertrophy (LVH), fibrosis and dysfunction] and not atheromatous coronary artery disease is the principal cause of CV death and disease in CKD (20), large elastic arteries arteriosclerosis could contribute to the effect of CKD on CV events.

The reduction in carotid-femoral pulse wave velocity, a measure of large elastic arteries stiffness, is associated with improved survival independent of blood pressure changes in patients with ESKD (21). Several treatment options have been proposed to improve carotid function in various clinical settings, including CKD (19); the early identification of patients with increased large elastic arteries stiffness could be useful to reduce the progression of CKD and the risk for CV events.

In this review we aimed to discuss the specific carotid phenotype of CKD, the different vascular involvement in carotid and muscular arteries, the effect of carotid stiffness on ventricular-vascular coupling and the mechanisms at the origin of the increased cardio- and cerebrovascular risk in CKD patients.

We present the following article in accordance with the Narrative Review checklist (available at http://dx.doi.org/10.21037/atm-20-5001).

Methods

A literature search of studies in humans was performed using MEDLINE, Scopus, ISI Web of Science, and Google Scholar databases (last accessed on 01 September 2020) without restrictions on the year of publication using the terms "carotid artery", "arterial stiffness", or "intima-media thickness" in combination with "chronic kidney disease", "inflammation", or "hypertension". The inclusion criteria included peer-reviewed publications of randomized controlled trials, observational studies, reviews, meta-analyses and guidelines in English. First, the titles of these articles were screened for relevance. Second, publications with titles or abstracts appearing to meet the aims of this review were selected. The reference lists of the analyzed articles were also searched. These articles were subjected to the same selection procedures. We discuss both the findings and their relevance in the subsections below.

Discussion

Carotid phenotype in CKD

In patients with CKD, 2 distinct and partially overlapping alterations of the carotid arteries are detectable, atherosclerosis and arteriosclerosis. Atherosclerosis is a disease of conduit arteries with a patchy distribution, caused by lipid deposition in the intima layer of the arterial wall that leads to intima-media thickening and atherosclerotic plaque formation (22). In contrast, arteriosclerosis is caused by functional (i.e., endothelial dysfunction) and/or structural alterations of the arterial wall (i.e., changes of the intrinsic characteristics of the biomaterial, thickening and calcification of the medial arterial layer). In patients with CKD, arterial remodeling seems to differently affect elastic (i.e., aorta and common carotid artery) and muscular arteries (i.e., brachial, femoral and renal artery).

Carotid atherosclerosis in CKD

Atherosclerosis is a progressive disease that includes subclinical lesions [increased carotid intima-media thickness (cIMT) (23)] and more advanced lesions (plaque and stenosis). The involvement of the carotid district is considered a proxy of systemic atherosclerosis (24).

Carotid plaque rupture or stenosis are two critical complications in the evolution of atherosclerotic plaque (25,26). Plaque formation is characterized by the deposition of cholesterol in the intima layer. The further production of connective tissue by fibroblasts, and calcium deposition contribute to the sclerosis and hardening of the atherosclerotic lesions and reduction of the arterial calibre (27). In patients with CKD, further studies are needed to test whether alterations of the Wnt/β-catenin signalling pathway is involved in the development of atherosclerotic lesions (28,29). Moreover, atherosclerotic lesions can stimulate clot formation and thrombosis, with the consequent sudden obstruction of blood flow. Finally, plaque rupture can lead to the cholesterol crystal embolization syndrome (30,31), a manifestation of atherosclerotic disease and a relatively rare complication of invasive arterial procedures, with important clinical manifestations ranging from peripheral cutaneous manifestations (e.g., livedo reticularis, blue toe syndrome) and renal failure to global neurologic deficits, depending on the arterial district involved. The changes in plaque composition, inflammation and geometry may
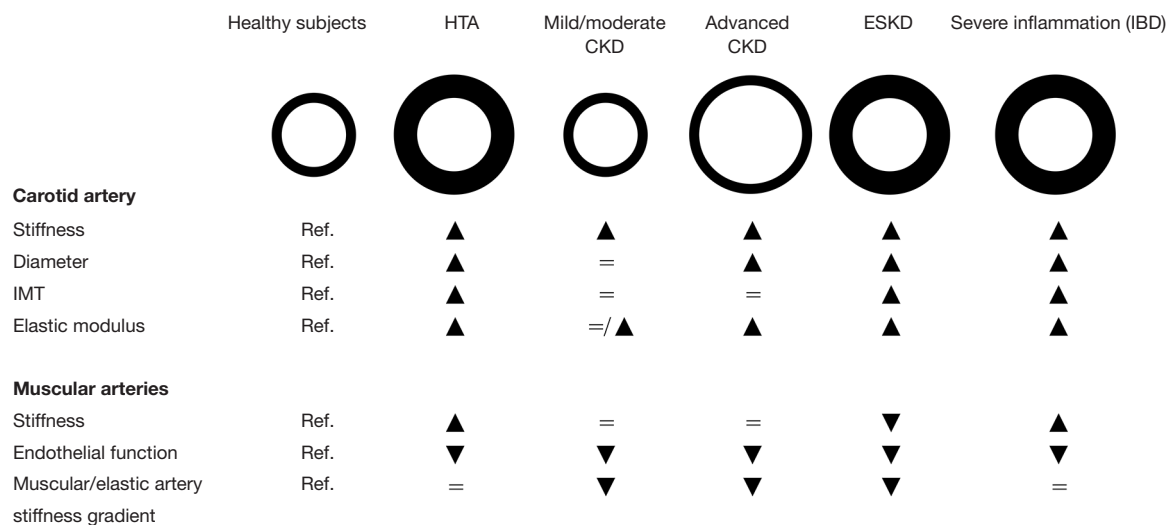
	Healthy subjects	HTA	Mild/moderate CKD	Advanced CKD	ESKD	Severe inflammation (IBD)
Carotid artery						
Stiffness	Ref.	▲	▲	▲	▲	▲
Diameter	Ref.	▲	=	▲	▲	▲
IMT	Ref.	▲	=	=	▲	▲
Elastic modulus	Ref.	▲	=/▲	▲	▲	▲
Muscular arteries						
Stiffness	Ref.	▲	=	=	▼	▲
Endothelial function	Ref.	▼	▼	▼	▼	▼
Muscular/elastic artery stiffness gradient	Ref.	=	▼	▼	▼	=

Figure 1 Arterial phenotypes. CKD, chronic kidney disease; ESKD, end-stage kidney disease; IBD, inflammatory bowel disease; IMT, intima-media thickness; HTA, hypertension; Ref., reference group (healthy state).

predispose to plaque rupture (32,33). In this regard, the common carotid artery at the level of the plaque is stiffer than the adjacent segment (34). This may limit the strain of the whole arterial wall and increase the arterial wall stress, predisposing carotid plaques to a greater risk of rupture (35). Carotid remodelling is more evident at the level of the plaque since the stiffness and the mechanical properties of the common carotid artery measured in a section free of plaque is comparable to that observed in patients without carotid plaque (34). In patients with advanced CKD, the enlargement of the carotid artery (*Figure 1*) may contribute to the increased in arterial wall stress and risk of plaque rupture.

From carotid atherosclerosis to CKD progression and CV events

Carotid atherosclerosis is associated with an increased CV risk in the general population (36,37) and in patients with CKD (38-40). In particular, the risk for stroke is high in CKD patients with advanced atherosclerotic lesions (41) and increases according to the decline in renal function (42).

The link between carotid atherosclerosis and GFR, weak in patients with normal kidney function and in those with diabetes, increases in patients with CKD (43-48). However, it is difficult to dissect the role of CKD from the cluster of risk factors that may accompany carotid atherosclerosis (e.g., hypertension, diabetes, dyslipidaemia and inflammation)

in these patients (49-51). In this context, qualitative and quantitative lipid abnormalities have been reported in these patients (52-55) and linked to both carotid atherosclerosis (55-58) and CKD progression (59). Moreover, blood pressure, haemoglobin and several mineral metabolism parameters predict carotid atherosclerosis progression in CKD patients (60,61). Finally, the association between GFR and carotid atherosclerosis is greatly reduced or lost after adjustment for CV risk factors (43,62) and it has been suggested that cIMT can even be comparable between patients with CKD and healthy controls (63). Accordingly, in a recent study, known vascular risk factors only explained a small proportion of variance in cIMT whereas the addition of GFR did not significantly contribute to the cIMT variance (64). Considered together, these studies suggest that the role of kidney dysfunction as an independent risk factor for carotid atherosclerosis should be better clarified.

Carotid arteriosclerosis in CKD

The increase of large elastic arteries stiffness, a vascular biomarker (24) and an independent CV risk predictor (65), is reported in patients with CKD (63,66-68), even in those with a very mild reduction in GFR (60–90 mL/min/1.73 m^2 without proteinuria) (69).

Several mechanisms are involved in the pathogenesis of carotid and aortic stiffening in CKD (19). Briefly, several uraemic toxins (i.e., hypercalcaemia, phosphates,

increased levels of parathyroid hormone, uric acid, endothelin, advanced glycation end-products, and asymmetric dimethylarginine) are also vascular toxins. They may contribute, directly or through the development of endothelial dysfunction (70,71), inflammation (72), oxidative stress (73,74), and vascular calcification (75,76), to functional and/or structural arterial stiffening (19).

Functional alterations of the arterial wall could precede structural arterial stiffening in CKD since endothelial dysfunction is reported in participants with a mild reduction in GFR (77,78) whereas the changes of the characteristics of the biomaterial and the outward remodeling (enlargement and thickening) of the arterial wall are evident in patients with advanced CKD and ESKD but not in early stages of CKD (63,68,69). In this context, the enlargement of the carotid arterial wall is probably due to the inability of the arterial wall to sustain a repeated alternating deforming force and the consequent thinning and fragmentation of elastic fibers (elastic fatigue); qualitative and quantitative alterations of elastic fibers have been involved in the enlargement of the arterial wall in experimental CKD models (79,80). Carotid thickening has been reported in patients with ESKD and in those with CKD and hypertension (81). In this regard, carotid thickening is considered a compensatory mechanism aimed at normalizing circumferential wall stress in the presence of dilatation or increased blood pressure. Therefore, considering that carotid enlargement precedes wall thickening (63), circumferential wall stress is increased in advanced CKD. Moreover, carotid plaque, carotid intima-media thickness, and coronary calcification, known non-invasive measures of atherosclerosis, equally discriminate prevalent CV disease in patients with reduced renal function (82).

Muscular elastic arteries stiffness in CKD

In contrast to the carotid artery, the stiffness of brachial and femoral arteries is not increased and can be even reduced in patients with CKD (83,84). In these patients, an inward remodeling (reduction of diameter) of the renal arteries has been also reported and associated with an increased risk of CV events (85,86). The association between GFR and renal artery diameter was confirmed in patients with and without renal artery stenosis, and was age, sex, body surface area, diabetes, hypertension and smoking independent (85).

Stiffness mismatch in CKD

Physiologically, arterial stiffness is lower in the carotid and aorta, two central elastic arteries, than in peripheral muscular arteries in youth. However, central elastic arteries stiffness increases with aging whereas the stiffness of muscular arteries remains almost unchanged or increases to a lesser extent (87). The consequence of this differential effect of aging on muscular and elastic arteries is that the elastic/muscular arteries stiffness gradient is first equalized (elastic arteries stiffness = muscular arteries stiffness), and then reversed (elastic arteries stiffness > muscular arteries stiffness). This process is referred to as stiffness mismatch (88-90) and has important haemodynamic and clinical consequences since in youth the physiological stiffness gradient helps to reduce the transmission of the forward pressure wave into the microcirculation whereas with advancing age the increased carotid and aortic stiffness leads to the inversion of the stiffness gradient and causes an enhanced transmission of forward energy waves into the microcirculation. This may cause vascular damage (90), contributing to the pathogenesis of white matter lesions of the brain (91), renal dysfunction (92,93) and, at least in patients with ESKD, increased mortality (94).

In contrast to what happens in other models of increased arterial stiffness (*Figure 1*), in patients with ESKD carotid and aortic stiffening can be accompanied by the reduction in stiffness of muscular arteries (94). This mechanism is useful to dampen the backward wave reflections and to mitigate the effects of increased central elastic arteries stiffness on central blood pressure; this is potentially cardioprotective. Moreover, the reduced stiffness of muscular arteries could help to smooth the forward waves and prevent an enhanced transmission of these waves to the microcirculation of target organs.

Ventricular-vascular coupling in CK

Physiologically, left ventricular (LV) function is coupled with arterial function to ensure maximum cardiac work and efficiency (95). The coupling ratio between arterial elastance (Ea), a measure of ventricular afterload determined by the ratio of end-systolic pressure to stroke volume, and LV systolic elastance (Ees), a measure of ventricular stiffness at end systole determined by the ratio of end-systolic pressure to end-systolic volume (is generally 0.7–1.0). Therefore, LV work efficiency is physiologically maximised. Ees falls

in the presence of systolic dysfunction and increases in the presence of a stiff vascular system (increased Ea), to maintain cardiac efficiency (Ea/Ees =0.7–1.0) and to ensure a proper transfer of blood to the arterial tree without excessive changes in pressure. This compensatory mechanism is useful to maintain cardiac performance but leads to the reduction in cardiac reserve and diastolic function, haemodynamic instability and increased susceptibility to flash pulmonary oedema (95). In CKD, the increase of carotid and aortic stiffness leads to a parallel increase of LV stiffness (96). Therefore, considering that large elastic arteries stiffness is increased even in patients with a very mild reduction of GFR (60–90 mL/min/1.73 m^2 without proteinuria) (69), the abnormalities of LV function could start early in patients with CKD. Further studies are needed to test this hypothesis in patients with a mild reduction of GFR.

Vascular phenotypes in other models of increased arterial stiffness

Carotid and aortic stiffness is increased in CKD, hypertension and several diseases characterized by a chronic severe inflammation, such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) (97,98). However, according to the different pathogenesis and clinical features, also the mechanisms involved in the arterial stiffening process and the arterial phenotypes may be different in these diseases (*Figure 1*).

Arterial phenotype in hypertension

The acute increase of blood pressure leads to an increase of carotid diameter and, consequently, circumferential wall stress and arterial stiffening. In patients with hypertension, the chronic increase of carotid diameter and circumferential wall stress leads to an adaptive increase of the arterial wall thickness (63). The consequence of this process is an increased carotid stiffness and outward remodeling (increased arterial diameter and thickness). The impact of high-normal blood pressure and hypertension on stenosis were more evident in subjects with CKD (99). Moreover, the elastic modulus, a measure of the elastic properties of the biomaterial of the arterial wall, of the carotid artery is increased in patients with hypertension (63). Therefore, considering that the stiffness of muscular arteries can also be increased in these patients, the muscular/elastic artery stiffness gradient can be comparable between controls and patients with hypertension (100).

Arterial phenotype in patients with chronic severe inflammation

The arterial phenotype of patients with CKD differs from that of patients with chronic severe inflammation (i.e., IBD and RA). Elastic artery stiffness is increased in patients with either chronic severe inflammation or CKD compared with their respective controls (101,102). Interestingly, the stiffness of the brachial artery, a muscular artery, increases with aging in IBD but not in CKD (83) and is higher, (I) in IBD and RA patients than in matched healthy control subjects (83,101), and, (II) in IBD patients than in CKD patients with a comparable stiffness of the aorta (83). Moreover, the stiffness of both muscular and elastic arteries is positively correlated with disease duration in IBD (101,103). Considered together, these findings suggest that both elastic and muscular arteries stiffness could increase in patients with chronic severe inflammation; in support of this hypothesis, the vessel targets of inflammation (elastin, collagen and smooth muscle cells) can be found in both elastic and muscular arteries. Inversely, the increase of elastic arteries stiffness accompanied by the reduction of muscular arteries stiffness could be a feature of CKD.

From large elastic artery stiffening to CV events

Physiologically, the arterial system has 2 important functions, the conduit and "cushioning" functions. The former is involved in the delivery of blood from the heart to peripheral tissues whereas the latter is involved in the dampening of the pulse wave during systole, achieving a continuous flow in peripheral blood vessels. In this regard, approximately 50% of the stroke volume is momentarily stored within large elastic arteries thanks to the elastic deformation of the arterial wall during systole and returned to the circulation by the discharge of the energy stored in the arterial wall during diastole (104). In the presence of stiffened arteries, the cushioning function of the carotid artery and aorta is altered and a larger part of the stroke volume is directly forwarded to the peripheral tissues during systole, leading to a rise in central systolic blood pressure (SBP) and a drop in central diastolic blood pressure (DBP). The rise of central SBP leads to a parallel increase in LV work and oxygen requirement and is involved in the development of LVH, present in >70% of patients with ESKD and detectable even in patients with early stages of CKD (105,106); the drop of central DBP leads to decreased coronary artery perfusion pressure and is associated with an

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increased risk of myocardial ischaemia; finally, the increase of central pulse pressure leads to an increased risk of stroke. In patients with ESKD and renal transplant recipients, the increase of carotid stiffness is associated with an increased risk in all-cause mortality and CV events (13,107).

Increased carotid stiffness and baroreflex dysfunction

Baroreflex dysfunction is reported in advanced CKD and ESKD and is associated with an increased risk of sudden death and all-cause mortality in hypertensive patients with ESKD (108). Baroreceptors are located within the arterial wall in the carotid bulb and are stretch-sensitive mechanoreceptors. Therefore, considering that the increase of large elastic arteries stiffness is associated with the drop in orthostatic SBP in stage 3-4 CKD patients (109), the impaired baroreflex function reported in patients with increased carotid stiffness (110) could be caused by the reduced stimulation of the baroreceptors rather than an alteration of the neural component of the baroreflex arc (111). Further studies are needed to test whether the neural component of the baroreflex arc is altered in patients with early stages CKD, in whom an increased carotid stiffness is reported (69).

Treatment options

Several therapeutic options have been proposed to improve carotid function (19,112). Statin therapy is useful to reduce the risk of CV events and contrast-induced acute kidney injury in patients with carotid artery disease (113-115) and in those with CKD (116-118). Statin therapy is useful to reduce also all-cause mortality, CV death, myocardial infarction and proteinuria in patients with CKD whereas has uncertain effects on stroke and CKD progression (118,119). The use of statins may improve patient and graft survival after kidney transplantation (120). Moreover, in patients with severe carotid artery stenosis, statin pretreatment may decrease the periprocedural complications of carotid artery stenting (CAS) (113,121) and carotid endarterectomy (CEA) (113). These benefits can be explained by the lipid lowering effect as well as the antiproliferative effect on smooth muscle cells, the stabilisation of atherosclerotic plaques, improvement of endothelial function and arterial stiffness, decreased oxidative stress and antithrombotic effect of statins (112). Interestingly, the effect of statins on cIMT could be reduced in patients with CKD (122), confirming that several mechanisms are involved in the thickening process of the carotid artery in these patients.

CEA and CAS are options for the management of severe carotid artery stenosis. In these patients, renal function should be evaluated with GFR rather than serum creatinine since the former measure was more sensitive in detecting perioperative stroke/death after CEA in patients with CKD (123). Moreover, CEA has shown promising results for stroke risk reduction in CKD patients with high-grade symptomatic carotid stenosis (124). In a National Inpatient Sample surveyed for CAS and CEA among CKD stage 3–5 and ESKD patients, although CAS was independently associated with in-hospital major adverse CV and cerebrovascular events (MACCE), propensity score matching showed no risk difference in MACCE between CAS and CEA (125). After intervention for carotid artery stenosis, stroke rate is low in patients with moderate-severe CKD whereas mortality increases with worsening renal function at 30-day (126); severe CKD is associated with cerebrovascular events or death at 1 and 5 years of follow-up (126,127). Carotid revascularization in ESKD has been recently questioned since both CAS and CEA were associated with 4-fold higher odds of in-hospital mortality (128). Moreover, considering that CAS requires the administration of contrast media, the risk of contrast-induced acute kidney injury should be considered (115) and CAS performed in selected symptomatic high-risk patients if CEA is not suitable (124). CAS in asymptomatic patients with severe renal dysfunction should be considered with caution since the risks of repair may outweigh the benefits in these patients (129,130). Further treatments tested to improve carotid function include antihypertensive, anti-inflammatory and immunosuppressive drugs, renal transplantation and dialysis modalities (19). However, more large-scale and randomized trials are needed to confirm the efficacy of these treatment options in the reduction of CV events or delay of the progression of CKD. In this regard, only one trial, performed in 150 ESKD patients monitored for 51±38 months, has demonstrated that the CV risk is reduced in those with improved arterial stiffness (21).

Conclusions

Carotid arteriosclerosis and atherosclerosis are reported in patients with CKD and are associated with poor outcome. The stiffening process of the carotid artery starts early, in patients with a mild reduction in GFR, whereas an outward remodeling is evident in more advanced stages of CKD. In

muscular elastic arteries, a reduced stiffness is reported in patients with advanced CKD and an inward remodeling is evident during early stages of CKD. An increase in cIMT and plaque formation is evident in patients with advanced CKD. Contrast-induced acute kidney injury and kidney function, in general, deserve more attention from vascular surgeons.

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Footnote

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