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CKJ REVIEW

SGLT2 inhibition to target kidney aging

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ABSTRACT

Anti-aging therapy is the latest frontier in the world of medical science, especially for widespread diseases such as chronic kidney disease (CKD). Both renal aging and CKD are characterized by increased cellular senescence, inflammation and oxidative stress. A variety of cellular signalling mechanisms are involved in these processes, which provide new potential targets for therapeutic strategies aimed at counteracting the onset and progression of CKD. At the same time, sodium–glucose co-transporter 2 inhibitors (SGLT2is) continuously demonstrate large beneficial effects at all stages of the cardiorenal metabolic continuum. The broad-spectrum benefits of SGLT2is have led to changes in several treatment guidelines and to growing scientific interest in the underlying working principles. Multiple mechanisms have been studied to explain these great renal benefits, but many things remain to be solved. With this in mind, we provide an overview of the experimental evidence for the effects of SGLT2is on the molecular pathway's ability to modulate senescence, aging and parenchymal damage, especially at the kidney level. We propose to shed some light on the role of SGLT2is in kidney care by focusing on their potential to reduce the progression of kidney disease across the spectrum of aging and dysregulation of senescence.

Keywords: aging, chronic kidney disease, molecular pathways, senescence, SGLT2 inhibitors

INTRODUCTION

Aging and chronic diseases have been regarded as critical issues due to the increase in the elderly population and its impact on global health. Physiologic kidney aging and several kidney diseases share common biologic processes and molecular pathways [1], including cellular senescence, inflammation, fibrosis, vascular rarefaction, loss of glomeruli and tubular dysfunction, which lead to glomerulosclerosis and tubulointerstitial fibrosis [2, 3]. Nevertheless, the processes driving the progressive decline of kidney function performance during aging and the interrelation between aging and disease are yet not fully understood. In fact, correctly defining the cellular and molecular processes of aging is truly a challenge [4]. Aging-associated response mechanisms such as metabolic adaptation, senescence or apoptosis are mainly programmed. Therefore, aging can be defined as failure to counteract damage, and this failure causes functional decline, pathology and death. Factors causative in the initiation of kidney aging might be stochastic, consisting of acute kidney injury (AKI) or chronic diseases such as glomerulonephritis and diabetic kidney disease. The timely accumulation of different entities of cellular insults causes increased storage of senescent cells driving detrimental effects, thereby leading to accelerated nephron loss [5].

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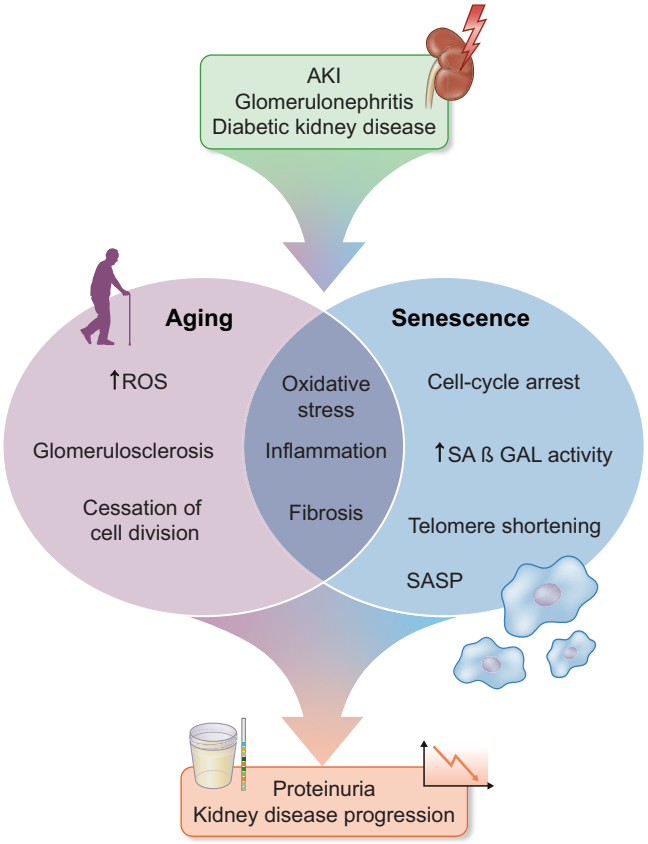

Figure 1: Structural and functional changes in the kidney across the senescence–aging spectrum. AKI, glomerulonephritis and diabetic kidney disease lead to microscopic and macroscopic changes cutting across the senescence–aging spectrum. These changes imply kidney damage that is expressed in proteinuria and kidney function decline.

Certainly the balance between tissue dysfunction and repair progressively diminishes during aging. In response to a variety of stressors, cells can either undergo apoptosis or enter a secretory phenotype featuring changes in morphology and transcriptional profile and resistance to apoptosis, namely senescence. Cellular senescence was initially considered with regard to its physiological and homeostatic effects, particularly during embryonic development and wound healing, but it is now seen as a pathological process that contributes to aging as well as to various diseases and metabolic disorders. The characteristic triad of senescence includes arrested cell growth, resistance to apoptosis and senescence-associated secretory phenotype (SASP), which typically lead to macromolecular damage and altered metabolism [6]. In fact, senescent cells are characterized by morphological alterations including large, flat bodies and organelle abnormalities and chromatin organization, as well as loss of physiological functions [7]. In particular, cellular senescence is characterized by altered transcriptome and secretome, sharing characteristic features with kidney aging and leading to chronic kidney disease (CKD) progression (Fig. 1). Interestingly, although aging at the organismal level might be irreversible, the kinetics can be decelerated.

In *in vitro* or *in vivo* models, sodium–glucose co-transporter 2 inhibitors (SGLT2is) have been shown to correct or improve many of the pathological processes involved in the development and progression of kidney aging, including inflammation, endothelial dysfunction, mitochondrial injury, fibrosis and cellular senescence [8]. These protective effects are likely to underlie the ability of these agents to slow progression of established CKD as demonstrated in large prospective clinical trials [9]. We believe detailed analysis of their potentiality might stimulate further experimental studies to outline new therapeutic targets in the context of kidney aging prevention and treatment. For these reasons, in this review we attempt to describe the aging-related changes in the kidney cells and the prospects of SGLT2is in the therapeutic management of kidney aging, focusing on its associated molecular pathways.

KIDNEY AGING AND SENESCENCE

The kidney in healthy aging

In clinical studies, aging-associated changes are related to a decrease in renal function [both glomerular filtration rate (GFR) and renal plasma flow (RPF)] [10], with an average yearly decline of GFR of 0.7–0.9 ml/min/1.73 m^2 in otherwise healthy individuals [11]. The fundamental origins of the decrease in GFR with healthy aging are not fully understood, but it is a phenomenon related to a slowly progressive loss of nephrons from age 30 years onward. From a histological point of view, kidney aging is mainly characterized by nephrosclerosis, i.e. global glomerulosclerosis, interstitial fibrosis/tubule atrophy (IF/TA) and arteriolosclerosis [12], and the rate of GFR decrease is the result of several mechanisms leading to reduced glomerular density [13]. As a matter

of fact, nephron hyperfiltration occurring in residual nephron and haemodynamic stress on podocytes contributes to their degeneration, altering hydraulic permeability and the surface area available for filtration [14].

While healthy aging is associated with structural changes in the kidney and a decrease in GFR, this does not always involve a substantive increase in the risk of end-stage kidney disease (ESKD) or mortality. For this reason, some authors have proposed an age-based modification to the definition of CKD. According to this vision, the definition of CKD when estimated GFR (eGFR) is $<$75 ml/min/1.73 m^2 in younger adults (age $<$40 years) [15] and when eGFR is $<$45 ml/min/1.73 m^2 in older adults (age $>$65 years) [16] appears to be properly balanced.

However, due to the pivotal role of the kidney in the development of hypertension and regulation of body volume and metabolic homeostasis, GFR decline and the age-related changes in the structure and function of kidney cells actually increase the overall risk class. Animal and human studies report that age is related to changes in the permeability of the capillary wall in glomeruli, increased susceptibility to podocyte injury, changes in tubular reabsorption and secretory capacities, changes in urinary concentration and production of kidney-derived hormones and bioactive molecules [17], increased apoptosis, oxidative stress and inflammation [18, 19]. The subsequent deterioration of the integrity of the slit pore membrane in glomeruli defines both GFR decline and albumin permeability alteration. In other words, healthy kidney aging could be viewed as a compound of physiological changes with pathological implications. For these reasons, specific management strategies that are of actual benefit to older patients with decreased GFR warrant attention.

Aging in kidney disease

In the context of contemporary nephrology research, the effect of age on the fate of CKD patients is a critical issue. The kidneys of elderly patients are more vulnerable to the detrimental effects of proteinuria due to the greater degree of renal fibrosis and ischaemia, significantly increasing the risk of ESKD in older CKD patients [20].

Research attention has been recently drawn to the knowledge gaps of age-related differences in the mechanisms and pathways that contribute to progression to ESKD. In contrast with healthy aging, the global glomerulosclerosis related to GFR decline in kidney diseases [21] is a result of visceral glomerular podocyte degeneration, inadequate repair and autophagy impairment. Autophagy, a conserved lysosomal pathway for the degradation of cytoplasmic components, is essential to the maintenance of kidney homeostasis, and its reduction has been shown to be detrimental to kidney structure and function. Autophagy defects in kidney cells of both tubular and glomerular compartments have been shown to contribute to the development of diabetic kidney disease, focal segmental glomerulosclerosis and polycystic kidney disease [22–24].

The mechanisms underlying the aging-related reduction of autophagy in podocytes have largely been investigated in mice. Mitochondrial damage, endothelial reticulum stress and accumulation of oxidized and ubiquitylated protein aggregates and lipofuscin were found in a mouse model of autophagy-deficient podocytes. Proteasome activity has been shown to be increased in aged mice, probably for the purpose of clearing protein aggregates and compensating for the loss of autophagy [25]. Another mouse model of podocyte-specific deletion of a lysosomal protease further demonstrated the importance of lysosomal activity in podocyte maintenance during aging. Defective autolysosome degradation in podocytes triggered the accumulation of toxic lipofuscins and protein aggregates, leading to apoptotic podocyte death. As a result, lysosomal-defective mice developed proteinuria and kidney failure [23].

One more longevity factor is sirtuins (SIRT), a family of NAD$^+$-dependent class III histone deacetylases, which are involved in metabolic regulation and are activated by increased NAD$^+$ levels. SIRT1 cross-talks with other pathways regulating different mechanisms involved in energy metabolism and cell survival, including autophagy [26]. Interestingly, it was reported that podocyte-specific knockdown of SIRT1 aggravated age-associated kidney injury in aging mice [27]. Sirtuins role in anti-aging interventions has been confirmed in several experimental studies testing the role of caloric restriction (CR) on aging. CR is well known to enhance lifespans and health spans, preventing many age-related diseases. The biochemical mechanisms by which it increases kidney health is linked, at least in part, to enhanced mitochondrial Ca^{2+} uptake rates, regulating several aspects of mitochondrial function, including oxidative phosphorylation and redox balance [28, 29].

Accelerated cellular senescence in the kidney

Cellular senescence not only contributes to aging, but also plays a causal role in numerous age-related diseases; in particular, it has been proven to be involved in the pathogenesis of AKI, AKI to CKD transition and many types of CKD [30]. Cell senescence may develop during an acute response after injury as a mechanism of tissue repair [30]. This kind of ‘acute senescence’ is a tightly controlled process that participates in repair mechanisms and limits fibrosis. In contrast, in chronic diseases, senescent cells accumulate in the kidney in response to a variety of stressors, including metabolic stress, telomere shortening [31], oncogenic mutations, inflammation and mitochondrial dysfunction [32]. These stressors promote cell-cycle arrest via pathways either dependent or independent of the DNA damage response. Differently from the ‘acute senescence’ setting, in chronic diseases, senescent cells are scarcely removed by apoptosis or immune clearance and are increasingly considered to be mediators of disease progression [33, 34]. Data from animal models suggest that senescent interstitial and tubular epithelial cells contribute to ischaemia–reperfusion injury and AKI, as well as to AKI to CKD progression. Endothelial cell, podocyte and mesangial cell senescence might contribute to diabetic kidney disease [35]. Tubular epithelial cell senescence has also been detected in many forms of CKD, including obesity-related nephropathy, membranous nephropathy, lupus nephritis, minimal change disease, unilateral ureteral obstruction and immunoglobulin A nephropathy. In contrast, cellular senescence occurs as part of sequential and tightly orchestrated stress-induced effector programs involving metabolic changes associated with obesity and diabetes. High glucose drives *in vitro* senescence in kidney podocyte, mesangial and tubular cells [36]. Furthermore, hyperglycaemia causes cellular senescence via an SGLT2-dependent pathway in proximal tubules in the early stage of diabetic nephropathy [37].

Regardless of the kidney disease, the major changes in GFR with aging can be attributed primarily to nephron loss. The last evidence shows that the drawbacks of accelerated cell senescence in kidney diseases are 2-fold. First, senescence causes a cell cycle arrest, with a consequent loss of tissue repair capacity; this is especially relevant for cells with low replication rates, like podocytes. Second, senescent cells produce

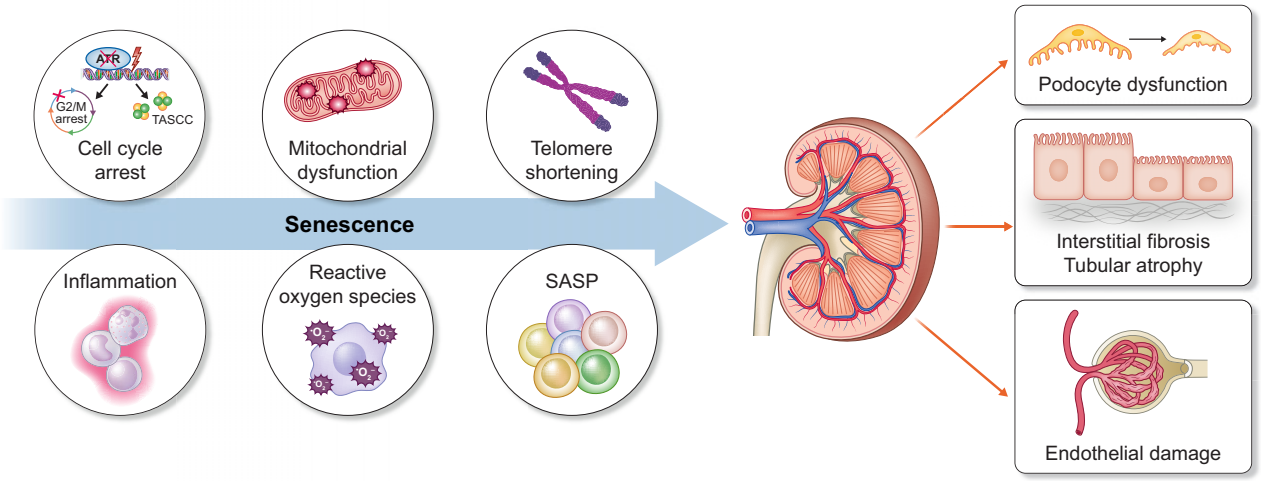

Figure 2: Overview of various mechanisms involved in cellular senescence. The cell cycle becomes dysfunctional as telomere shortening and mitochondrial dysfunction cause DNA damage, the extracellular matrix is expanded and there is organelle injury and senescent cells develop a SASP that leads to chronic inflammation. All the kidney cells are involved—podocytes, tubules and endothelial cells.

pro-inflammatory and matrix-degrading molecules in what is known as the SASP, leading to development and progression of glomerulosclerosis and IF/TA [38] (Fig. 2). Accordingly, the commonly used biomarkers of *in vitro* senescent cells are enzymatic activity of the lysosomal hydrolase senescence-associated β-galactosidase (SA-β-GAL), reflecting an increase in lysosomal mass [39, 40], the development of an SASP [41] and arrested cell growth [5].

Many of the cell senescence inducers, namely metabolic stress, telomere shortening [31], inflammation and mitochondrial dysfunction [32], cause overexpression of the cyclin-dependent kinase inhibitors p16INKA and/or p21cip1. Their binding to CDK4/6 inhibits cyclin D-CDK4/6 complex and induces cell cycle arrest at the G1/S cell cycle checkpoint. Activation of p16INKA/Rb and p53/p21 tumour suppressor networks implements this growth arrest in the nucleus [38], composing a key signalling cascade implicated in kidney cell senescence. Experimental models of CKD showed that accumulation of senescent cells later the G2/M phase triggers a secretory phenotype, resulting in fibrosis [42]. Interestingly, SIRT1 has been shown to inhibit cellular senescence through regulation of the p53/p21 pathway. Podocyte-specific knockdown of SIRT1 accelerated age-related glomerulosclerosis and podocyte loss in mice kidneys [27].

In contrast, a number of signalling molecules have been identified to exacerbate renal cell senescence and renal aging. For instance, Wnt9a/β-catenin signalling seems to promote renal tubular senescence and renal fibrosis in diseased kidneys, as evidenced by the upregulated expression of p16INK4a, p53 and p21, and increased SA–β–GAL activity in renal tubules [43].

Reactive oxygen species (ROS) can induce cellular senescence by regulating the p16INK4a/prb and p53/p21 pathways. In turn, senescent cells produce ROS [44], perpetuating a vicious cycle of cellular damage. Accumulation of ROS results in lipid peroxidation, which leads to elevated advanced glycation end-products and advanced lipoxidation end-products, both of which regulate cellular senescence [45]. One of the shared links between oxidative stress and cellular senescence might be inflammation, which drives and results from both processes and contributes to CKD.

ROS signalling also mediates autophagy-delaying cell senescence and leads to SASP, a distinctive secretome consisting of a various pro-inflammatory molecules, metalloproteases and growth factors [39]. SASP components include interleukin (IL)-1β, IL-6 and IL-8 and transforming growth factor (TGF)-β1, and these can act in a paracrine and autocrine fashion, leading to persistence and propagation of senescence within tissues [46]. Direct evidence in the kidney is lacking and specific studies are needed. Detection of cells displaying the SASP in the kidney would be a major step in determining the choice of treatment.

EFFECT OF SGLT2 INHIBITION IN KIDNEY AGING AND SENESCENCE

Geroscience represents a novel paradigm whereby biological aging is recognized as the major modifiable driver of age-related diseases and other late-life conditions. Some authors have proposed a standardized process for evaluating US Food and Drug Administration (FDA)-approved medications for their geroscience potential, and SGLT2i demonstrated the most robust clinical evidence for a reduction of death from any cause [47].

SGLT2 inhibition has pleiotropic effects on multiple organ systems. As for the heart, there have been several demonstrations of the mechanisms underlying the cardioprotective effect conferred by inhibition of SGLT2 activity, including a reduction of myocardial fibrosis and remodelling, ischaemia–reperfusion injury, oxidative stress and inflammation and improved myocardial contractility [48, 49], which lead to a reduction in heart failure and cardiovascular events [50, 51]. It has also been shown that mitochondrial function is improved and amyloid plaque deposition in the brain is reduced, ameliorating age-related and neurodegeneration disease [52, 53].

Studies on the effect of defective senescent cell formation have provided a major step forward in our understanding of the effects of treating cell senescence. Baker *et al.* [54] identified a causal link between cellular senescence and aging phenotypes by showing that the clearance of senescent cells in a mouse progeroid model *in vivo* can delay age-related tissue dysfunction. More recently, it was demonstrated that the removal

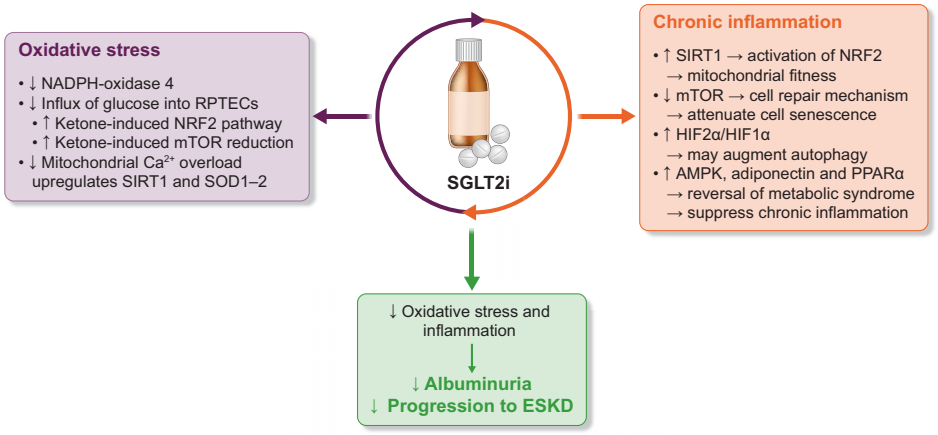

Figure 3: Molecular effects of SGLT2is on kidney aging. SGLT2is act on different metabolic pathways in order to protect kidney function and prevent damage: SIRT1 is able to deacetylate and activate NRF2 that regulates mitochondrial fitness; inhibition of mTOR mediates renoprotection; autophagy is affected by an elevated HIF-2α:HIF-1α ratio; and upregulation of AMPK, adiponectin and PPAR-α results in inhibition of chronic inflammation through energy deprivation. Furthermore, SGLT2is decrease oxidative stress in different ways: they inhibit NADPH-oxidase 4 and reduce the influx of glucose into RPTECs in order to increase ketone activation of the NRF2 pathway and mTOR inhibition; the decreased mitochondrial calcium overload contributes to upregulation of SIRT1 and SOD1 and 2. PPAR-α: peroxisome proliferator-activated receptor α.

of senescent cells delays aging, increases lifespan and restores organ function, including the blood vessels [55] and kidney [56], without increasing the risk of cancer. As changes at the molecular level due to SGLT2i involve inflammation, oxidative stress and DNA damage (Fig. 3), we aim to gain a clearer picture of the current scientific understanding of the potential of SGLT2is related to targeting aging and senescence in the kidney (Table 1).

SGLT2is effect on aging: the role of caloric restriction

Several experimental models have contributed to the conviction that SGLT2is may exhibit anti-aging effects by providing protection against ROS-induced cellular senescence, DNA damage and attenuated inflammation, reducing end-organ fibrosis and improving endothelial function [57]. Moreover, SGLT2is have been shown to modulate the nutrient-sensing pathways, known drivers of aging. By urinary caloric loss, SGLT2is activate a fasting-like metabolic state and reduce insulin signalling in response to a decrease in the glucose level. These events reduce the insulin:glucagon ratio and increase hepatic and kidney glucose production from glycogenolysis and gluconeogenesis [58]. The compensating formation of ketone bodies, in addition to be a direct energy source for damaged proximal tubular epithelial cells (PTECs), was shown to prevent PTEC and podocyte damage by inhibiting mammalian target of rapamycin (mTOR) signalling in mice models of proteinuric and non-proteinuric diabetic kidney disease [59]. By promoting a nutrient deprivation state, SGLT2is upregulate the energy deprivation sensors adenosine 5′-monophosphate-activated protein kinase (AMPK) and SIRT1, inhibit the nutrient sensors mTOR and insulin/insulin-like growth factor 1 and modulate the closely linked hypoxia-inducible factor (HIF)-2α/HIF-1α pathways [57]. Activation of the AMPK/SIRT1 axis has recently been suggested as a novel target for the treatment of high-glucose-induced endothelial cell injury and dapagliflozin abrogated high-glucose-induced endothelial cell dysfunction by AMPK/SIRT1 pathway up-regulation in human umbilical vein endothelial cells [60].

Several studies have been conducted on the effects of CR on longevity across various animal species, demonstrating an increase in lifespan and improved health outcomes [61]. Among involved molecular processes, DNA methylation has been shown to play a critical role: CR has resulted in attenuation of age-related methylation drift in mice and rhesus monkeys [62, 63]. The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) randomized controlled trial found that CR modified DunedinPACE, a DNA methylation biomarker of the pace of aging. This finding supports the geroscience hypothesis that proposed this strategy to slow or reverse molecular changes that occur with aging, delaying or preventing multiple chronic diseases and extending healthy lifespan [64]. SGLT2is belong to the category of CR mimetics, specifically the downstream type, regulating intracell signalling proteins [65]. Therefore, they represent a fascinating and promising class of drugs that modify cellular mechanisms to mimic the effects of caloric restriction. Their complexity and potential to modulate multiple pathways make them an exciting area of research in the quest to promote healthy aging [66].

SGLT2i: redox control of senescence (oxidative stress and mitochondrial dynamics)

Excess ROS can directly or indirectly damage DNA, proteins and lipids, thereby inducing transgenation, conformational changes in proteins and lipid peroxidation [67, 68]. There is increasing evidence that oxidative stress causes oxidative tissue damage and disrupts cellular metabolism [69, 70], especially in the kidney, which has fast metabolic processes. The increased influx of glucose into the renal proximal tubular epithelial cells (RPTECs) under high-glucose conditions leads to a burst of ROS production, both by the mitochondria and by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase or xanthine oxidase [71]. By decreasing the influx of glucose into RPTECs, dapagliflozin and tofagliflozin significantly ameliorate the high-glucose-induced oxidative stress and the consequent DNA damage response, especially in high-glucose conditions [72, 73].

Oxidative stress is known to be a common pathogenic substrate in chronic disease and may occur in the diabetic kidney at an early time. Specifically, dysregulated mitochondrial

Table 1: Experimental models proving mechanisms involved in kidney protection from aging and/or senescence with SGLT2i treatment

Organs/cells/tissues	Experimental models	SGLT2i tested	Mechanisms involved	References
Renal proximal tubular cells (mice)	Mice with or without diabetes in which HHIP was present or specifically knocked out in renal tubules	Canagliflozin	Inhibited β-galactosidase activity	[70]
Proximal tubules (mice)	Damaged proximal tubules of ApoE knockout mice fed a high-fat diet (model of non-proteinuric diabetic kidney disease)	Empagliflozin	Elevation of ketone body that corrects mTORC1 hyperactivation	[53]
Kidney cortex (rats)	Male hereditary hypertriglyceridaemic rats fed a standard diet with or without SGLT2i	Empagliflozin	Increased activity of GSH-dependent enzyme GSH-Px and SOD decreased levels of lipoperoxidation products	[64]
Kidney tissue sections (mice)	Mice aged by subcutaneous injection of D-galactose	Empagliflozin	Upregulated SIRT1 levels	[65]
Endothelial cells (ECs) (pigs and male rats)	ECs were isolated from porcine coronary arteries and arterial segments from rats, incubated in the absence or presence of either NADPH oxidase inhibitor, an AT1R antagonist, SGLT1 and/or SGLT2i, then Ang II or a nitric oxide synthase inhibitor	Empagliflozin	Abolished pro-oxidant responses, SA-β-GAL activity, expression of senescence markers p53 and p21 and p16 protein	[63]
Aorta tree and aortic valve (mice)	Spontaneously atherosclerotic mice	Empagliflozin	Improved protein expression level of p-AMPK affected by ox-LDL in cell; reduced gene expression level of inflammatory factors and protein expression level of NF-κB	[69]
Human renal proximal tubular epithelial cells (hRPTECs)	hRPTECs were incubated under high-glucose conditions	Dapagliflozin	Reduced p16, inhibited ROS production with blunted DNA damage, ataxia telangiectasia mutated kinase (ATM) and p53 phosphorylation; decreased high-glucose-induced IL-1 and IL-8 production; normalized TGF-1 level	[60]
hRPTECs	hRPTECs were incubated under high-glucose conditions	Tofogliflozin	Reduced MCP-1 gene expression and apoptotic cell death	[61]
Human renal tubular epithelial cell line (HK-2 cells)	HK-2 cells pretreated with hydrogen peroxide to induce cellular senescence	Dapagliflozin	Inhibited cellular senescence and oxidative stress via ketone-induced NRF2 activation	[66]
Human endothelial cells (hECs)	hECs were plated on glass-bottom dishes and treated with different concentrations of glucose	Empagliflozin	Reduced mitochondrial Ca^{2+} overload and ROS production attenuated cellular permeability and improved cell viability in response to oxidative stress	[62]
Human umbilical vein endothelial cells (HUVEC)	HUVEC were incubated under high-glucose conditions	Dapagliflozin	Abrogated high-glucose-induced endothelial cell dysfunction by AMPK/SIRT1 pathway up-regulation	[54]

fitness has been proposed as a potential root of age-related frailty. Empagliflozin has been shown to significantly reduce mitochondrial Ca^{2+} overload and ROS production triggered by high glucose in human endothelial cells, attenuate cellular permeability and improve cell viability in response to oxidative stress [74]. These findings were associated with decreased frailty in diabetic and hypertensive patients after 3 months of treatment with empagliflozin as compared with the control group.

This protective role of SGLT2is on endothelial damage has been confirmed by the demonstration that pro-oxidant responses, SA-β-GAL activity, the expression of senescence markers p53 and p21 at both the messenger RNA and protein levels and p16 protein were upregulated by angiotensin II (Ang-II) and abolished by SGLT2i in endothelial cells isolated from porcine coronary arteries [75]. Ang-II up-regulates SGLT1 and 2 protein expression in endothelial cells and arterial segments, promoting sustained oxidative stress, senescence and dysfunction. Such a sequence contributes to coronary artery disease microparticle–induced endothelial dysfunction. Since AT1R/NADPH oxidase/SGLT1 and 2 pathways promote endothelial dysfunction, inhibition of SGLT1 and/or 2 appears as an attractive strategy to promote endothelial health.

Trnovska *et al.* [76] tested the effect of empagliflozin on metabolic parameters and insulin resistance using non-obese hereditary hypertriglyceridaemic rats, a strain characterized by elevated concentrations of triglycerides and insulin resistance. They observed that empagliflozin reduces oxidative stress in the kidney tissue. In fact, in the kidney cortex, activity of the γ-glutamyl-cysteinyl-glycine (GSH)-dependent enzyme GSH-Px and superoxide dismutase (SOD), an antioxidant enzyme, was increased in the empagliflozin-treated group while levels of lipoperoxidation products were decreased. Empagliflozin can also exert antioxidant effects by upregulating SIRT1 levels through upregulation of SOD1 and 2 in a mice model of senescence [77].

Moreover, dapagliflozin prevented the progression of diabetic kidney disease by inhibiting cellular senescence and oxidative stress via ketone-induced nuclear factor erythroid 2–related factor 2 (NRF2) activation. In particular, expression levels of ageing marker genes (*p21*, *p16* and *p53*) and the expression levels of SASP in the kidney were reduced in a type 2 model of db/db mice, primarily focusing on cellular senescence and oxidative stress, when treated with dapagliflozin [78]. The fact that such improvement was not observed in the subgroup of mice treated with sulfonylurea suggests that dapagliflozin has antisenescent and antioxidant properties, which is independent of its glucose-lowering effect.

SGLT2is effect on kidney cellular senescence: inflammation pathways

Since SGLT2is promote ketogenesis from a shift toward fatty acid oxidation, one may postulate that they have anti-inflammatory effects similar to CR, with promising effects on longevity and the advantage of not being difficult to adhere to.

Results suggest that SGLT2is possess a tangible activity against low-grade inflammation, an effect possibly mediated by their ability to lower uric acid and insulin concentrations [79]. Moreover, reducing the glucose influx in senescent cells is likely to result in attenuation of their inflammatory affects. In fact, *in vitro* experiments detected that dapagliflozin decreased high-glucose-induced IL-1 and IL-8 production and normalized the level of TGF-1 in renal tubular epithelial cell culture supernatants [60]. Moreover, both monocyte chemoattractant protein-1 (MCP-1) gene expression and apoptotic cell death were reduced by SGLT2is [80].

The interaction between SGLT2is and the AMPK signal pathway was studied in both spontaneously atherosclerotic mice *in vivo* and an oxidized low-density lipoprotein (ox-LDL)-induced macrophage inflammation model *in vitro*. Empagliflozin can improve the protein expression level of phosphorylated AMPK (p-AMPK) affected by ox-LDL in cells and reduce the gene expression level of inflammatory factors and protein expression level of nuclear factor (NF)-κB, thus removing the effect of diabetes in terms of inflammation-mediated damage [81].

Hedgehog interacting protein (HHIP) encodes a protein of 700 amino acids attached to the cell membrane, regulates cellular function and is essential in organ development. HHIP is detectable in renal endothelial and epithelial cells in the normal, mature kidney and is believed to promote SASP through the release of a variety of inflammatory cytokines in remodelled kidney cells, thereby exacerbating the progression of diabetic kidney disease. In human renal proximal tubule HK2 cells, high-glucose-induced HHIP overexpression promoted increased SGLT2 protein expression and cellular senescence [82]. Moreover, their increased β-GAL activity was inhibited by canagliflozin, reaffirming a potential role of SGLT2is in the modulation of inflammaging.

CONCLUDING REMARKS AND FUTURE PROSPECTS

Targeting aging and senescence pathways offers myriad beneficial effects, particularly in the context of chronic disease. We depict aging and senescence as being interacting or intercalating, but different processes are becoming increasingly recognized as possible causes of disease pathophysiology throughout the cardiorenal system.

SGLT2is are antihyperglycaemic drugs that have been shown to protect the kidneys and heart of patients with or without type 2 diabetes and to preserve kidney function or reduce kidney failure. Recent research has provided further insights into the aging treatment paradigm. Many *in vivo* and *in vitro* studies are aimed at revealing the pathways underlying the pleiotropic effects of SGLT2is, both blood glucose-dependent and -independent mechanisms [83].

Understanding how aging and senescence of kidney cell types contributes to specific disease phenotypes and how the pathways involved can be regulated by SGLT2is will allow researchers to develop improved, targeted therapies to delay or prevent aging-associated diseases in the kidney.

While other strategies related to CR or the use of molecules such as metformin, rapamycin or resveratrol that interfere with SASP signalling factors are promising in order to delay the onset of age-associated diseases [84, 85], further basic and clinical research is needed to define the potential effects and complex mechanisms of SGLT2is in aging and senescence processes.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design, data collection, and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research. All data supporting the findings of this study are available within the paper.

CONFLICT OF INTEREST STATEMENT

All authors and co-authors declare no conflicts of interest.

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