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Reviving the microcirculation; the protective role of SGLT2 inhibitors in counteracting capillary rarefaction

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ABSTRACT

Capillary rarefaction, as the loss of microvascular density and architecture, is a hallmark of chronic tissue hypoxia seen in diabetes, hypertension, and various forms of chronic kidney and heart disease. It promotes inflammation, fibrosis, and eventual loss of organ function by diminishing oxygen delivery, nutrient exchange, and waste removal. In diabetic nephropathy, intrarenal hypoxia accelerates capillary rarefaction, creating a destructive feedback loop of progressive renal impairment. The restoration of microvascular integrity by SGLT2 inhibitors encompasses a series of glucose-independent actions, involving both metabolic and cellular signaling pathways. These compounds modulate the renal and systemic microcirculation through several key lines. Preclinical data demonstrate improved endothelial function, characterized by enhanced nitric oxide production, decreased oxidative stress, and normalized mitochondrial homeostasis. These drugs stimulate angiogenic pathways and endothelial cell viability, directly promoting the regeneration of microvessels and counteracting rarefaction. These agents have also been shown to attenuate inflammation within the microvasculature, reducing cytokine-driven vascular injury and remodeling. In both animal studies and early-phase clinical investigations, SGLT2 inhibitors foster improved vasodilation and hemodynamic stability, which are crucial to maintaining capillary networks.

Implication for health policy/practice/research/medical education:

SGLT2 inhibitors offer a novel therapeutic approach for reviving the microcirculation by counteracting capillary rarefaction through endothelial restoration, anti-inflammatory actions, metabolic recalibration, and macrohemodynamic improvements. By targeting the cellular and molecular drivers of rarefaction, these agents strengthen tissue oxygenation and nutrient supply, decelerate progression of organ dysfunction, and foster long-term health outcomes in patients with diabetes, kidney disease, and heart failure alike.

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Introduction

In kidney, the network of microscopic blood vessels, arterioles, capillaries, and venules forms the vital interface by diffusion of oxygen and nutrients into tissues, while waste products and carbon dioxide are removed (1,2). This microcirculation, far from being a passive plumbing system, is a dynamic, highly regulated ecosystem essential for organ function, metabolic homeostasis, and overall vitality (1,2). Its deterioration, particularly through a process known as capillary rarefaction, as the pathological reduction in the number and density of functional capillaries represents a silent but profound

driver of multi-organ dysfunction across a spectrum of chronic diseases, most notably diabetes mellitus and its frequent companions, heart failure and chronic kidney disease (3). For decades, therapeutic strategies focused primarily on macrovascular events and systemic risk factors, often overlooking this critical microvascular dimension (4). The emergence of sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially heralded for their potent glucose-lowering effects in type 2 diabetes, has exposed a paradigm-shifting revelation (5). These drugs possess remarkable, direct protective properties on the microvasculature, actively countering capillary

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rarefaction and revitalizing microcirculatory health (6). This profound off-target effect, extending far beyond glycemic control, underpins their unprecedented benefits in reducing heart failure hospitalizations, slowing chronic kidney disease progression, and improving survival, fundamentally altering our understanding of vascular protection and offering a beacon of hope for preserving organ integrity at its most fundamental level (7). Capillary rarefaction is not merely a consequence of disease; it is an active pathological process and a significant contributor to disease progression (8,9). It manifests as a reduction in capillary density detectable through various techniques, by nailfold videocapillaroscopy in the skin, retinal imaging in the eye, contrast-enhanced ultrasound or magnetic resonance imaging in deeper tissues, and eventually, histological examination in biopsies or post-mortem samples (8,10,11). This loss is not random; it involves both structural regression (permanent loss of capillary segments) and functional non-perfusion (capillaries present but not conducting blood flow adequately due to impaired vasomotion, endothelial dysfunction, or increased blood viscosity) (8,12). The mechanisms driving rarefaction are multifactorial and often intertwined. Chronic hyperglycemia in diabetes, for instance, fuels the production of advanced glycation end-products (AGEs) which stiffen the extracellular matrix and impair endothelial cell function (3,13). Then, AGEs bind to their receptor, triggering pro-inflammatory and pro-oxidative pathways (13,14). Sustained oxidative stress, a hallmark of metabolic diseases, directly damages endothelial cells, reduces nitric oxide bioavailability crucial for vasodilation and angiogenesis, and promotes apoptosis (15). Chronic low-grade inflammation, characterized by elevated cytokines like tumour necrosis factor alpha (TNF- α) and interleukin 6, further disrupts endothelial barrier function, promotes leukocyte adhesion, and inhibits pro-angiogenic signals (16,17). Hemodynamic stress, particularly glomerular hypertension in the kidney or elevated cardiac filling pressures in heart failure, exerts mechanical strain on the delicate capillary walls, leading to endothelial injury and dropout (12,18). Neurohormonal activation, especially the renin-angiotensin-aldosterone system and sympathetic nervous system, contributes to vasoconstriction, fibrosis, and inflammation, all detrimental to capillary survival (12,19). Hypoxia itself, resulting from initial capillary loss, creates a vicious cycle by upregulating anti-angiogenic factors like thrombospondin-1 while impairing the function of pro-angiogenic factors like vascular endothelial growth factor (VEGF), paradoxically hindering the necessary reparative response. The consequences of this microscopic attrition are profound and systemic (20,21). In skeletal muscle, rarefaction impairs oxygen delivery during exertion, contributing to exercise intolerance and fatigue, common complaints in heart failure and diabetes (22). In the heart, reduced coronary microvascular density limits

oxygen supply to cardiomyocytes, especially under stress, promoting ischemia, fibrosis, diastolic dysfunction, and eventually contributing to heart failure with preserved ejection fraction (23). In the kidney, peritubular capillary loss is a critical early event in diabetic kidney disease and other chronic kidney diseases, driving tubular hypoxia, inflammation, interstitial fibrosis, and the relentless decline in glomerular filtration rate (21). In the retina, capillary dropout is the foundation of diabetic retinopathy, leading to vision-threatening ischemia and neovascularization. Even in the skin and nerves, microvascular insufficiency contributes to impaired wound healing and neuropathy (24,25). Capillary rarefaction, therefore, is not a bystander but a central pathological mechanism linking metabolic insults to end-organ damage across multiple systems (26). This overview sought to discuss on the protective role of SGLT2 inhibitors in counteracting capillary rarefaction.

Search strategy

To identify relevant literature for this overview, we searched multiple databases—PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar—using keywords including “SGLT2 inhibitors,” “capillary rarefaction,” “chronic kidney disease,” “peritubular capillary,” “type 2 diabetes,” “renal hypoxia,” “inflammation,” and “diabetic kidney disease.”

Mechanistic impact of capillary rarefaction

SGLT2 inhibitors have been detected as a class of drugs whose clinical benefits extend beyond glycemic control and include preservation and restoration of microvascular integrity in multiple organs, thereby counteracting capillary rarefaction and improving tissue perfusion and function (27). Preclinical and translational studies across cardiac, renal, cerebral, skeletal muscle and pulmonary vascular beds have demonstrated that SGLT2 inhibition reduces microvascular loss, preserves capillary density, and attenuates the pathological processes that drive rarefaction such as inflammation, oxidative stress, pericyte loss, impaired angiogenic signalling, and dysregulated cellular metabolism (12,28). Capillary rarefaction, as the progressive reduction in capillary density contributes to organ dysfunction by increasing tissue hypoxia, impairing nutrient delivery, promoting fibrosis and worsening clinical outcomes in conditions including hypertension, diabetes, chronic kidney disease and heart failure, so interventions that preserve or restore capillarization have major therapeutic potential (3,29). Multiple mechanistic pathways link SGLT2 inhibition to preservation of microvasculature. These pathways can be grouped into modulation of local inflammatory and oxidative signalling, improvement in endothelial cell and pericyte viability, enhancement of pro-angiogenic signalling and metabolic reprogramming that favors cellular survival and repair (21,30). Inflammatory activation and oxidative stress are central drivers of microvascular injury and capillary

dropout, and SGLT2 inhibitors attenuate these processes by reducing reactive oxygen species generation, down-regulating pro-inflammatory cytokines, and improving mitochondrial homeostasis in endothelial and perivascular cells (31). By lowering local oxidative stress and inflammation, SGLT2 inhibitors help maintain endothelial nitric oxide bioavailability and endothelial-dependent vasodilation, thereby preserving capillary perfusion and preventing functional non-perfusion that can progress to structural rarefaction (32,33). Preservation of pericytes and perivascular support cells is another key mechanism by which SGLT2 inhibition sustains capillary networks, since pericytes regulate capillary stability, angiogenic signalling, and endothelial survival (24). Recent preclinical studies show that empagliflozin and other SGLT2 inhibitors can prevent pericyte loss and increase pericyte coverage of microvessels in diabetic and ischemic models, stabilizing the microvascular bed and reducing progression to rarefaction (31). Additionally, SGLT2 inhibitors influence pro-angiogenic growth factor pathways, including VEGF-A signalling and downstream regulators, which can promote capillary maintenance and repair after injury (34). Several studies from kidney and cardiac models indicate that SGLT2 inhibition sustains or restores VEGF-related signalling that counteracts capillary dropout in aging and injury settings (35). Metabolic reprogramming underlies many of these protective effects; by modifying cellular substrate utilization, improving energy homeostasis, activating AMPK and related nutrient-sensing pathways, and modulating mTOR (mechanistic target of rapamycin) signalling, SGLT2 inhibitors create a molecular milieu that favors autophagy, survival, and regenerative responses in endothelial cells and pericytes rather than apoptosis and senescence that lead to loss of microvessels (36,37). The net result of these cellular and molecular effects is preservation of structural capillary density as well as improvement in functional microcirculatory parameters such as coronary flow reserve and myocardial flow reserve in some experimental settings, which translates into better organ perfusion and protection from hypoxia-induced fibrosis and dysfunction (12,31). The renal microcirculation has been among the best studied targets for SGLT2-mediated protection against capillary rarefaction, as renal hypoxia, inflammation, and peritubular capillary loss are central features of chronic kidney disease progression (20). Animal models also show that SGLT2 inhibitors preserve peritubular capillary density, reduce proteinuria, and reprogram aged renal transcriptomes, supporting a role in attenuating rarefaction and slowing fibrotic remodeling (38). Mechanistic studies suggest SGLT2 blockade reduces intrarenal hypoxia and the maladaptive responses that lead to capillary dropout, including amelioration of inflammation and restoration of angiogenic signals, thereby interrupting the feed-forward loop that amplifies microvascular loss and fibrosis in diabetic and non-

diabetic kidney injury (20). In models of age-dependent renovascular decline, SGLT2 inhibition preserved microvascular structure and improved functional indices, indicating that benefits extend beyond glycemic contexts and can influence aging-related capillary rarefaction (39). In the heart, coronary microvascular rarefaction and dysfunction are implicated in heart failure, particularly heart failure with preserved ejection fraction, and preclinical studies demonstrate that SGLT2 inhibitors improve coronary microvascular function, maintain capillarization, and protect against microvascular structural abnormalities in diabetic and prediabetic models (40,41). Accordingly, empagliflozin treatment improved coronary flow velocity reserve, attenuated microvascular structural changes, and enhanced cardiac contractile performance in animal models, and these changes were associated with improved endothelial nitric oxide availability and reduced oxidative stress (42). The capacity of SGLT2 inhibitors to preserve cardiac capillaries has implications for limiting myocardial ischemia, microinfarction and interstitial fibrosis, as the processes that contribute to impaired diastolic function and progression to heart failure (43). Translating preclinical microvascular findings into clinical outcomes has yielded variable but promising signals; some small trials have observed reductions in resting myocardial blood flow and increases in myocardial flow reserve with SGLT2 treatment, while others found no significant change in coronary flow reserve over short-term follow-up, highlighting heterogeneity by study population, duration, and measurement modality and underscoring the need for larger and longer mechanistic trials (40,44). The diversity of clinical results likely reflects differences in baseline microvascular pathology, comorbidities, and sensitivity of the techniques used, and does not negate the robust preclinical data demonstrating structural preservation of capillary networks in experimental models (9,12). Beyond heart and kidney, cerebral and skeletal muscle capillary rarefaction are modulated by SGLT2 inhibitors in animal studies, where empagliflozin or combination therapies prevented capillary loss, improved capillary density, and restored microvascular-dependent tissue function, suggesting broad systemic benefits on the microcirculation that may translate into improved exercise capacity, cognitive resilience, and organ-specific protection (45). Pulmonary vascular research also indicates that SGLT2 inhibition can enhance pulmonary microvascular function, which is relevant given that pulmonary vascular remodeling and microcirculatory impairment contribute to right heart strain and cardiorespiratory dysfunction (46). The preservation of capillary networks by SGLT2 inhibitors is mechanistically tied to effects on endothelial cell viability and angiogenic potential (21). Meanwhile, SGLT2i improve mitochondrial health within endothelial cells, reduce endothelial apoptosis, and support reparative angiogenesis while

simultaneously mitigating maladaptive fibrotic signalling that follows microvascular loss (47). Hence, stabilization of endothelial–perivascular cell interactions through pericyte preservation is particularly important as pericyte detachment and death are early events in capillary rarefaction, and SGLT2 inhibitors have been shown to maintain pericyte coverage and function in diabetic heart models (48).

Molecular mechanisms of improving microcirculation by SGLT2i

At the molecular level, activation of AMPK and suppression of excessive mTOR signalling under SGLT2 inhibition provide a favorable environment for autophagy and cellular repair, as the processes that protect endothelial and perivascular cells from stress-induced demise and thereby prevent microvascular attrition (49–52). Moreover, SGLT2 inhibitors influence nitric oxide-cGMP-PKG pathways by reducing oxidative reducing of nitric oxide and supporting endothelial-dependent vasodilation, which maintains capillary perfusion and prevents functional non-perfusion that predisposes to structural rarefaction (23,53–57). Another important pathway is modulation of transforming growth factor- β and fibrogenic cascades. Previous investigations also detected that, SGLT2 inhibitors reduce TGF- β (transforming growth factor- β) activity and collagen deposition in experimental models, limiting the fibrotic sequelae of microvascular loss that further impair capillary function and organization (58,59). The anti-inflammatory profile of SGLT2 inhibition includes reductions in leukocyte recruitment, macrophage activation, and proinflammatory cytokines, thereby interrupting the local immune-driven microvascular injury that accelerates capillary dropout in metabolic and ischemic disease contexts (16,60). In several experimental models, these combined effects translate to sustained or restored capillary density, improved tissue oxygenation and metabolic support, and attenuation of subsequent fibrosis and functional loss (12,58). Therefore, the combination of mechanistic data as, reducing oxidative stress and inflammation, preserving endothelial and pericyte survival, enhancing pro-angiogenic and nutrient-sensing pathways, and limiting fibrosis provides a coherent biological rationale for SGLT2 inhibitors to counteract capillary rarefaction across organs (21,61). It seems that, SGLT2 inhibitors protect the microcirculation by preserving capillary density, stabilizing endothelial–pericyte interactions, attenuating inflammation and oxidative stress, and promoting pro-survival and angiogenic signalling, thereby counteracting capillary rarefaction and its downstream consequences on tissue hypoxia, fibrosis and dysfunction (21,62,63).

Conclusion

Capillary rarefaction is both a cause and a consequence of organ dysfunction. When capillaries are lost, tissue

oxygen diffusion distances increase and regional hypoxia emerges, triggering pathways that favor extracellular matrix deposition, pericyte activation, and vascular regression. Conversely, inflammation, oxidative stress, dysregulated angiogenic signalling, and mechanical forces such as increased interstitial pressure can directly damage endothelial cells and pericytes, initiating a self-reinforcing cycle of microvascular dropout. In the kidney and heart rarefaction correlates with disease progression. Capillary rarefaction worsens chronic kidney disease through loss of peritubular capillaries. SGLT2 inhibitors represent a promising class of agents that counteract capillary rarefaction through a multifactorial repertoire by hemodynamic unloading, metabolic reprogramming, anti-inflammatory and antioxidant actions, pericyte preservation, anti-fibrotic effects, and modulation of angiogenic signalling. Evidence from experimental and emerging clinical studies supports their capacity to preserve microvascular integrity in organs vulnerable to rarefaction, with translational signals of improved perfusion and structural preservation.

Conflicts of interest

The author declares that she has no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author utilized Perplexity to refine grammar points and language style in writing. Subsequently, the author thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

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