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Can Sodium Glucose Co-Transporters Inhibitors Replace Immunosuppressive Drugs in Management of Chronic Glomerulonephritis?

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Abstract

Chronic glomerulonephritis (CGN) is the most frequent cause of end-stage renal disease (ESRD) in children and the 3rd cause in adults worldwide. Treatment of most cases of CGN is based, most of the time, on steroids and a wide scale of other immunosuppressive (IS) agents. The anti-diabetic sodium glucose co-transporters inhibitors (SGLT2Is) have shown in the last 2 years a significant delay in the rate of progression of chronic renal disease in patients suffering from focal segmental glomerulosclerosis (FSGS) or IgA nephropathy (IgAN). These results should stimulate the Nephrology research workers to design prospective controlled multicenter trials to compare SGLT2Is versus IS agents in the management of different subtypes of CGN. This review illustrates the value of SGLT2Is in these cases. Nephrology practice became revolutionized after SGLT2Is.

Keywords: Chronic Glomerulonephritis, Empagliflozin, Canagliflozin, Dapagliflozin, Focal Segmental Glomerulosclerosis (FSGS), IgA Nephropathy, Membranoproliferative Glomerulonephritis (MPGN), Membranous Glomerulonephritis (MGN), Lupus Nephritis (LN)

Introduction

Primary or secondary GN is the sequence of either autoimmune disease, systemic infection, malignancy, or exposure to medications, chemicals, or poisons. GN comes as the 3rd frequent cause of ESRD after diabetes mellitus and systemic hypertension. On the other hand, GN is the most common cause in children, teenagers, and young adults [1].

The established treatment of GN in many cases of GN is steroids and other IS treatments. This applies mainly to lupus nephritis (LN), anti-neutrophil cytoplasmic antibody (ANCA) associated GN, minimal change nephrotic syndrome (MCN), membranoproliferative glomerulonephritis (MPGN), primary focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), and membranous glomerulonephritis (MGN). In many of these cases, steroids and other IS drugs are used for long duration and sometimes lifelong [2].

This treatment carries a high risk of adverse effects including opportunistic infections, metabolic bone disease, development of diabetes mellitus, weight gain, systemic hypertension, psychosis, gastritis, duodenitis, gastroduodenal erosions or ulcerations, cataracts, and cardiovascular disease. The rate of opportunistic infection in GN patients treated with steroids and /or other IS drugs exceed 5 folds the rate in those not exposed to such treatment [3].

In addition, patients suffering from heavy non-selective proteinuria suffer an increased chance of opportunistic infection secondary to the urinary loss of immunoglobulins [4]. For these reasons, a careful balance of the risk and benefits should be weighed before using these agents in individual GN subtypes.

A couple of years ago, the Dapagliflozin (Dapa) in Patients with Chronic Kidney Disease (DAPA-CKD) study was prematurely terminated thanks to the significant results that demonstrated for the first time that DAPA (a member of SGLT2Is) reduced the sustained decline of e GFR by >50%, ESRD, and overall mortality in non-diabetic chronic kidney disease patients by 39%. This favorable effect was not associated with an increase in the incidence of adverse events in comparison to the placebo [5].

Urine albumin excretion (UAE) decreased by 15% in non-diabetic patients assigned to DAPA [6]. The addition of DAPA to the established treatment regimen of a male patient suffering from FSGS succeeded in the reduction of UAE in this patient [7].

EMPA-kidney study confirmed the significant reduction in the progression of kidney disease and cardiovascular mortality in patients with either diabetic kidney disease (DKD) or non-diabetic chronic kidney disease (CKD). Results were consistent regardless of the estimated glomerular filtration rate (eGFR).

Empagliflozin (EMPA) exerted an equally favorable effect in diabetic and non-diabetic patients. EMPA-kidney followed 6609 patients for a median of two years. Again, EMPA did not increase the rate of serious adverse events compared to the placebo [8]. Many of the non-diabetic CKD patients in DAPA-CKD and EMPA-Kidney studies had FSGS and IgA nephropathy. In this review, we will discuss the different mechanisms that underlie the progression of GN to ESRD and illustrate the mechanisms that make SGLT2Is a safer alternative to steroids and other IS in the management of different types of GN.

Pathogenesis of GN Progression

Role of Proteinuria

Proteinuria is a strong independent predictor of CKD progression and ESRD. The glomerular barrier is composed of 3-layers, the endothelium, the glomerular basement lamina, and the podocytes' foot processes. Glomerular proteinuria is consequent to either increased intraglomerular hydrostatic pressure or glomerular barrier damage. Albumin filtered through the glomerulus is reabsorbed by the PCT through receptor-mediated endocytosis. This is followed by transport into lysosomes for degradation. Megalin and cubilin are the multi-ligand receptors responsible for tubular albumin uptake. Megalin delivers albumin to the lysosomes within PCT cells (Fig 1,2).

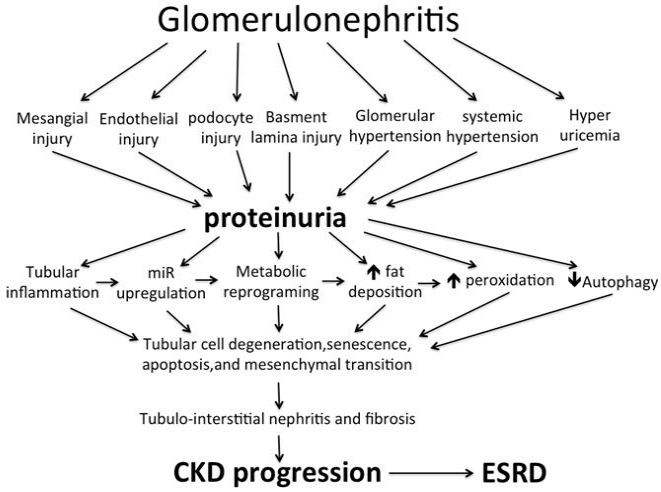

Figure 1: mechanism of chronic kidney progression in patients suffering chronic glomerulonephritis.

miR= micro RNA;
CKD= chronic kidney disease;
ESRD= end stage renal disease.

SGLT2Is combat different renal cells injury, glomerular hypertension, systemic hypertension, hyperuricemia, tubular cell inflammation, miR upregulation, metabolic reprogramming, fatty infiltration, free oxygen radical injury, and induce autophagy.

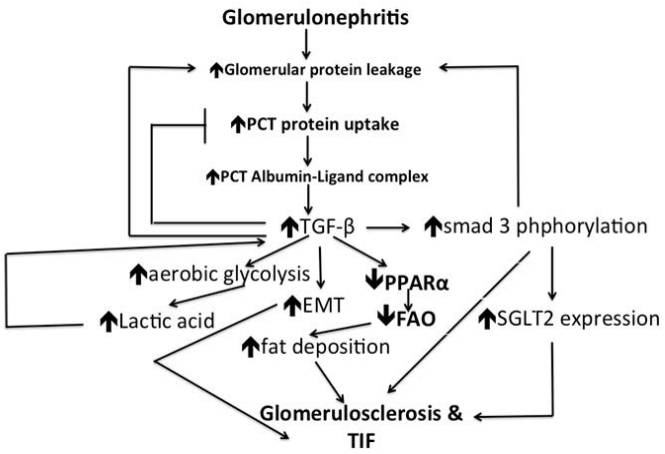

Figure 2: Interplay between increased glomerular protein leakage, TGF-β, metabolic reprogramming and consequent glomerular or tubulointerstitial fibrosis.

PCT= proximal convoluted tubule;
TGF= transforming growth factor;
PPAR= peroxisome proliferator-activated receptors;
EMT= epithelial mesenchyme transition;
FAO= fatty acid oxidation;
SGLT2= sodium glucose co-transporter2;
TIF= tubulointerstitial fibrosis.

Low molecular weight (LMW) proteins are freely filtered at the glomerulus of normal kidneys. The filtered LMW proteins are almost completely actively reabsorbed by the PCT [9]. The normal kidneys leak about 9.6 g of LMW proteins and 3g of albumin. These proteins are completely reabsorbed by PCT [10]. Megalin dissociates from albumin after delivery to the lysosomes. This dissociation enables megalin to deliver more albumin from the tubular lumen. Hydrogen produced by ATPase in the lysosomes activates this dissociation. H+ATPase is inhibited by angiotensin II (ATII). Renal Angiotensin II increases in response to hyperglycemia or free oxygen radicles within the cytoplasm and is Inhibited by renin-angiotensin system (RAS) blockers with a consequent increase of megalin availability to enhance tubular albumin absorption [11]. In the case of renal disease, protein leakage exceeds the tubular capability to reabsorb. Proteinuria indicates either an increased albumin leakage through the glomerular filtration barrier or tubular dysfunction. Albumin prevails in case of glomerular damage while LMW protein is the major constituent in case of tubular dysfunction [11]. Glomerular proteinuria occurs in active glomerular disease, glomerular hyperfiltration, or in case of glomerular scarring [12]. Glomerular disease occurs as a sequence of inflammatory cell infiltration, the proliferation of glomerular cells, or podocytopathy secondary to nephrin or podocin defects.

Albumin-ligand complex induces the expression of inflammatory and fibrogenic mediators within the PCT cells. Transforming growth factor- β (TGF-β) is the most important of these mediators. TGF-β thus induced by albumin exposure stimulates expression of SGLT2 through smad3 phosphorylation [13]. TGF-β may also act in a feedback mechanism by increasing glomerular albumin leakage and inhibiting megalin- and cubilin-mediated

albumin endocytosis. These actions will lead to increased urine albumin excretion (UAE) [14-16]. In addition, increased induction of chemokines and activation of cytokines and complement within PCT cells will lead to interstitial nephritis and fibrosis and consequent loss of kidney function [16]. Through stimulation of the SMAD pathway, TGF-β is responsible for glomerulosclerosis and renal interstitial fibrosis. SMAD3 plays an important role in the pathogenesis of glomerulosclerosis and renal interstitial fibrosis in patients suffering from GN. In addition, proteinuria is highly SMAD3-dependent [17].

The selectivity of proteinuria has a significant impact on CKD progression. Non-selective proteinuria is more injurious. This might be related to the more potentially toxic proteins in the non-selective protein ultrafiltrate like complement proteins, immunoglobulins, and growth factors [12,16]. However, the by-products of albumin breakdown within PCT cells can induce the dendritic cells to induce inflammation [18]. Higher proteinuria carries a higher likelihood of CKD progression [19-21].

Role of the PCT

Recent studies have focused on the PCT instead of the glomerulus and renal interstitium as the primary leader of CKD progression in most renal diseases including chronic GN. Although the kidneys get 25% of the cardiac output, the increased oxygen consumption by the PCT endangers the epithelium of these tubules to the risk of hypoxia. PCT epithelium has 2 evident criteria that render PCT cells vulnerable to injury. These cells are dependent on oxidative phosphorylation as the main source of energy produced by the packed mitochondria within these cells. These two criteria make PCT cells liable to degeneration and death if exposed to ischemia, hypoxia, oxidative stress, metabolic changes, and/or urinary obstruction [22,23]. Excess protein leakage through injured glomeruli with consequently increased protein absorption by PCT leads to tubular degeneration. Excess tubular protein absorption is associated with increased activity of heme oxygenase and monocyte chemoattractant protein (MCP1) [24]. Injured epithelial cells fail to produce enough vascular endothelial growth factor (VEGF). Deficiency of VEGF causes rarefaction of peritubular capillaries that lead to ischemia of PCT with consequent perturbation of tubular damage [22].

Initially, the response of PCT epithelium to GN includes disturbed metabolism, suppression of autophagy, de-differentiation, and cell cycle changes. This response starts as an adaptive reaction, but with the persistence of inflammation, this response can become maladaptive and promote tubulointerstitial fibrosis (TIF). TIF is the hallmark of CKD and the best predictor of ESRD [23]. Growth factors produced by damaged PCT cells include the transforming growth factor beta (TGFβ), Wnt proteins, and platelet-derived growth factor β (PDGF-β). These growth factors stimulate myofibroblast formation, proliferation, and extracellular matrix (ECM) production [22].

Role of Metabolic Reprogramming

The kidney comes after the heart at the rate of oxygen consumption. Adenosine triphosphate (ATP) consumption by the renal tubules is tremendous. The different active pumps involved in the reabsorption of most of the filtered water and valuable solutes and the elimination of different waste products consume this huge amount of ATP [19]. Fatty acid oxidation (FAO) and gluconeogenesis represent the main source of energy in PCT while the distal convoluted tubules (DCT) rely mainly on anaerobic glycolysis due to the low oxygen supply to these tubules [25].

The maintenance of healthy structure and function of the kidney is dependent on adequate energy metabolism. Metabolic reprogramming was first discovered in cancer cells that try to adapt to the changes in environmental conditions and to face the energy consumption and proliferation requirements and was globally described as the Warburg effect. Renal cells have recently demonstrated their capability of metabolic reprogramming which proved to play a pivotal role in the progression after kidney injury. Metabolic reprogramming involves disturbed glucose and lipid metabolism that manifests in patients progressing to ESRD [19].

In response to inflammation, PCT cells shift from oxidative phosphorylation to aerobic glycolysis of glucose (glycolysis in presence of adequate oxygen in contrast to anaerobic glycolysis). The switch to aerobic glycolysis reduces acetyl-CoA production, and thus increases the expression of fibrotic genes within the tubular epithelium, podocytes, and fibroblasts [26]. Decreased oxidative phosphorylation results in a decline in FAO with consequent accumulation of unused fatty acids and their storage as triglycerides. Excess cell fat induces epithelial degeneration [27-29].

The damage induced in renal tubular epithelial cells by metabolic reprogramming allows the recruitment of inflammatory cells to the renal interstitium. Consequently, these inflammatory cells produce numerous pro-inflammatory and pro-fibrotic cytokines. Macrophages and T lymphocytes constitute the majority of recruited inflammatory cells. The M1 macrophage subtype prevails in the case of activated aerobic glycolysis instead of the M2 subtype that prevails during normal oxidative phosphorylation [30]. T-cell infiltration occurs during kidney injury and may directly increase the inflammatory response, and the pro-fibrotic phenotype of macrophages [31]. Metabolic reprogramming is closely related to the activation of T cells [32]. Metabolic changes promote epithelium mesenchymal transition [33]. In this process, epithelial cells that transform into fibroblasts produce an extracellular matrix to heal tissues injured by inflammation and stabilize the injured tubules [34]. Acute inflammation can recover, while persistent or severe inflammation leads to fibrosis. Fibrosis is irreversible and gradually leads to complete damage to the kidneys [35].

In addition to the injured parenchyma, the infiltrating inflammatory cells represent another source of the cytokines that influence metabolic reprogramming leading to renal fibrosis. TGF-β is the most eminent of these cytokines and was found to downregulate peroxisome proliferator-activated receptors (PPARs) that have a role in FAO [36], and causes the shift of glucose metabolism from oxidative phosphorylation to aerobic glycolysis despite of adequate oxygen supply. Aerobic glycolysis is a faster source of adenosine triphosphate (ATP) [37] and redirects carbon to the

production of pentoses, nucleic acids, and non-essential amino acids such as glycine. 35% of the structure of Collagen is composed of glycine [26,38, 39]. Lactic acid produced by glycolysis increases cytoplasm acidity that stimulates TGFβ activity and thus a vicious cycle ensues [40].

The metabolic changes that occur as a consequence of inflammation are responsible for the observed abnormal cell proliferation, the extracellular matrix accumulation, the suppression of autophagy, and the increased apoptosis that are observed in CKD [41-43]. The vicious cycle ensued by TGF-B activation would render the initial activation of fibroblasts to continue autonomously independent of inflammation [33]. The positive feedback loop between hypoxia-inducible factor-1α (HIF-1α) and TGF-β represents a novel mechanism that promotes glomerulosclerosis and TIF [44,45].

The role of metabolic reprogramming was supported by the trial done by Zhao et al. Stimulation of FAO in this trial succeeded to suppress extracellular matrix (ECM) accumulation and fibrosis in human skin [46].

Role of Sirtuin 1 (SIRT1)

SIRT1 is a member of sirtuins, the class III family of nicotinamide adenine dinucleotide-(NAD) dependent histone deacetylases. It can inhibit intracellular inflammation and oxidative stress [47]. Sirt1 activation prevents mesangial proliferation in rats [48]. Within PCT cells, high basolateral glucose suppresses Sirt1 while SGLT2Is induce SIRT1 upregulation [49].

SGLT2Is can augment SIRT1 and bind to the mammalian target of rapamycin (mTOR) in isolated cells and tissues even if these cells lack SGLT2. This phenomenon would explain the augmenting action of SGLT2Is on autophagy in different cells even if these cells were not subject to changes in environmental glucose [50]. Autophagy removes dysfunctional organelles from the cytoplasm. Accumulation of such dysfunctional organelles would affect ion channels and trigger cell inflammation. By stimulating autophagy, SGLT2Is would decrease the accelerated damage of podocytes, mesangial cells, endothelial cells, and renal tubular cells within the kidney [51].

Role of Hypoxia-Inducible Factor-1α

Although HIF-1 is usually regulated by cellular oxygen tension, other elements of the inflammatory microenvironment were shown to influence its activity under normal oxygen conditions. TGF-β increases HIF-1α protein stability and thus stimulates HIF-1α accumulation and activity [52]. In cases of LN, intraglomerular HIF-1α correlates with the renal activity index and the clinical manifestations of the disease [53]. HIF-1α eminently accumulates within the glomerulus, PCT, and interstitium of LN patients. Similar findings were observed in kidneys surgically removed from IgAN patients [54].

MicroRNAs and Glomerulonephritis

As small non-coding ribonucleic acid molecules, MicroRNAs (MiRs) have a recognized role in post-transcriptional gene regulation. In pre-clinical and clinical studies, MiRs have demonstrated a role in the pathogenesis of GN and tubulointerstitial fibrosis [55]. They interfere with the protein synthesis run by the transcription of messenger RNA molecules or degrade the different RNA subtypes involved in protein synthesis. Therefore, miRs modulate the expression of the different proteins implicated in cell differentiation, proliferation, and apoptosis. So far, thousands of miR molecules were discovered in human beings. Different miRs are found in different human organs settled in different cells and in different diseases. Concerning GN, cases suffering from FSGS have shown increased expression of miR-193a, cases having ANCA-associated GN have shown increased expression of miR-155, while cases suffering from IgAN and LN have increased expression of miR-148b, and miR-148a-3p respectively [56].

Other studies disclosed elevated urinary miR-155 in IgAN [57]. miR-155 is accused in renal fibrosis even in cases of ureteric obstruction [58]. MiR-21 upregulation aggravates metabolic reprogramming within the PCT through the silencing of PPAR-mediated FAO and the silencing of the genes responsible for reactive oxygen species inhibition[59].

Impact of SGLT2Is in GN (Clinical Trials)

While the administration of RAS blockers and IS treatment fail most of the time to prevent the progression of GN to ESRD, the DAPA-CKD study has demonstrated promising results. DAPA-CKD study included 104 patients that have biopsy-proven FSGS having eGFR 25–75 mL/min/1.73m2, UAE 200–5000 mg/g, and were prescribed a stable dose of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for at least 4 weeks before enrolment into the trial. These cases were randomized to either DAPA 10 mg or placebo. The primary outcome occurred less frequently and the rate of eGFR decline was lower in the DAPA group [60]. The DAPA-CKD study included 271 IgAN patients, a number that was never achieved in all known IgA trials. IgAN patients showed an unprecedented 71% reduction in the primary outcome [61]. These results indicate that SGLT2Is may be more beneficial than immunosuppression at least in IgAN patients.

DAPA 10mg was studied in 17 Chinese LN cases (16 females and one male, suffering from the disease for 7.3 ± 5 years, and having UAE 0.5-3g/day). DAPA was administered in addition to their standard of care treatment (prednisolone 16.3±7.1 mg/day, 6 were on prednisolone >20 mg/day, 6 were on mycophenolate mofetil, 3 on cyclophosphamide, and 2 on tacrolimus). DAPA continued for 6 months. The safety profile of DAPA was acceptable. Despite being administered on top of other IS treatments, the patients did not experience an increased propensity to infections. The rate of eGFR decline showed appreciable improvement after the DAPA administration [62].

Although patients with AAV and LN were excluded from DAPA-CKD and EMPA-kidney trials, a specific targeted therapy combined with SGLT2Is in these patients deserves a trial in these patients. AAV and LN patients have a significantly increased risk for cardiovascular morbidity and mortality. Renal involvement, systemic inflammation, and long-term use of IS

contribute to this risk. SGLT2Is use in these patients may alleviate systemic inflammation, decrease the need for IS, and hamper the progression of CKD and thus would have a positive effect on patient outcomes in these patients like other forms of GN [63]. On revising the literature, there are no studies, so far, performed in AAV.

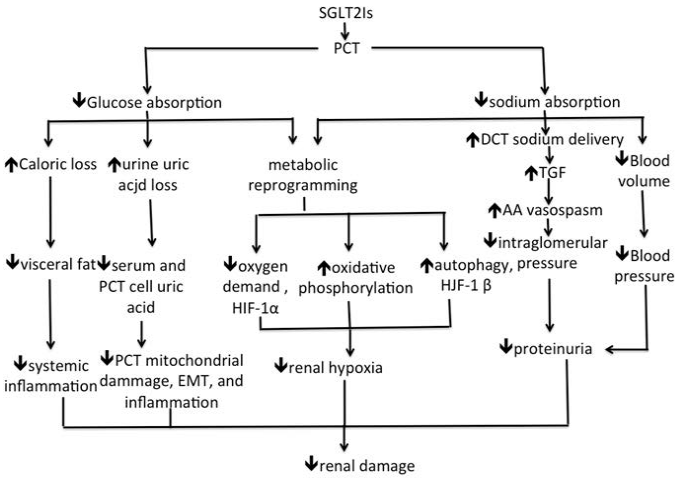

Figure 3: Mechanisms of action of sodium glucose transporters inhibitors (SGLT2Is) in cases of glomerulonephritis.

PCT= proximal convoluted tubules;
EMT= epithelial – mesenchyme transition;
HIF= hypoxia inducible factor;
DCT= distal convoluted tubules;
TGF= tubuloglomerular feedback;
AA= afferent arteriole.

SLC5 is a family of carriers in different tissues that are responsible for the active transport of different sugars, anions, vitamins, and short-chain fatty acids coupled with sodium [64]. Sodium-glucose co-transporters (SGLTs) are members of the SLC5 family. In the PCT SGLT2 are located in S1 and S2 segments and are responsible for the absorption of 90% of glucose delivered to PCT, while SGLT1 are located in the S3 segment and absorb the remaining 10%. SGLT2Is inhibit glucose and sodium in PCT. While the primary renoprotective action of SGLT2Is is mediated through their tubular action, they have many other actions that ameliorate the downstream injury from the original glomerular damages. These potential Reno protective mechanisms include Inducing diuresis and natriuresis through inhibition of SGLTs and the renal sodium-hydrogen exchanger3 (NHE3) isoform. This effect is mainly through NHE3 inhibition. Empa fails to induce natriuresis in normoglycemic NHE3 knock-out mice [65]. Increased sodium delivery to DCT stimulates increased active sodium absorption by DCT. Increased consumption of ATP by DCT leads to increased adenosine production with consequent afferent arteriolar vasospasm, normalization of tubuloglomerular feedback, and a decrease in glomerular hyperfiltration [51]. By decreasing the oxygen consumption in the PCT, SGLT2Is decrease the chance of HIF-1 α expression and thus decrease inflammation and fibrogenesis [66]. HIF-1 α expression is upregulated within FSGS kidneys. This may explain the favorable impact of SGLT2Is In FSGS patients [67]. Increased sodium delivery to DCT stimulates excess active sodium absorption in this segment. The increased demand for ATP leads to hypoxia in DCT that increases induction of HIF-1 β with consequently increased erythropoiesis, decreased inflammation, and fibrogenesis [68]. Reduction of glucose uptake, even in normoglycemic patients augments AMPK/SIRT1 signaling and stimulates autophagy within the PCT, thereby decreasing the accelerated damage of renal tubular cells as well as podocytes [69,70,71]. AMPK Stimulation leads to mammalian target of rapamycin (mTORC1) inhibition. mTORC1 is responsible for podocyte and renal tubular damage, proteinuria, and renal fibrosis [72].

Although the SGLT2s' existence within human podocytes is still uncertain, the amelioration of proteinuria after the use of DAPA is associated with decreased effacement of foot processes [73]. The presence of SGLTs in renal endothelial cells is controversial but accumulating evidence suggests a direct action of SGLT2Is on these cells. SGLT2Is modulate the adhesion molecules and reduce production of inflammatory cytokines in these cells [6, 74].

SGLT2Is decrease Aldose reductase activity within PCT cells with a consequent decrease in intracellular fructose and uric acid (UA) synthesis [7,75]. Intracellular UA stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which increases the production of reactive oxygen species (ROS). Increased intracellular UA and ROS activate Nalp3 which induces the activation of caspase 1 [76]. Calorie depletion induced by SGLT2Is causes and simulates fasting or nutrient deprivation state leads to increased FAO, decreased hexosamine production, and decreased lipid accumulation. These metabolic changes suppress protein kinase C (PKC) and TGF β activation [51].

Suppression of PKC and TGFβ decreases epithelial mesenchyme transition (EMT), endothelial mesenchyme transition (EnMT), interstitial nephritis, and fibrosis. Through inhibition of smad3 phosphorylation, SGLT2Is decrease glomerular protein leakage, and inhibit glomerulosclerosis, and interstitial fibrosis [77]. Further reduction of ROS and improvement of FAO can be achieved by the improvement of miR signature by SGLT2Is [59]. With the loss of some nephrons due to GN, the remaining nephrons compensate by glomerular hyperfiltration. The podocyte shear stress induced by the glomerular hyperfiltration ultimately leads to podocyte detachment, an increase in glomerular protein leakage, and secondary focal segmental glomerulosclerosis that gradually proceeds to diffuse global glomerulosclerosis [78,79]. The metabolic overload imposed over PCT cells promotes the irreversible loss of these cells and ultimately proceeds to tubule atrophy. These events lead to CKD progression and kidney loss [80]. SGLT2Is prevent these events (Fig4).

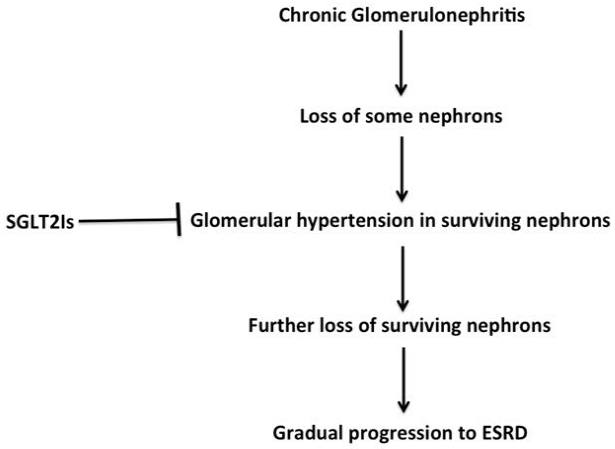

Figure 4: SGLT2Is combat chronic kidney disease progression through control of glomerular hypertension in the surviving nephrons.

Mechanism of Action of SGLT2Is on Renal Cells Lacking SGLT2

SGLT2Is can induce nutrient deprivation signal and autophagy in different renal cells. Nutrient deprivation signal and autophagy lead to the reduction of cell stress, improved metabolism, and survival in these cells although they do not have SGLT2. Urine glucose loss even in normoglycemic patients stimulates a system-wide up-regulation of nutrient deprivation signal in different cells in the body. Administration of SGLT2Is for seven days reduces the glucose renal threshold from 196 to 22 mg/dl [81]. The nutrient deprivation signal does not depend on the presence or absence of cellular SGLT2 [82]. SGLT2Is stimulate ketogenesis. Ketone bodies and nutrient deprivation signal stimulate AMPK and decrease mTOR phosphorylation with a consequent increase in the expression of PPAR-1α, increase in FAO, and promotion of autophagy [83].

In addition, SGLT2 was detected in podocytes of mice and was found to be upregulated after injection of these mice by bovine serum albumin [73]. SGLT2Is may also act directly on renal endothelial cells through modification of the effect of adhesion molecules and reduction of intracellular inflammatory cytokines and free oxygen radicals [74].

Adverse effects of SGLT2Is

In the DAPA-CKD trial, there was no discrepancy in the rate of serious adverse events in patients treated with DAPA versus the placebo group and DAPA was well tolerated. Severe hypoglycemia was not reported in non-diabetic CKD patients [5]. EMPA-kidney study disclosed nearly similar incidence of side effects in patients treated with EMPA in comparison to the placebo group [8]. For the fear of increased incidence of infections, the CKD patients treated with steroids and/or other IS drugs were excluded from these 2 studies. However, many small observational studies failed to observe an increased incidence of adverse events, including infections, in patients treated with the combination of SGLT2Is and IS drugs [84-86].

Perspectives

Despite of the tremendous efforts paid to the pharmacological interventions of GN, acute and chronic glomerular diseases still lead to substantial morbidity and mortality. Most of the time, glomerular pathology underlies the progression of CKD. This phenomenon can explain the prevailing focus on the glomerulus in CKD research as the target in the management of CKD progression. However, the tubular damage became more appreciated as the predictor of kidney function decline. The amazing favorable effect of SGLT2Is in controlling CKD in DKD and non-diabetic CKD has fortified this impression. These agents offered a significant impact on both renal and patient survival. These results should make the use of SGLT2Is a mandate in these cases. In addition, this shift would increase the awareness of the renal tubules and interstitium as therapeutic targets in the management of GN. Therefore, it seems that a tandem glomerular and tubular therapeutic approach would be better for cases suffering from chronic GN.

The frequently used steroids and other IS agents in the management of chronic GN carry the potential risks of jeopardizing the quality of life of these patients and may accelerate mortality. The updated guidelines for the management of GN offered by the kidney disease improved global outcome (KDIGO) in 2021 suggested the use of ACEi/ARBs as the first-line treatment in patients with GN, hypertension, and proteinuria. The ACEi/ARBs should be up-titrated according to the blood pressure response till the maximum dose tolerated is achieved [1].

These guidelines were issued before the disclosure of DAPA-CKD and EMPA-kidney results. It seems that SGLT2Is should be added to ACEI/ARBs to gain the optimal therapeutic benefit in the management of chronic GN patients. The introduction of SGLT2Is should be added on top of the maximum tolerable dose of ACEI/ARBs to all cases suffering GN.

Expectedly, this approach will significantly negate or at least reduce the need for steroids and other IS agents. This approach is also more economic since SGLT2Is are much cheaper and safer than most IS treatments. Severe cases that may still need IS treatment can be safely prescribed these agents on top of ACEi/ARBs and SGLT2Is. The doses of IS drugs in this situation would be, expectedly, much less than that in the time being. We still need further studies that look after the impact of the addition of fenofibrate to SGLT2Is and the maximum tolerable dose of ACEi/ARB on the outcome of GN in different ages.

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Conflict of Interest

The authors have nothing to declare.

Authors contribution

The authors shared equally in the creation of this manuscript.

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