Capillary rarefaction

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REVIEW PAPER

Capillary rarefaction: a missing link in renal and cardiovascular disease?

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Abstract

Patients with chronic kidney disease (CKD) have an increased risk for cardiovascular morbidity and mortality. Capillary rarefaction may be both one of the causes as well as a consequence of CKD and cardiovascular disease. We reviewed the published literature on human biopsy studies and conclude that renal capillary rarefaction occurs independently of the cause of renal function decline. Moreover, glomerular hypertrophy may be an early sign of generalized endothelial dysfunction, while peritubular capillary loss occurs in advanced renal disease. Recent studies with non-invasive measurements show that capillary rarefaction is detected systemically (e.g., in the skin) in individuals with albuminuria, as sign of early CKD and/or generalized endothelial dysfunction. Decreased capillary density is found in omental fat, muscle and heart biopsies of patients with advanced CKD as well as in skin, fat, muscle, brain and heart biopsies of individuals with cardiovascular risk factors. No biopsy studies have yet been performed on capillary rarefaction in individuals with early CKD. At present it is unknown whether individuals with CKD and cardiovascular disease merely share the same risk factors for capillary rarefaction, or whether there is a causal relationship between rarefaction in renal and systemic capillaries. Further studies on renal and systemic capillary rarefaction, including their temporal relationship and underlying mechanisms are needed. This review stresses the importance of preserving and maintaining capillary integrity and homeostasis in the prevention and management of renal and cardiovascular disease.

Keywords Chronic kidney disease · Cardiovascular disease · Capillary rarefaction · Endothelial dysfunction

Introduction

Chronic kidney disease (CKD) affects 10–15% of the population worldwide, and its incidence rises with the increased global prevalence of hypertension, diabetes and obesity [1, 2]. CKD is divided into five stages based on the extent of albuminuria and/or renal function decline for a period longer than 3 months [3]. In CKD stage 1 glomerular hyperfiltration and mild albuminuria occurs, while in CKD stage 5 there is end stage renal disease (ESRD). Patients with CKD have

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an increased risk for cardiovascular morbidity and mortality [2], and the underlying pathophysiological mechanisms are incompletely understood [1]. Capillary rarefaction may be both a cause and a consequence of CKD [4]. In experimental animal models a decrease in peritubular capillary density precedes interstitial fibrosis and tubular atrophy (IF/TA) development, which is a final common pathway in renal function decline [5]. We hypothesize that capillary rarefaction, i.e., a loss of capillary density, occurs in both human renal and cardiovascular disease, and thus may be a missing link bridging renal and cardiovascular pathology.

The microvasculature is composed of arterioles, capillaries and venules, and plays a major role in the maintenance of tissue homeostasis by bringing oxygen and nutrients and removing waste products [6]. Microvascular function can be assessed non-invasively in skin, bulbar conjunctiva, sublingual mucosa, and retina, using video-microscopy, laser-Doppler flowmetry, and/or fundus photography [7]. Capillary rarefaction, i.e., a decrease in capillary density, is found using multiple of these non-invasive techniques in individuals with hypertension, obesity, diabetes, low birth weight, and CKD (reviewed in [6, 7]), which all are risk factors for cardiovascular and renal disease. Both functional and structural capillary rarefaction are discerned, and they can also occur concomitantly [4, 6]. Functional rarefaction is seen as a reversible state with arteriolar vasoconstriction leading to mal-perfusion and eventually non-perfusion of capillaries. Structural rarefaction is characterized by anatomically absent vessels and irreversible vessel regression [6]. Carmeliet et al. reviewed how a disturbance in the balance between angiogenic and angiostatic factors can lead to capillary instability and regression [8, 9]. In brief, vessels are composed of endothelial cells, a basement membrane and supporting mural cells, and have a large phenotypic plasticity in different organs and tissues. After injury, endothelial cells can contribute to vessel growth in a pro-angiogenic milieu, which is followed by stabilization of newly formed vessels, with coverage of endothelial cells by extracellular matrix and mural cells. When angiogenic factors are not sufficient, or when there is an increase in angiostatic factors, endothelial channels are not covered by mural cells, leading to fragile instable vessels [8, 9].

Pathological investigation of tissue enables the use of technical platforms that can analyze both known and unknown alterations in tissue, however studies on capillary rarefaction are scarce. Therefore we summarize current human pathology data (till March 1, 2023) on capillary rarefaction in both the renal and non-renal microvasculature in relation to CKD and cardiovascular disease. In the kidney there are two capillary beds, the glomerular capillary bed located behind the afferent arteriole, and the peritubular capillary (PTC) bed which originates from the efferent arteriole. First, we separately summarize studies on the glomerular and PTC beds, according to a four phase model describing development of capillary rarefaction: from the normal "physiological" state (A) going to capillary hypertrophy (B), which may progress to a decreased capillary density (C) and subsequent capillary regression with fibrosis (D). Secondly, we review data from human pathology studies on capillary rarefaction in other tissues than the kidney (i.e., systemically) in patients with cardiovascular risk factors and/or disease. We postulate that studies are urgently needed to determine their temporal and causal relationship to facilitate the detection, prevention and treatment of the progression of CKD and its related cardiovascular disease.

Glomerular capillary hypertrophy and loss

Both kidneys contain between 600,000 and 3,000,000 glomeruli, that are capillary beds functioning under arterial blood pressure. Glomerular capillaries maintain a constant blood pressure, i.e., in case of high blood pressure there is vasoconstriction of the afferent arteriole and vasodilatation of the efferent arteriole, while the reverse occurs under conditions of low arterial blood pressure. The "Brenner hypothesis" explains why chronic renal injury progresses to scarring once there is sufficient renal damage (reviewed in [10]). In the setting of a decreased number of functioning glomeruli, there is loss of autoregulation with failure of the physiological constriction of the afferent arteriole leading to increased intraglomerular pressure and hyperfiltration. This results in glomerular hypertrophy and is associated with efferent arteriolar vasoconstriction and angiotensin II generation. Subsequently, there is denudation of the glomerular basement membrane with detachment of podocytes, adhesions with Bowmans' capsule and involution with obsolescence of the glomerulus [11]. As explained below, we hypothesize that in the glomerular hyperfiltration phase of early CKD hypertrophy of glomerular capillaries occurs, advancing to glomerular capillary rarefaction and/or focal and segmental glomerulosclerosis (see Fig. 1, phases A–D).

Human pathology studies show that a larger glomerular volume, i.e., glomerular hypertrophy (phase B), is found in individuals with hypertension [12–17] and low birth weight [13, 18], and is regarded as a compensatory response to lower nephron endowment at birth. Larger glomerular volume is also associated with an increased body mass index (BMI) [13, 15], and/or older age [15, 19, 20], which is thought to be secondary to a relative nephron shortage due to a higher metabolic demand or age-related nephron loss respectively. In individuals undergoing a nephrectomy for a malignancy or as a living kidney donor [21, 22], increased glomerular volume is related to CKD progression. Quantification studies confirm our hypothesis that in hypertrophic

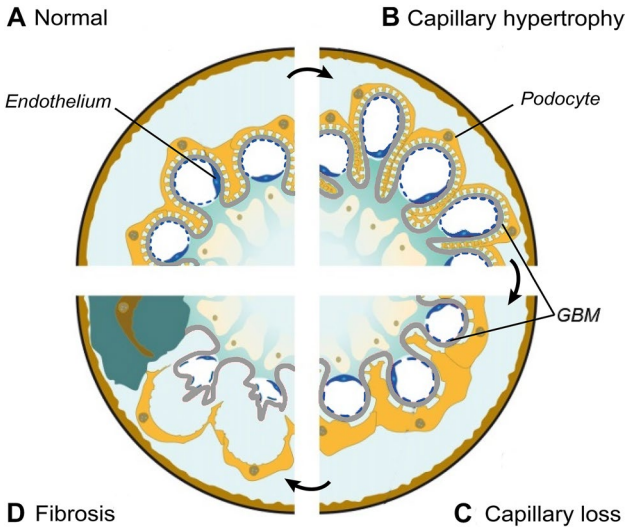

Fig. 1 Hypothetical pathway of glomerular capillary rarefaction during chronic kidney disease (CKD) development. In a glomerulus of a normal adult (**A**) the glomerular capillaries are lined by fenestrated endothelium, with podocytes covering the glomerular basement membrane with intact foot processes. Glomerular capillary hypertrophy (**B**) occurs in patients with microvascular endothelial dysfunction, with enlarged surface area of the glomerular capillary wall, and increased number of capillary cross-sections. Persistent injury, in conjunction with, e.g., aging and/or advanced hypertension, may lead to ischemic-appearing glomeruli (**C**), which are smaller and show wrinkling and thickening of the glomerular basement membrane. Podocyte foot process effacement and an altered composition of the glomerular basement membrane (GBM) might occur. Ultimately glomerulosclerosis (**D**) develops with loss of glomerular capillaries and sclerosis, and adhesions of visceral to parietal glomerular epithelial cells, resulting in glomerular sclerosis

phase B glomeruli there is an increase in the number of glomerular capillary cross-sections [23].

We hypothesize that in a later stage of glomerular injury, capillary rarefaction occurs with presence of smaller glomeruli (phase C). These ischemic-appearing glomeruli morphologically show wrinkling of the glomerular capillary wall and lamellation of Bowman's capsule in association with a decrease in capillary numbers [24]. At older age the percentage of ischemic-appearing glomeruli increases [15]. Podocyte detachment is found in glomeruli with wrinkling of glomerular capillaries, tuft collapse and periglomerular fibrosis [25]. Whether capillary rarefaction plays a central pathophysiological role in development of ischemic-appearing glomeruli remains to be established.

In phase D glomeruli glomerulosclerosis is present with a collapse of the glomerular capillary tuft. Focal and segmental glomerulosclerosis (FSGS) is found secondary to severe hypertensive and/or diabetic renal disease, oligonephronia and inflammatory glomerulonephritis [26], but also in kidneys from individuals with low birth weight [27]. A decrease in glomerular vascular endothelial growth factor (VEGF) expression is associated with decreased endothelial and podocyte markers in advanced diabetic nephropathy [28]. FSGS has been reported in conjunction with PTC loss in two prematurely born adolescents [29]. In global glomerulosclerosis no opened glomerular capillaries can be discerned, and presence of global glomerulosclerosis, regarded as sign of nephron loss, increases with higher age [30]. FSGS and focal global glomerulosclerosis (FGGS) may result from separate pathways and have glomerular capillary tuft collapse and podocyte loss as common denominator [25].

All parts of the glomerular capillary wall (i.e., podocytes, glomerular basement membrane (GBM) and endothelial cells) are involved in the different stages leading to capillary rarefaction as shown by electron microscopical (EM) studies. For instance, in glomerular hypertrophy, there is an expansion of the capillary loops with hypertrophy of podocytes (i.e., a relative decrease in podocyte number [31]), and podocyte foot process effacement [26]. Patients that are treated with anti-VEGF for metastasized carcinoma, have an increased risk to develop albuminuria and hypertension [32], and biopsies of these patients show swollen endothelial cells ("endotheliosis") and glomerular basement membrane alterations [33]. In individuals with type 1 diabetes there is a decrease in capillary filtration area, with an increase in the mesangial cell and matrix area compared to glomerular volume, next to thickening of the GBM [34]. At present abnormalities in the glomerular capillary wall by EM in the ischemic-appearing glomeruli of phase C are not well known, and merit further investigation.

Peritubular capillary (PTC) loss

The peritubular capillary network forms a coalescing vascular plexus surrounding tubuli that actively reabsorb water and solutes. In contrast to the glomerular capillary bed, PTCs function under a lower blood pressure, and the tubulo–interstitium has a steep decrease in oxygen gradient [35, 36]. In analogy to glomerular capillary rarefaction, PTC rarefaction can theoretically be divided in 4 phases (see Fig. 2).

After acute injury a pro-angiogenic phase might occur with increased capillary density (phase B), and this phase may become stable and silent upon proper restoration. However, when there are more angiostatic than angiogenic factors, endothelial dysfunction and disrupted endothelial-pericyte crosstalk can lead to vascular regression with inflammation and fibrosis (IF/TA) formation (phase C). In the final phase, there is more severe cortical PTC loss and IF/TA (phase D). Evidence for the occurrence of these stages from human pathology studies is summarized below. Of note, most studies focus on PTCs located in the cortex. Farris et al. also studied medullary PTCs and found a correlation between cortical and medullary PTC numbers [37].

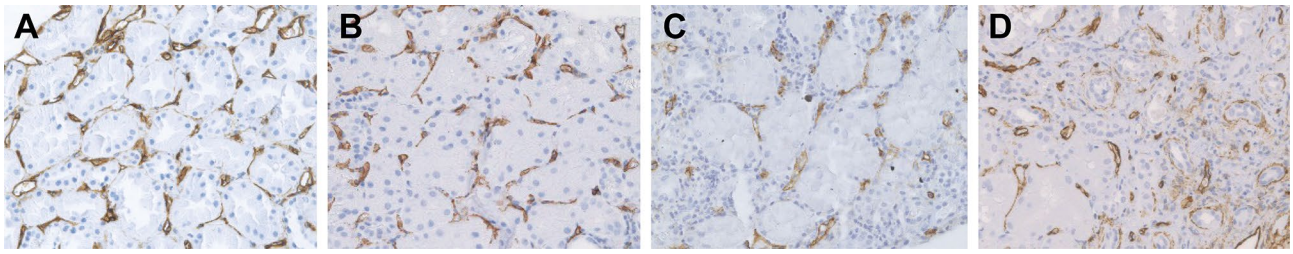

Fig. 2 Immunohistochemical CD31/CD34 staining illustrating PTC density in protocol renal biopsies taken before (**A**), 3 months (**B** and **C**), and 12 months (**D**) after kidney transplantation (examples from Steegh et al. [48]). In a normal state (**A**) PTCs are present in a regular pattern and surround tubuli that are oriented 'dos a dos', with small distance between tubuli and PTCs facilitating easy fluid and solute exchange. After renal transplantation without additional injury, for instance of living kidney donors, hypertrophy of the remaining kidney may occur with (mild) increase in numbers of PTCs per tubule (**B**). If additional injury occurs, for instance after transplantation of a deceased after circulatory death kidney with ischemia/reperfusion injury (see [48]), PTC capillary rarefaction is found with inflammation and mild IF/TA, in this case involving less than 25% of cortex (**C**). When inciting insults are more severe, and the angiogenic/angiostatic balance is not restored, there is a vicious circle with more extensive PTC loss, inflammation and IF/TA, e.g., over 50% of the renal cortical area (**D**), ultimately leading to end stage renal disease (ESRD) cq chronic transplant dysfunction. Magnification 400×

Unlike for phase B of glomerular hypertrophy, there is no clear evidence from human pathology studies that PTC hypertrophy occurs. Only Konda R et al. [38] found a heterogenous increase in PTC density, presumably in the collecting duct area of end-stage kidneys removed because of scarring after urinary tract disease. A pro-angiogenic switch in phase B is suggested by studies on VEGF expression. In early CKD, the pro-angiogenic VEGF is increased in morphologically intact and hypertrophic tubules in patients with CKD, while there is decreased VEGF expression in atrophic tubuli [39, 40]. An increased VEGF expression in conjunction with more inflammation is also seen after transplantation [41], and in a subset of patients with lupus nephritis [42]. However, the majority of studies reports PTC loss only.

Seron et al. first described a decreased number of PTCs (phases C and D) in renal biopsies of patients with IF/TA and decreased renal function in 1990 [43], which was confirmed in a more extensive study by Bohle et al. in 1996 [44]. After renal transplantation, the extent of PTC rarefaction correlates with severity of IF/TA [45]. Therefore, we suggest that in phase C a relatively smaller area of the cortex is affected by PTC loss than in phase D. After the first studies with seminal observations, multiple studies found a decrease in PTC numbers. PTC loss is found in patients with renal failure, independent of the underlying cause, i.e., in CKD in association with hypertension or diabetes, autoimmune diseases, and congenital nephropathy (Table 1).

In PTC rarefaction a disturbed angiogenic/angiostatic balance has been found. In advanced CKD there is decreased VEGF expression, increased hypoxia induced factor (HIF) and/or a more angiostatic phenotype [28, 39, 41, 46]. Also, in experimental studies a diminished VEGF expression is found in advanced disease (reviewed in [4, 10]). In post-stenotic kidneys a decrease in PTCs is associated with greater expression of angiopoietin-1 [47]. Although in experimental models interventions with, e.g., the angiogenic/angiostatic cascade have shown decreased renal capillary rarefaction in conjunction with diminished renal disease [4], studies pointing to a causal relationship have not yet been performed in humans. Interestingly, we observed more PTC loss after transplantation of grafts from deceased after cardiac death (DCD) donors as compared to kidneys from living donors [48], indicating that acute ischemic injury can accelerate progression between phases of PTC rarefaction. Thus, in line with experimental studies, PTC rarefaction may be an important pathway in the transition of acute kidney injury (AKI) to CKD (reviewed in [49]).

All components of the capillary wall, i.e., endothelial cells, basement membrane and pericytes, are involved in PTC rarefaction. EM analysis in experimental models shows reduced number of endothelial fenestrations with focal widening of the subendothelial space with thickening of the PTC basement membrane, although no difference in EM structure between human control and fibrotic kidneys was found [50]. In advanced human kidney disease alterations in composition of the PTC wall are visible ultrastructurally as summarized in [50]. Pericytes play an important role in interstitial fibrosis development via endothelial to mesenchymal transition [51]. An increase in pericyte density, with presumed pericyte detachment, was seen in the context of enhanced fibrosis and diminished PTC density in human post-stenotic kidneys [47]. Experimental studies show that upon renal injury pericytes can migrate away from PTCs, and dedifferentiate into myofibroblasts [52–54]. Tubulo–vascular crosstalk is important for maintenance of PTC stability [55], and further pathology research is needed to investigate both capillary and tubular density in relation to functional and structural rarefaction. We hypothesize that structural rarefaction occurs in cases where there already is

Table 1 Evidence for the occurrence of peritubular capillary loss in chronic kidney disease from human biopsy studies

Authors	Disease	Population	Control	PTC density	Detection/Antibody	Read-out	Fibrosis	Tub atrophy	Inflammation	Renal function
Seron D et al., 1990 [43]	CKD	$n=46$	$n=7$ (preTx)	↓	PHMS | PAL-E	Mean PTC/area	↑	↑	↑	↓
Bohle A et al. 1996 [44]	CKD	$n=310$	–	↓	silver staining	% PTC / area	↑			↓
Konda R et al. 1999 [38]	ESRD urinary	$n=26$	$n=5$ (MCD) $n=4$ (TN)	↑	CD34	Mean PTC/area	↑		↑	
Choi Y et al., 2000 [39]	CKD	$n=27$	$n=5$ (TN)	↓	CD34	Mean PTC/area	↑	↑		
Katz A et al., 2002 [113]	DN (DMI)	$n=15$	$n=9$ (LD)	↓	EM	% PTC/tub volume cap/int	↑	↑		=
Namikoshi T. et al., 2006 [40]	IgAN	$n=23$	$n=5$ (MCD)	↓	CD34	Mean PTC / field	↑	↑		↓
Yang L et al., 2007 [114]	AA-ATN	$n=8$	$n=9$ (a-ATN) $n=10$ (MCD)	↓	Factor VIII	Mean PTC / field capillaries / glom	↑	↓		
Lindenmeyer M et al., 2007 [46]	DN (DMII)	$n=10$	$n=3$ (n.s.)	↓	CD31	% PTC / area	↑	↑		
Baelde H et al., 2007 [28]	DN (DMII)	$n=28$	$n=3$ (NK) $n=7$ (Tx) $n=12$ (TN)	↓	CD31	% PTC / area	↑	↑		↓
Kaukinen A. et al., 2009 [115]	NPHS1	$n=44$	$n=10$ (preTx) $n=14$ (MCD)	↓	CD31	Mean % PTC/tub mean PTC/tub	↑		↑	↓
Thacker S et al., 2010 [116]	LN	$n=25$	$n=5$ (TN) $n=5$ (ANCA)	↓	CD31	% PTC / area % capillaries/glom			↑	
Kimura N et al.; 2015 [117]	CKD	$n=30$		↓	CD34	% mean PTC/area				
Stillfried von S et al. 2016 [118]	CKD	$n=6$ $n=3$	$N=5$ (TN) $N=3$ (autopsy)	↓	CD31	%PTC/area				
Anutrakulchai S et al., 2016 [42]	LN	$n=253$	$n=13$ (preTx)	↓	CD31	% positive PTC area				↓
Asada N et al. 2017 [29]	LBW	$n=2$	–	↓	CD31/CD34	%postive PTC area				
Sun I et al.; 2018 [119]	Renovas hypertension	$n=7$	?	↓	H&E stain	mean PTC/area				
Klomjit N et al. 2022 [47]	Artery stenosis	$N=5$	$N=7$ donor kidney	↓	CD31 and H&E	%CD31 and PTC/tubule	↑			

AA-ATN aristolic acid induced ATN, *TN* tumornephrectomy, *PreTx* pretransplantation biopsy, *MCD* minimal change disease, *MG* membranous glomerulopathy, *ANCA* ANCA vasculitis, *a-ATN* antibiotic induced ATN, *LD* living donor, *CsAT* cyclosporin A induced toxicity, *Tx* transplantation biopsy, *EM* electron microscopy, *NPHS1* congential nephrotic syndrome of the Finnish type, *BMT* basement membrane thickening, *LBW* low birth weight, Capillaries/glom, mean glomerular capillaries per glomerular cross section. ↓ decreased; ↑ increased; = equal

IF/TA, with tubular atrophy and capillary regression occurring concomitantly.

Systemic capillary rarefaction in CKD

Advanced CKD is associated with morbidity in multiple organs [2], and capillary rarefaction is found systemically in human pathology studies as recently reviewed in [56]. A capillary decrease of approximately 32% is found in end-stage renal disease patients in biopsies of skeletal muscle, omental fat and heart. In addition, capillary alterations are described in biopsies of skin, and skeletal muscle, with, e.g., thickening of endothelial cells and basement membranes [56]. Capillary rarefaction was also found in the heart of patients with stage 3–4 CKD [57]. Thus far, no biopsy studies have been performed on capillary rarefaction in individuals with stage 1 or 2 CKD. In patients with CKD stages 3–5 capillary rarefaction is detected by non-invasive measurements in skin using video–microscopy and laser–Doppler flowmetry and in retina by fundoscopy (reviewed in [7]), and systemic capillary rarefaction is observed by nail-fold or sublingual capillaroscopy in patients with renal failure after transplantation [58, 59].

Albuminuria, indicative of stage 1 or stage 2 CKD is associated with skin and retinal capillary rarefaction [60–62]. Albuminuria is also regarded as a sign of systemic microvascular endothelial dysfunction, and it is associated with cardiovascular disease [63], retinopathy [64], heart failure [65], impaired cognitive performance [66], and depression [67]. Recent reports from the Maastricht Study, a population-based cohort of individuals aged > 40 years enriched for diabetes, show that these conditions are all associated with systemic capillary rarefaction measured with multiple non-invasive techniques [68]. Microalbuminuria can occur in individuals with type 2 diabetes with and without renal structural abnormalities, while von Willebrand factor plasma levels as sign of more severe endothelial dysfunction were only elevated in individuals with more advanced tubulo–interstitial and arteriolar than glomerular changes [69]. More tubulo–interstitial fibrosis in kidneys of patients undergoing a nephrectomy for a renal cell carcinoma predicted non-cancer mortality [22].

Systemic capillary rarefaction in cardiovascular disease

Literature was reviewed to examine whether capillary rarefaction is found in tissue biopsies (i.e., skin, fat and skeletal muscle) and organ biopsies (brain and heart) of individuals with cardiovascular risk factors. As summarized in Table 2, capillary rarefaction appears a common thread in biopsies taken from individuals with hypertension, obesity and/or glucose intolerance (without mentioning the presence or absence of CKD), despite differences in form and function of the microvasculature in the various tissues and organs examined.

In individuals with hypertension a decreased capillary density is found in skin, and skeletal muscle [70–72]. Using electron microscopy, endothelial in-foldings into the lumen were found in muscle biopsies, with vessel occlusion and degeneration. Sometimes the endothelial cell area covered by pericytes was increased, and basement membranes were irregularly increased in width or reduplicated, which overall resulted in an increased wall thickness/lumen ratio [72]. A decrease in capillary tortuosity was found in skeletal muscle in older people with hypertension, in conjunction with more endomysial fibrosis and capillary rarefaction [73]. In individuals with obesity, insulin resistance, and/or diabetes, capillary rarefaction is found in fat tissue [74–78]. EM revealed basement membrane thickening in visceral adipose tissue of individuals with diabetes type 2 [78]. A lower capillary density correlates with lower fat VEGF expression [74]. Older age is associated with capillary rarefaction in skeletal muscle [79]. Pathological injury at older age is associated with the aging process itself but is also influenced by, e.g., birth weight and the accumulation of diseases and/or cardiovascular risk factors during life.

Regarding end-organ disease, the focus of the search was on the brain and heart as these organs are highly perfused and affected by cardiovascular diseases, like the kidney. In individuals with hypertension there is a decrease in capillary density in heart and brain tissue [80, 81]. A decreased capillary density is also found in heart biopsies of individuals with insulin resistance, obesity and/or diabetes [82–85], with a thickening of the capillary basement membrane in people with diabetes [82, 86], with less pericyte coverage [87]. In aged brain, micro–vessels have a thickened basement membrane, and more basement membrane remnants are seen of capillaries that have lost their endothelium -so-called string vessels (reviewed in [88]). In individuals with cognitive decline due to Alzheimer disease more string vessels are found in brain tissue [88, 89], as well as an absence of endothelial staining in capillary profiles [90], and basement membrane protrusions between capillary cells [91]. This cerebral capillary pathology is in line with recent clinical insight that diabetes and hypertension are risk factors for dementia [92, 93], i.e., that cognitive decline may occur as "end organ damage" in hypertension and diabetes.

Several studies have questioned whether capillary pathology occurs concomitantly in more than one microvascular bed. In older individuals with diabetes skeletal capillary rarefaction is found together with a sublingual reduction of glycocalyx on the surface of endothelial cells [94]. In individuals with type 1 diabetes an increased muscular

Table 2 Evidence for the occurrence of capillary loss in human biopsies of individuals with hypertension, diabetes, obesity or older age

Authors	Tissue	Risk factor	Population	Control	Capillary density	Decline	Detection/Antibody	Read-out	Remarks
Paiardi S et al. 2009 [70]	Skin	HT	$N=14$	$N=7$	↓	40%	CD31	%CD31 stained area	Frozen dermal sections
Pasarica M et al. 2009 [74]	Fat	Obesity	$N=12$	$N=9$	↓	44%	UEAlectin	Vessels per mm area	Abdominal subcutaneous fat
Pasarica M et al. 2010 [75]	Fat	DM	$N=6$	$n=9$	↓	53%	UEA lectin	Vessels per mm area	Abdominal subcutaneous fat Diabetic patients were also obese
Spencer M et al. 2011 [76]	Fat	Obesity	$N=9$	$N=9$	↓	58%	CD31	Capillaries/mm area	Abdominal subcutaneous fat
Goossens G et al. 2011 [77]	Fat	Obesity	$N=10$	$N=9$	=	n.s	CD31/CD34	Capillaries/fat cell	Abdominal subcutaneous fat
Belligoli A et al. 2019 [78]	Fat	Obesity Ob + IR Ob + DM	$N=62$ $N=58 N=57$	$N=18$	↓	± 20% ± 20% ± 20%	CD31	Capillaries/mm area	In subcutaneous and visceral fat
Henrich HA et al. 1988 [120]	Muscle	HT	$N=15$	$N=12$	↓	37–51%	Toluidine blue	Capillaries/mm area	Quadriceps and pectoralis major
Marin P et al. 1994 [71]	Muscle	DM	$N=29$	$N=70$	↓	18%	PAS-amylase	Capillaries/fiber	Vastus lateralis
Chilibeck PD et al. 1997 [79]	Muscle	Old age	$N=9$	$N=11$	=	n.s	PAS	Capillaries/mm area	Gastrocnemius/non-sedentary
Hernandez N et al. 1999 [72]	Muscle	HT	$N=8$	$N=8$	=	n.s	PAS-amylase	Capillaries/mm area	Quadriceps muscle
Gavin TP et al. 2005 [121]	Muscle	Obesity	$N=8$	$N=8$	↓	21%	ATPase	Capillaries/mm area	Vastus lateralis
Croley AN et al. 2005 [122]	Muscle	Older age	$N=9$	$N=11$	↓	22%	ATPase	Capillaries/fiber	Vastus lateralis/sedentary women
Ryan NA et al. 2006 [123]	Muscle	Older age	$N=7$	$N=8$	↓	25%	ATPase	Capillaries/fiber	Vastus lateralis/sedentary men
Prior SJ et al. 2009 [124]	Muscle	IR	$N=15$	$N=15$	↓	16%	UEA/collagen IV	Capillaries/area	Vastus lateralis, matched for stroke
Groen BB et al. 2014 [94]	Muscle	DM	$N=15$	$N=15$	↓	9%	CD31	Capillaries/fiber	Vastus lateralis/young control group
Gueugneau M et al. 2016 [73]	Muscle	Old HT	$N=11$	$N=7$	↓	27%	CD31	Capillaries/fiber	Vastus lateralis
Rizzoni D et al. 2009 [125]	Brain	HT	$N=13$	$N=15$	↓	32%	CD31	Stained area	Cerebral cortex next to tumor
De Ciuceis C et al. 2014 [80]	Brain	HT	$N=10$	$N=10$	↓	34%	CD31	Stained area	Cerebral cortex next to tumor
Hunter JM et al. 2012 [89]	Brain*	Old / AD	$N=6$	$N=5$	=	n.s	Collagen type IV	Stained area	Gray and white matter
Yarom R 1994 [82]	Heart	Diabetes	$N=14$	$N=18$	↓	39%	Toluidin blue	Capillaries/area	Right atrium (auricle)
Amann K. et al. 1998 [81]	Heart	HT	$N=9$	$N=10$	↓	35%	UEA	Cap. Length/volume	Left ventricle at autopsy
Campbell DJ et al. 2011 [83]	Heart	DM/MS	$N=33$	$N=13$	=	n.s	CD31	Cap Length/volume	Left ventricle biopsy
Campbell DJ et al. 2013 [84]	Heart	Obesity	$N=24$	$N=33$	↓	16%	CD31	Cap. Length/volume	Left ventricle biopsy
Hinkel R et al. 2017 [85]	Heart	DM	$N=4$	$N=5$	↓	42%	CD31	Cells/area	Left ventricle at transplantation

In none of the studies renal function (and/or presence or absence of chronic kidney disease) is reported. In muscle tissue, data on capillary in relation to type II fibers is given if known

*There is large variation in reporting on cerebral capillary density in aging and Alzheimer Disease as reviewed in Brown WR 2011, hence no firm conclusions can be drawn, and only a recent paper is given

HT hypertension, *UEA* Ulex Europaeus, *PAS* periodic acid Schiff stain, *DM* diabetes mellitus type 2, *n.s.* non-significant, *Ob* obesity, *IR* insulin resistance, *NIDDM* non-insulin dependent DM, *EM* electron microscopy, *AD* Alzheimer Disease, *MS* metabolic syndrome

basement membrane width correlated with glomerular basement membrane width [95]. A capillary decrease is found in skin biopsies [96] and skeletal biopsies [97] of patients with heart failure with preserved ejection fraction (HFpEF). Myocardial capillary rarefaction is also found in patients with heart failure, including HFpEF [98] and idiopathic dilated cardiomyopathy [99]. In patients with chronic heart failure, a decrease in sublingual vessels [100] and in skin capillaries [101] is found by capillaroscopy.

Capillary rarefaction in renal and cardiovascular disease

The studies summarized above clearly demonstrate that capillary rarefaction occurs in both renal and cardiovascular disease. Further studies are needed to investigate whether this merely is because they share the same risk factors, and/or whether there is a causal relationship between renal and systemic capillary rarefaction (see Fig. 3).

In individuals with cardiovascular risk factors such as obesity, insulin resistance, hypertension, and older age capillary rarefaction occurs in the systemic circulation, as sign of endothelial dysfunction. In individuals with these risk factors glomerular hypertrophy occurs with an increased number of glomerular capillaries. It is well known that hypertension and diabetes mellitus are important causes of progression of CKD. In individuals with advanced CKD there is glomerulosclerosis and a PTC decrease, and capillary loss is found systemically in fat, muscle and heart biopsies. The latter may be caused by endothelial apoptosis, dysregulated angiogenesis, hypertension and the uremic milieu in individuals with end stage renal failure, all factors that contribute to higher cardiovascular morbidity and mortality in patients with renal failure [56].

Whether the kidney plays a causal role in (aggravation of) systemic capillary rarefaction remains to be established. This is suggested by the increased risk for gestational hypertension and pre-eclampsia after kidney donation [102], and for non-cancer mortality in individuals with mild CKD that undergo a nephrectomy [22, 103]. In line, individuals with low nephron endowment more often develop primary hypertension [12, 14], and individuals with borderline hypertension or a familial predisposition for hypertension have capillary rarefaction at capillaroscopy (reviewed in [6, 7]). Although more severe capillary rarefaction measured by nailfold capillaroscopy is related to worse renal function [104], there is little data on the prognostic value of non-invasive microvascular measurements for CKD development or progression. In individuals with CKD stage 2–4, retinal arteriolar narrowing was associated with renal end points such as dialysis or a 50% reduction in renal function [105]. Two longitudinal population based cohort studies did not find associations between retinal arteriolar diameters and incident CKD [106, 107], while one study did [108]. At present biopsy and mechanistic studies on systemic and renal capillary rarefaction in individuals with early CKD, or who are at risk for CKD either with or without hypertension, are lacking.

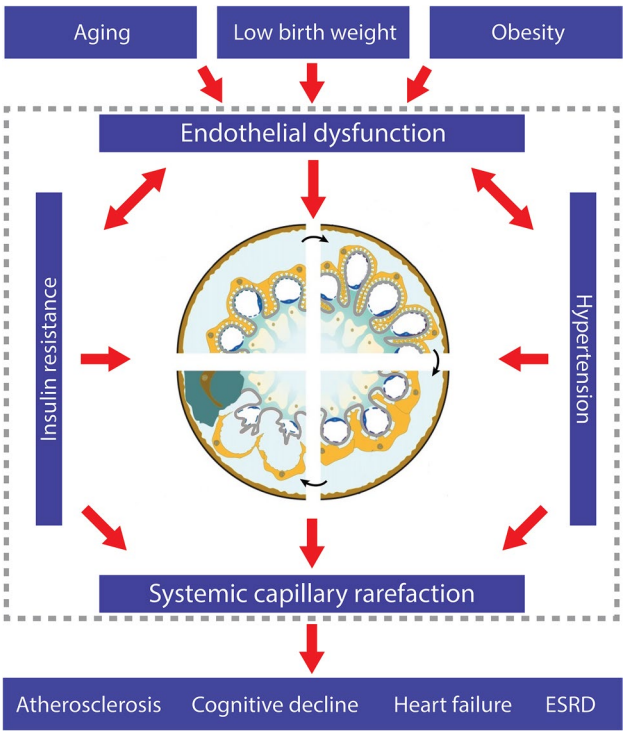

Fig. 3 Potential interrelationship between renal and systemic capillary rarefaction in the acceleration of cardiovascular disease. Generalized microvascular endothelial dysfunction is driven by risk factors, such as aging, low birth weight and obesity, that also are associated with early stages of CKD. These risk factors may directly propagate CKD development and progression, by initiating glomerular hypertrophy, followed by glomerular capillary loss (i.e., the sequence of events depicted as stages A–D in Fig. 1). Hypertension, insulin resistance and/or diabetes mellitus can aggravate both renal capillary rarefaction with CKD development and progression, as well as systemic capillary rarefaction with cardiovascular disease. In addition, we hypothesize that glomerular hypertrophy followed by PTC loss can accelerate systemic rarefaction, in line with experimental studies showing that subtle tubulointerstitial injury with PTC rarefaction predisposes to salt-sensitive hypertension [104, 105]. Further temporal and mechanistic studies on renal and systemic capillary rarefaction are needed, hence this is depicted in dashed lines as a "gray box". Abbreviations: LBW: low birth weight; CKD: chronic kidney disease; ESRD: end-stage renal disease

We hypothesize that glomerular hypertrophy with a disturbed renal autoregulation in the context of a (relative) nephron shortage, instigates PTC loss. Experimental animals that have subtle tubulo–interstitial pathology with PTC rarefaction are prone to develop salt-sensitive hypertension, which may lead to systemic vasoconstriction to increase the blood volume [109]. The disturbed renal autoregulation

can lead to generation of vasoactive mediators that further enhance hypertension and renal and systemic capillary rarefaction [110]. PTC rarefaction is associated with impaired tubulo–vascular crosstalk and development of IF/TA, resulting in decreased removal of waste products. The perpetuating cycle of renal and systemic capillary rarefaction can accelerate cardiovascular disease and organ function decline in the heart, brain, and kidneys, and thus may play an important role in inter-organ crosstalk.

This review aimed to give an overview of current human pathology investigations on capillary rarefaction and paves the way for more temporal and mechanistic pathology studies on renal and systemic capillary rarefaction. The urgency to further understand capillary rarefaction is increased by the recent pandemic, as corona virus induced disease (COVID-19) appears to be a multi–systemic microvascular disease [111], and impaired capillary recruitment may occur during and after corona virus infection [112]. Future studies on capillary rarefaction may lead to prevention and treatment of CKD-related cardiovascular morbidity and mortality.

Author contributions FS, MD and CPK developed the concepts described in this review. AK, PH, TR, AH, KR, and CS further contributed to the concepts. FS and CPK performed literature research. All authors were involved in writing the paper and gave their final approval.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed for this review article.

Declarations

Competing interests The authors declare no competing interests.

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