The nephrological perspective on SGLT-2 inhibitors in type 1 diabetes

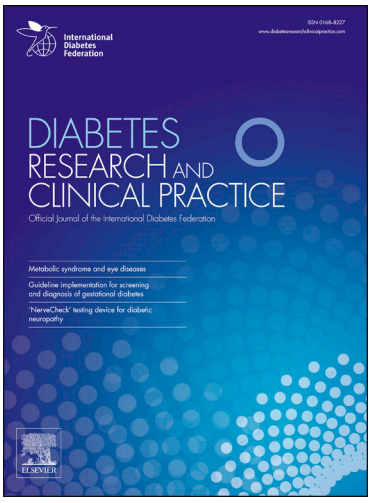
Gillard, Pieter

2020-12

Gillard , P , Schnell , O & Groop , P-H 2020 , ' The nephrological perspective on SGLT-2 inhibitors in type 1 diabetes ' , Diabetes Research and Clinical Practice , vol. 170 , 108462 . https://doi.org/10.1016/j.

http://hdl.handle.net/10138/341323
https://doi.org/10.1016/j.diabres.2020.108462

Journal Pre-proofs



Review

Working Title: The Nephrological Perspective on SGLT-2 Inhibitors in Type 1 Diabetes

Pieter Gillard, Oliver Schnell, Per-Henrik Groop

PII: S0168-8227(20)30715-4
DOI: https://doi.org/10.1016/j.diabres.2020.108462
Reference: DIAB 108462

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 20 July 2020
Revised Date: 10 September 2020
Accepted Date: 16 September 2020

Please cite this article as: P. Gillard, O. Schnell, P-H. Groop, Working Title: The Nephrological Perspective on SGLT-2 Inhibitors in Type 1 Diabetes, *Diabetes Research and Clinical Practice* (2020), doi: https://doi.org/10.1016/j.diabres.2020.108462

Working Title: The Nephrological Perspective on SGLT-2 Inhibitors in Type 1 Diabetes

Pieter Gillard [1] (MD), Oliver Schnell [2,3] (MD); Per-Henrik Groop[4,5,6,7] (MD)

Affiliations

[1] Department of Endocrinology, University Hospitals Leuven, KU Leuven, Belgium

[2] Sciarc GmbH, Baierbrunn, Germany

[3] Forschergruppe Diabetes e.V., München - Neuherberg, Germany

[4] Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland

[5] Abdominal Centre, Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[6] Research Program for Clinical and Molecular Metabolism, University of Helsinki, Helsinki, Finland

[7] Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia

Corresponding author: Oliver Schnell (Email: Oliver.Schnell@lrz.uni-muenchen.de)

Abstract

Prevalence of type 1 diabetes mellitus (T1DM) is globally continuously increasing. T1DM is accompanied by a high risk of developing cardiovascular and renal comorbidities and is one of the leading causes of end-stage renal disease (ESRD).

However, current therapeutic approaches for chronic and/or diabetic kidney disease (CKD/DKD) existed for a long time, and offer room for improvement, particularly in T1DM. In 2019, the European Medicines Agency (EMA) approved a first sodium/glucose co-transporter 2 inhibitor (SGLT-2i) and a first dual SGLT-1/-2i to improve glycaemic control, as an adjunctive treatment to insulin in persons with T1DM and a body mass index $\geq$27 kg/m^2. Of note, SGLT-1/2is and SGLT-2is are not approved by the Food and Drug Administration (FDA) as an adjunct treatment in T1DM, nor approved for the treatment of CKD or DKD by EMA and FDA.

SGLTis have shown to mediate different renoprotective effects in type 2 diabetes mellitus in corresponding cardiovascular and renal outcome trials. First efficacy trials offer insights into potential positive effects on renal function and kidney disease of SGLTis in T1DM. This review summarizes and discusses latest available data on SGLT inhibition and provides an update on the nephrological perspective on SGLTis, specifically in T1DM.

Keywords:

Diabetes; Type 1 Diabetes Mellitus; SGLT Inhibition; SGLT-2 inhibitor; Kidney disease; Diabetic kidney disease; Renal effects

Abbreviations:

ACE-2, angiotensin-converting-enzyme-2; ACEi, angiotensin-converting-enzyme inhibitor; AGEs, advanced glycosylation end-products; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; Cana100/300, canagliflozin 100mg / 300mg; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; Dapa5/10, dapagliflozin 5mg / 10mg; DBP, diastolic blood pressure; DEPICT, Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DM, diabetes mellitus; DPV, German Diabetes Prospective Follow-up Registry; EASE, Empagliflozin as Adjunctive to inSulin thErapy, EASE-program; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; Empa10/25, empagliflozin 10mg / 25mg; ESRD, end-stage renal disease; FDA, U.S. Food and Drug Administration; FGF-21, fibroblast growth factor 21; GBM, glomerular basement membrane; HbA1c, glycated haemoglobin A1c; HR, hazard ratio; IR, insulin resistance; IU, international unit; LSM, least square matching; NaCl, sodium chloride; NALFD, non-alcoholic fatty liver disease; ND-CKD, non-diabetic chronic kidney disease; Nrf2, nuclear factor erythroid 2-related factor 2; RAGE, receptor for advanced glycosylation end-products; RAS, renin-angiotensin-system; RCT, randomized controlled trial; ROS, reactive oxygen species; SBP, systolic blood pressure; SE, standard error; SGLT-1/-2is, dual sodium/glucose co-transporter 1 and -2 inhibitors; SGLT-2, sodium/glucose co-transporter 2; SGLT-2is, sodium/glucose co-transporter 2 inhibitors; SGLTs, sodium/glucose co-transporters; Sota400, sotagliflozin 400mg; STAT1, signal transducer and activator of transcription 1; T1DM, type 1 diabetes mellitus; T1DX, U.S. Type 1 Diabetes Exchange Registry; T2DM, type 2 diabetes mellitus; TF, tubuloglomerular feedback; TGF-beta, transforming growth factor beta 1; TIR, time in range; UACR, urinary albumin-to-creatinine ratio; WHO, world health organization

Dualities of Interest

PG serves or has served on the advisory panel for Novo Nordisk, Sanofi, Boehringer-Ingelheim, Janssen Pharmaceuticals, Roche, Medtronic and Bayer. Financial compensation for these activities has been received by KU Leuven; PG serves or has served on the speakers' bureau for Merck Sharp and Dohme,

Boehringer-Ingelheim, Bayer, Medtronic, Abbott and Roche. Financial compensation for these activities has been received by KU Leuven. KU Leuven received for PG non-financial support for travel from Sanofi, A. Menarini Diagnostics, Medtronic and Roche.

OS is founder and General Manager of SCIARC GmbH.

P-H G has received lecture honoraria from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, Merck Sharp & Dohme (MSD), Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi, SCIARC and is an advisory board member of AbbVie, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, Merck Sharp & Dohme (MSD), Novartis, Novo Nordisk, and Sanofi.

Funding Information

AstraZeneca has provided a sponsorship grant towards this independent programme. The sponsor had no influence on the creation of this manuscript.

Acknowledgments

We thank Dr. Constantin Stautner and Dr. Katharina Fritzen, Sciarc GmbH, for their excellent editorial and writing support of the manuscript.

1. Background

The number of persons burdened with type 1 diabetes mellitus (T1DM) increases every year. A current global approximation estimates around 1.1 million existing cases of T1DM in children and adolescents (0-19 years) with an estimated overall annual increase of around 3%, yet with substantial geographic variance [1]. Worldwide, a large proportion (10% - 67%) of end-stage renal disease (ESRD) is attributable to diabetes mellitus (DM) [1] and epidemiological data suggest that 2% - 12% of persons with T1DM ultimately may develop ESRD, as illustrated later.

Sodium/glucose co-transporter 2 (SGLT-2) inhibitors (SGLT-2is) have demonstrated cardiovascular (CV) and renal benefit in their corresponding cardiovascular outcome trials (CVOTs) in type 2 diabetes (T2DM), an effect mainly beyond their glucose-lowering capabilities in T2DM [2-5]. First efficacy trial programs with SGLT-2is as an adjunct therapy to insulin in T1DM have provided insights on glycaemic efficacy as well as safety and feasibility of use of SGLT-2is in T1DM [6-9], along with one dual SGLT-1/-2 inhibitor [10]. Based on the DEPICT- [7-9] and Tandem-trials [10-12], the European Medicines Agency (EMA) approved the SGLT-2i dapagliflozin [13] and the dual SGLT-1/-2i sotagliflozin [14], respectively, as an adjunct therapy to insulin in T1DM in 2019, "*when insulin alone does not provide adequate control of their blood glucose levels despite optimal insulin therapy*" [13,14]. In addition, "*patients should not have a body mass index (BMI) below 27 kg/m²*" [13,14]. In this review, we aim to highlight the nephrological perspective of SGLT-inhibition from a T1DM point of view, addressing the question if SGLT-inhibition also conveys renal benefits in T1DM.

1.1 T1DM and DKD – Epidemiology and Risk Factors

Lifetime risk for DKD in T1DM has been estimated very high (≥50% - 70%) in some early studies with cohorts of participants with older age [15,16], while other, more recent and conservative studies estimate an overall prevalence of diabetic kidney disease (DKD) of around 25% - 30% [17]. In any case, DKD is a major cause of premature mortality in T1DM [18, 19]. Generally speaking microalbuminuria is the earliest clinical manifestation of DKD in many but not in all cases, and has a cumulative lifetime incidence of around 50% - 60% in T1DM [20,21]. An estimated 25% of persons with microalbuminuria and T1DM may ultimately progress to ESRD [20]. However, some publications express a note of caution, stating that the high prevalence of DKD in T1DM may be attributable not only to DKD but also to non-diabetic chronic kidney disease (ND-CKD) or a combination of DKD and ND-CKD – reliably distinguishable only by kidney biopsy. However, kidney biopsies are too rarely performed in individuals with DM [22]. In a recent study from Norway which followed 7871 individuals with T1DM for up to 42 years, a rather low incidence of ESRD was observed: in fact, the incidence of ESRD was 0.7% after 20 years of diabetes duration, 2.9% after 30 years, and 5.3% after 40 years [23]. Overall, only 103 individuals (1.3%) developed ESRD, with a

mean time from diabetes diagnosis to development of ESRD of 25.9 years [23]. A limitation of this observational study, however, was that the definition of ESRD was only based on the initiation of dialysis or transplantation due to chronic renal failure, as data on estimated glomerular filtration rate (eGFR) were not available. In comparison, data from the U.S. estimated an incidence of ESRD of 9.3% - 11.3% 25 years after the T1DM diagnosis [24,25], data from Finland demonstrated an incidence of around 7.0% - 7.8% 30 years after the T1DM diagnosis [26,27] and data from Sweden showed a cumulative incidence of around 5.6% after up to 38 years of T1DM duration [28].

Risk factors for DKD are multifarious and include (1) susceptibility factors like age, race/ethnicity, sex and genetic risk factors, (2) initiation factors like hyperglycaemia, and (3) progression factors like hypertension or obesity [29]. A recent follow-up study [16] of the DCCT/EDIC trial demonstrated that, at 30 years of follow-up, a decline in eGFR and the presence of macroalbuminuria were the most important risk factors for the development of ESRD [16]. In the DCCT/EDIC trial, 15% of the participants developed a combination of macroalbuminuria and eGFR decline and 25% developed either macroalbuminuria or eGFR decline, 30 years after the T1DM diagnosis [16]. A recent nationwide multi-centre study from Finland reported that around 2% of T1DM cases showed non-albuminuric DKD at baseline, yet, associated with a heightened risk of cardiovascular disease (CVD) and all-cause mortality but not ERSD [30]. Of note, the majority of these individuals were female and elderly. Other single-centre and hospital-based studies reported that up to 10% of individuals with T1DM manifest with continuously declining GFR in the absence of macroalbuminuria [21,31]. In the DCCT/EDIC follow-up study, macroalbuminuria and the decline in eGFR were often not concordant, only 52% of the participants with decline in eGFR also developed macroalbuminuria [16]. Thus, a decline in eGFR and macroalbuminuria may not always be considered sequential steps in the pathogenesis of DKD, but also as independently degenerating conditions with different origin [31-34]. When stratifying baseline characteristics of the DCCT/EDIC participants to presence or absence of incident macroalbuminuria, the major risk factors were being in the conventional therapy group (HR 2.211; 95% CI 1.636-2.989; p<0.0001) and elevated HbA1c (HbA1c of 8.5% vs 9.7%; HR 1.429; 95% CU 1.324-1.541; p<0.0001) accordingly, hypertension (HR 2.098; 95% CI 1.074-4.097; p=0.03), male sex (HR 2.014; 95% CI 1.488-2.726; p<0.0001), elevated triglycerides (71 mg/dL vs. 86 mg/dL; HR 1.171 per 20% increase; 95% CI 1.113-1.233; p<0.0001), and age at baseline (adult vs. adolescent, HR 0.515; 95% CI 0.367-0.724; p=0.0001) [16]. Along this line, it was also observed in various other studies that the risk of ESRD is lower in persons who become diagnosed with T1DM before the age of 10 years [23,26,35]. Un- or minimally-adjusted time-dependent models of the DCCT/EDIC cohort demonstrated that, when adjusted for age, updated mean HbA1c, sex, lipids, and blood pressure (BP), daily insulin dose and any progression in retinopathy correlated strongly with the risk of incident macroalbuminuria, while BP, lipids, use of antihypertensive or lipid-lowering medication, the duration of T1DM, albumin excretion rate, retinopathy and glycaemia were associated

with elevated risk of incident decline in eGFR [16]. The authors conclude that higher long-term cumulative glycaemic exposure was the strongest independent risk factor for incident macroalbuminuria and reduced eGFR, followed by higher triglyceride levels and higher BP [16].

1.2 Pathology of DKD in T1DM and the Role of SGLTs

The pathology of DKD is better characterized in T1DM, compared to T2DM. Generally speaking, critical features of DKD are enduringly elevated albuminuria of >300 mg/24h (macroalbuminuria) or an urinary albumin-to-creatinine ratio (UACR) of >300 mg/g, and/or a progressive loss of eGFR (eGFR <60 ml/min/1.73m^2, corresponding to moderate to severe CKD stage 3 and below), with concomitant diabetic retinopathy and/or lack of other forms of kidney disease [16,36]. The pathology of DKD in DM is reviewed and compared to ND-CKD in detail elsewhere [22]. Key elements of DKD pathology are early changes such as hyperfiltration, an exaggerated reabsorption of glucose and sodium chloride (NaCl) in the proximal tubule, and hypertrophy of the glomerular tuft and capsule, as well as an elongation of the proximal tubule [22]. In the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications study, early hyperfiltration in persons with T1DM was, however, not associated with a higher long-term risk of decreased GFR [37]. The mentioned variations of kidney physiology are subsequently accompanied by later and enduring changes such as thickening of the glomerular basement membrane (GBM), haemodynamic changes, reduction of the tubulo-glomerular feedback (TF) and an over-activation of the renin-angiotensin-system (RAS), accompanied by renal ischaemia, abnormal cell signalling, local inflammatory signalling and processes, podocyte injury and subsequent loss, nephron loss and CKD progression, ultimately resulting in renal failure [22].
When focussing on the role of hyperglycaemia and sodium/glucose co-transporters (SGLTs) in the initiation and progression of kidney disease, several features need consideration. SGLT-2 is mainly expressed in the S1/S2 segment of the proximal tubule, while SGLT-1 is predominantly expressed in the small intestine and the late S2/S3 segment of the proximal tubule, as well as in some other tissues [38]. In the kidney, SGLT-2 is responsible for the majority (ca. 97%) of glucose reabsorption [39], however, SGLT-1 may exhibit substantial compensatory activity of up to 50% if SGLT-2 is blocked [38]. In individuals with diabetes, the maximal reabsorptive capacity of glucose in the kidneys was shown to be increased by up to 20%, largely driven by SGLT-2 mediated glucose-reabsorption [39], thus also increasing NaCl-reabsorption correspondingly. This reduces the downstream available NaCl to the macula densa, thereby dysregulating the tubulo-glomerular feedback, resulting in afferent vasodilation and increased glomerular pressure and finally glomerular hyperperfusion and hyperfiltration [40,41]. In addition, it has been confirmed that the metabolism of a diabetic kidney requires more oxygen compared to a healthy system as a secondary active transport process driving apical glucose uptake via SGLT-2s depends on basolateral Na^+/K^+-ATPase activity, thus resulting in intrarenal hypoxia [42,43]. Once established,

hyperfiltration further increases energy and thus oxygen demand by enhancing renal Na^+/K^+-ATPase activity [42].

1.3 Unmet medical need in T1DM from a nephrological perspective

Globally, DKD is a major cause of ESRD in individuals with T1DM [44] and in some countries even the leading footing for ESRD [45]. The unmet need in DKD in T1DM is manifold:

First, the natural history of DKD is characterized by a long period without apparent clinical symptoms [20]. As significant compensation occurs, when an eGFR of <60 ml/min/1.73m^2 is reached, already up to 50% of renal function may be lost and modifications of renal structures well established [20]. It has been demonstrated that already moderate CKD (stage 3 onwards, corresponding to eGFR <60 ml/min/1.73m^2) increases the risk of cardiovascular disease and premature mortality [46].

Second, DKD and subsequent development of ESRD contributes to higher mortality rates in T1DM. Furthermore, it was demonstrated by the Finnish Diabetic Nephropathy (FinnDiane) Study that the presence and severity of chronic kidney disease predicts all-cause mortality in T1DM [19]. The study clearly showed, that subjects with micro- or macroalbuminuria or hyper- or hypofiltration (>120 or <60 ml/min/1.73m^2) have decreased survival rates [19].

Third, while it has been thought for quite some time that the development of microalbuminuria is an early and implicit sign of DKD, it has been shown that it does indeed not seem to be a ubiquitously reliable marker for DKD. For example, in a study with 386 persons with T1DM and persistent microalbuminuria at baseline, in a 6 year follow-up period, only 19% progressed to overt proteinuria, while 59% regressed to normoalbuminuria [21]. Accordingly, it has been suggested that many individuals can follow a non-albuminuric pathway to renal dysfunction [47], as also discussed above. A recent study elucidated that, for both types of diabetes, persons who enter CKD stage 3 and are normo- and microalbuminuric at baseline have similar risk for kidney disease progression, while persons with macroalbuminuria have a comparably increased risk [46]. Thus, reliable *early* markers for the detection of DKD are needed.

Fourth, despite a variety of investigated promising treatment options, none have really met desired and needed expectations yet. The current standard is the inhibition of the RAA-system using angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) [20]. However, RAAS inhibition is unable to prevent the development of DKD in T1DM [46], as also demonstrated by larger trials such as the RASS- [48] and the AdDIT-trials [49]. In addition, combined use of ACEis and ARBs or direct renin-inhibition have failed to meet expectations, as observed in multiple trials in T2DM such as ONTARGET [50] or ALTITUDE [51]. In the ALTITUDE trial, the addition of a direct renin inhibitor (aliskiren) to the standard therapy with RAA-system inhibition increased significantly the risk for hyperkalemia and hypotension [51]. However, all of these trials with large cohorts have been conducted in T2DM and,

currently, no large randomized clinical trials are available in T1DM. Also, in the context of DKD in T2DM, other formally promising strategies like selective endothelin receptor-A antagonists (e.g. the SONAR trial [52]) or modulators of the Nuclear factor erythroid 2-related factor 2 (Nrf2) [53] did not yield promising results. In the SONAR trial, fluid retention and anaemia adverse events occurred more frequently in the group treated with the endothelin receptor-A antagonist than in the placebo group [52]. The administration of activators of the Nrf2 led to a higher rate of cardiovascular events in persons with T2DM and stage 4 chronic kidney disease in comparison to the placebo group [53]. Some glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RAs) have demonstrated moderate effects on renal function, reflected mainly in a reduction of (macro-)albuminuria, in their respective CVOTs [54]. However, so far, no data from dedicated renal trials for GLP-1 RAs in T1DM or T2DM are available. Another promising treatment approach for DKD are mineralocorticoid receptor antagonists, with first trials in DKD currently being conducted in T2DM[55-57]. In regard to CKD both selective (eplerenone) and non-selective (spironolactone) aldosterone antagonists reduced proteinuria and blood pressure in adults, who had mild to moderate CKD and were treated with ACEis or ARBs (or both), but increased hyperkalaemia and gynaecomastia [58]. In another study, the addition of eplerenone to an ACEi in persons with T2DM resulted in a significant reduction in albuminuria as measured by UACR. The extent of hyperkalaemia was found to be eplerenone dose-dependent [59]. Also, Vitamin D has been shown to have an effect on diabetic nephropathy [60]. The intramuscular application of Vitamin D (50000 IU, monthly for 6 months) reduced urine albumin, serum creatinine, and renin levels in individuals with DKD [61]. In another study, the administration of Vitamin D receptor activator calcitriol combined with RAAS inhibitors had an additional beneficial effect in lowering albuminuria in T2DM and DKD [62].

Fifth, metabolic syndrome and often associated overweight, inflammation, reduced insulin sensitivity and non-alcoholic fatty liver disease (NALFD) is also increasingly documented in persons with T1DM and has been linked to the initiation and progression of micro- and macrovascular comorbidities [20,63]. One study demonstrated a positive correlation between decreased insulin sensitivity and the development of microalbuminuria and rapid eGFR decline in persons with T1DM [64]. While the reasons for reduced insulin sensitivity in T1DM are not entirely clear [20], it seems in this context noteworthy that the number of persons with T1DM, who are overweight/obese and in addition develop the metabolic syndrome or “double diabetes” seems to increase continuously and is currently under-recognized. It was demonstrated in several studies that persons with T1DM who are obese are insulin resistant and have a higher CV risk profile, compared to non-obese individuals with T1DM, as also true for T2DM or the general population [65]. Effects of obesity in T1DM have been extensively reviewed elsewhere [66]. Several studies and registries estimating the prevalence of obesity in T1DM reached similar conclusions: for example, in a combined analysis of the U.S. T1D Exchange Registry (T1DX) and the German Diabetes Prospective Follow-up (DPV) registry with an overall of 32,936 participants [67], a

total of 24% of participants was found overweight and 12% obese, according to WHO standards [67]. This is mirrored in an international multicentre diabetes registry study participating in the SWEET prospective - 23,026 children with T1DM were analysed and an overall prevalence of overweight/obesity of a little over 30% was determined [65]. In a smaller cross-sectional study including 284 persons with T1DM in a Swedish diabetes clinic, an overall prevalence of 17% for abdominal obesity was revealed, related to an increased risk of dyslipidaemia, a HbA1c >8.6%, CV complications, and a reduced likelihood to reach treatment goals [68]. Similarly, the combined analysis of the T1DX and DPV found a significant increase of HbA1c in obese individuals, as well as a significant increase of persons with severe hypoglycaemic events with increasing BMI [67]. In addition, while there is variability in the definition of the metabolic syndrome in individuals with T1DM, and the concept is more often driven by the presence of hypertension than central obesity in contrast to persons with T2DM and the general population [69], it has been shown that not only obesity but also the occurrence of components of the "metabolic syndrome" increases strongly in individuals with T1DM. Consequently, a recent study reported as much as 25.5% of persons with T1DM to also present with the "metabolic syndrome" (defined as obesity, hypertension, and/or dyslipidaemia) [70, 69]. This has to be a major concern, as it has been demonstrated that outcomes such as diabetic nephropathy, CVD and mortality are augmented in persons with the "metabolic syndrome" and T1DM [71]. Furthermore, increased prevalence of obesity will most likely also impact the prevalence of concomitant NALFD in T1DM. Current estimates of the prevalence of NALFD in T1DM vary considerably and start at around 12% in adults [66]. As expected, the presence of NAFLD in T1DM has been shown to be accompanied by insulin resistance (IR) and high complication rates [66]. Thus, in summary, an increasing prevalence of obesity, NALFD and IR in T1DM, for which the reasons are manifold and often not entirely clear yet, may impose diabetes management in T1DM with significant additional challenges, as it can be assumed that effects will be detrimental, as true for the general population.

2. Available outcomes: risk-factors management and surrogate renal outcomes from SGLT-inhibitor trials in T1DM

Currently, best available data for renal outcomes with SGLT-inhibition in T2DM stem from the CREDENCE [2] trial in T2DM. Individuals with an eGFR ranging from 30 to <90 ml/min/1.73m^2 and an UACR between >300 and 5000 mg/g were included. The risk of the primary composite outcome and its components doubling of serum creatinine level (i.e. 57% reduction in eGFR), incidence of ESRD (by eGFR <15 ml/min/1.73m^2 and initiation of dialysis or kidney transplantation), renal or cardiovascular death was significantly reduced. Furthermore, the composite secondary outcome of ESRD, doubling of serum creatinine, or renal death was significantly reduced [2].

There are no (large) clinical trials reporting renal outcomes of SGLT-2is as an adjunct therapy in T1DM. So far, all SGLT-2i trials in T1DM have been safety and efficacy trials and have only provided some understanding of the effects of SGLT-2is on risk factor management in T1DM. So far, trial programs for empagliflozin (Empagliflozin as Adjunctive to inSulin thErapy, EASE-program [6,72]), dapagliflozin (Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes, DEPICT-program [7,9,73]), and sotagliflozin (inTandem-program [10-12]), as well as a phase II trial for canagliflozin [74] investigated the effects of SGLT-inhibitors as an adjunct treatment in T1DM.

In the EASE-program, empagliflozin 10 mg and 25 mg (Empa10 and Empa25) both significantly improved glycaemic control: mean HbA1c reductions, adjusted to placebo and after 26 weeks was dose-dependent and up to -0.54% ($p<0.0001$). The strongest, placebo-corrected HbA1c reduction after 52 weeks was observed in EASE-2 with a -0.45% reduction with Empa25 [6]. Concomitant, a significant increase of time-in-range (TIR) of up to 3.1 hours/day ($p<0.0001$ for Empa25) was observed. In addition, decreases in body weight (up to -3.6kg, $p<0.0001$), SBP (up to -4.7 mmHg, $p<0.0001$), and DBP (up to -2.3 mmHg, $p<0.0001$), all for Empa25 were observed [6]. No renal endpoints were assessed, since the adverse renal events were scarce, dose-dependent and comparable to placebo (1, 4, and 3 events for Empa10, Empa25, and placebo, respectively) [6]. Renal outcomes, also for T1DM, will be investigated in the dedicated kidney trial EMPA-KIDNEY [75].

In the DEPICT-trials, dose-dependent, placebo-corrected mean HbA1c-reductions of up to -0.42% (95% CI –0.53 to –0.30; $p<0.0001$ for the 10 mg dose dapagliflozin [Dapa10]) in the 24-week DEPICT-2 trial [73], and up to -0.45 (95% CI –0.58 to –0.31; $p<0.0001$ for Dapa10) in the 24-week DEPICT-1 trial [9] were observed, which were sustained with a mean, adjusted HbA1c reduction of up to -0.36% (Dapa10) in the 52-week DEPICT-1 trial [7]. This was, in both trials, accompanied by a significant increase of TIR, compared to placebo, by up to 10.7% ($p<0.0001$ for Dapa10) in both 24-week DEPICT-1/-2 trials [9,73]. Body weight was significantly reduced in both trials for both doses of dapagliflozin, by up to -3.74% (95% CI -4.49 to -2.99; $p<0.0001$ for Dapa10) [73], as well as a sustained decrease of SBP by -5.38 mmHg (95% CI –10.81 to 0.04; for Dapa10) was observed in the 52-week DEPICT-1 trial [7]. A follow-up analysis of the DEPICT-1/-2 trials showed that, at week 52, addition of dapagliflozin adjunct to insulin resulted in a dose dependent reduction of UACR (≥30 mg/g) of -13.3% (95% CI -37.2 to 19.8; for the 5 mg dose dapagliflozin [Dapa5]) and -31.1% (95% CI -49.9% to -5.2%; for Dapa10), compared to placebo [76]. Adjusted mean change in eGFR at week 52 in individuals with albuminuria at baseline was 3.3 ml/mg/1.73m^2 (95% CI -0.9 to 7.5, $p=0.1$ for Dapa5) and 2.1 ml/min/1.73m^2 (95% CI -2.0 to 6.3; $p=0.3$ for Dapa10), compared to placebo [76].

The inTandem trial program encompassed 3 trials with overall comparable outcome. In the 24-week inTandem3 trial, dose-dependent, placebo-adjusted least square matching (LSM) HbA1c reductions of up to -0.46% (95% CI -0.54 to -0.38; $p<0.001$ for the 400 mg dose of sotagliflozin [Sota400]) were

observed [10]. Mean change in body weight was up to -2.98 kg (95% CI -3.31 to -2.66) at 24 weeks. Mean, placebo-corrected difference in SBP was -3.5mmHg (95% CI -5.7 to -1.3; p=0.002 for Sota400) and, if baseline SBP ≥ 130 mmHg was present, a mean SBP-reduction of -6.6 mmHg (-10.9 to -2.3; p=0.004 for Sota400), at week 16 was seen. In the modified intention-to-treat (receipt of ≥1 dose of trial regimen), no significant mean changes in UACR (-20.09 mg/g [95% CI -43.04 to 2.87] p=0.09), serum creatinine level (0.006 mg/dl [95% CI 0.005 to 0.016] p=0.27) and eGFR (-0.24 ml/min/1.73m^2 [95% CI -1.52 to 1.04] p=0.71) were observed [10]. A follow-up analysis which pooled the 1,575 participants from inTandem1 and -2 largely confirmed the data from inTandem3, and demonstrated minor, dose-dependent effects on mean, placebo corrected eGFR with an initial decrease but subsequent return to near-baseline values (-2.8 ml/min/1.73m^2 [SE 0.6], p<0.0001 for Sota400 at week 4, and -0.5 ml/min/1.73m^2 [SE 0.8], p=0.52 for Sota400 at week 52) [77]. In the subgroup of participants (n=196) with mean elevated albuminuria (UACR ≥30 mg/g) at baseline, an initial dose-dependent reduction of mean albuminuria by -31.4% (SE 11.3, p=0.0032) from baseline was observed for Sota400 at week 24. This decreased to an overall mean reduction of -18.3% (SE 13.8, p=0.18) for Sota400 at week 52. At week 52, Sota400 reduced mean SBP by -3.6 mmHg (SE 0.7, p<0.0001) and DBP by -1.6 mmHg (SE 0.5, p=0.0008), relative to placebo. Mean serum haematocrit increased by 1.9% (SE 0.2, p<0.0001) at week 12, an effect persistent until week 52 (p<0.0001), relative to placebo. Similar, mean, placebo-corrected serum albumin concentration increased by 0.07 g/dl (SE 0.01, p<0.0001 for Sota400) by week 4 and 0.03 g/dl (SE 0.02, p=0.053) by week 52. A mean, placebo-corrected change in uric acid concentration of -0.42 mg/dl (SE 0.04, p<0.0001 for Sota400) was observed at week 4, which was persistent until week 52 (-0.28 mg/dl [SE 0.05], p<0.0001) [77].

The canagliflozin trial demonstrated placebo-corrected mean changes in HbA1c of -0.29% with the 100 mg dose of canagliflozin (Cana100) from baseline to week 18 and -0.25% with Cana300 [74]. Dose-dependent, placebo-corrected mean changes in body weight were -3.4% and -5.3% for Cana100 and Cana300, respectively [74]. Data on renal surrogate markers were not provided, osmotic-diuresis-related adverse events occurred at higher rates compared to placebo (9, 11, and 3 events for Cana100, Cana300, and placebo, respectively), as did volume depletion-related adverse events (4, 1, and 0 events for Cana100, Cana300, and placebo, respectively) [74]. Comparable outcomes were also observed in a small, real-world case series with 11 participants [78]. In summary, all trials showed added glycaemic efficacy, (minor) reductions in body weight and blood pressure, and if provided, positive effects on renal surrogate markers such as albuminuria. A comparison of mechanisms and transferability of outcomes of SGLT2 inhibition between type 1 and type 2 diabetes has also been published [79].

3. Mechanisms of SGLT-2is and SGLT-1/-2is relevant to DKD in T1DM

3.1 Hyperglycaemia, associated effects, and SGLT-inhibition in DKD

Hyperglycaemia is suggested as a major risk factor for the development of DKD. Anders and colleagues comprehensively reviewed early and late effects of hyperglycaemia on the kidney [22]. In summary, immediate effects of hyperglycaemia include hyperreabsorption of glucose and, as consequence, increases in the expression of glucose transporters, increases in energy-consuming transport processes in the proximal tubular cells, accompanied by a strong increase in oxygen demand in the renal cortex and outer medulla, ultimately inducing local ischaemia and cellular stress [22]. The increased reabsorption by co-transport of sodium decreases sodium availability at the macula densa, deactivates the tubulo-glomerular feedback, and induces vasodilation of the afferent arteriole, increasing the intraglomerular pressure and promoting glomerular hyperfiltration. Concomitantly and additively, an increase in renin secretion promotes vasoconstriction of the efferent arteriole, further aggravating the intraglomerular pressure and hyperfiltration. Ultimately, compensatory mechanisms lead to glomerular hypertrophy, pathing the way for further pathophysiological changes [22]. Postulated late, long-term effects of hyperglycaemia include endothelial dysfunction, glomerular basement membrane changes and mesangial cell expansion, podocyte injury, sterile local inflammation, and, to certain extent, also some metabolic memory[80,81].

As logic consequence, mainly SGLT-2- but also simultaneous SGLT-1-inhibition efficiently increases glycosuria – with concomitant intensification of NaCl delivery to the macula densa. This reinstates the tubulo-glomerular feedback, supporting afferent arteriole constriction, also associated with a decrease in renal energy demand and thus increased relative oxygen availability, and a decrease of the intraglomerular pressure and GFR [40,82]. This is consequently demonstrated in T2DM [2,3,5] by an initial drop of eGFR and subsequent recovery and long-term stabilization (as by reduced slope of eGFR decline). Furthermore, when extrapolating the rate and slope of eGFR decline in CREDENCE, it becomes clear that SGLT-2 inhibition may result in a substantial deferral of ESRD [2]. Also, there are first indications that SGLT-2is may have positive effects in individuals already presenting with albuminuria and declining GFR in T1DM. A post-hoc analysis of the DEPICT-1/-2 trials in individuals with existing albuminuria at baseline revealed that use of dapagliflozin (10 mg) resulted in a significant reduction of percent change in UACR [83]. However, first studies in T2DM suggest that an early start of SGLT-2 inhibition still in the normoalbuminuric range may be more efficient [84]. However, these effects seem rather to be mediated by ions like NaCl than by diminishing hyperglycaemia itself. Next to glycosuria, the use of SGLT-inhibition in T1DM has been shown to increase TIR and positively impact glycaemic variability [6,7,73,85,86]. High glycaemic variability is starting to be connected to adverse renal outcomes and a potential decline of renal function [20,87,88]. It has been shown that, in persons with T1DM, acute

hyperglycaemia increases urinary excretion of inflammatory cytokines and that it may also contribute to kidney injury by RAAS activation [20]. Also, by consequently reducing hyperglycaemia by increased renal elimination of glucose, long-term effects of hyperglycaemia may be prevented. Long-term reduction of hyperglycaemia has been suggested to positively impact oxidative stress levels and improving inflammatory processes and dysfunctional cellular pathways, e.g. through a reduction of advanced glycosylation end-products (AGEs) and activation of the corresponding pro-inflammatory AGE-RAGE (receptor for AGEs)-axis [89].

3.2 Renal (glomerular) hypertension and SGLT-inhibition

A fast and early decline of eGFR has been connected to subsequently increased risk of ESRD, thus, maintaining GFR is essential for preventing and decelerating the exacerbation of DKD to ESRD [31]. Elevated local concentrations of renin and, downstream, angiotensin II at the efferent arteriole, activated and supported by hyperglycaemia [90], result in vasoconstriction which in combination with the ablation of the tubulo-glomerular feedback, increases the intraglomerular pressure (glomerular hypertension) and glomerular hyperfiltration [29,91].

Consequently, and since a long time, first line treatment for hypertension and DKD in DM are inhibitors of the RAAS, as lowering systemic BP was shown to decelerate progression of DKD in T1DM [92]. However, there seem to be several issues with the RAAS inhibition for the prevention of DKD: first, RAAS blockers appear to be most effective in individuals with already high levels of albuminuria, and second, they rather delay the progression but do not prevent the development of DKD [31], as demonstrated by several trials such as the RASS- [48] and AdDIT-trials [49] . This has been proposed to be connected with their incapability to modify glycaemic control [31]. Third, RAAS inhibition is often contraindicated in individuals with advanced ESRD, particularly in those with stage-4/-5 kidney disease, due to a potentially negative impact on eGFR and the high risk of hyperkalaemia [31].

SGLT-inhibitors, on the other hand, have been shown to impact a multitude of factors related to systemic and renal BP control. First, as elucidated above, they directly impact (reduce) the intraglomerular pressure and the hyperfiltration by facilitating vasoconstriction of the afferent arteriole. Second, a systemic decrease of SBP and DBP has been observed in most major trials in T1DM [6-8,73]. This has been suggested to stem from the combination of modest weight loss, modest glucose-based osmotic diuresis and a small natriuretic effect [39]. Third, they have been shown to reduce cardiac pre- and afterload by several mechanisms, resulting in overall positive effects on the cardio-renal system and reducing renal blood flow [82,93]. Fourth, alongside impacting the tubulo-glomerular feedback, a recent study suggested that a combination of SGLT-inhibition with ACE inhibition may act in synergy and boost the alternate RAAS axis by inducing favourable ACE-2 levels, and possibly

decrease the risk of DKD in individuals with DM [94]. Fifth, a small decline of plasma uric acid due to an increase in glycosuria-related uricosuria has been observed with SGLT-2is [95].

However, while some trials [96] and reviews [97] have linked increased uric acid concentrations to reduced renal function, the FinnDiane Study showed by employing a Mendelian randomization approach (a method to study causality) that uric acid is not directly involved in the development of DKD in individuals with T1DM [98]. These data were confirmed by the randomized controlled trial PERL [99] designed to investigate how sustained lowering of serum uric acid by allopurinol associates with GFR decline and DKD in T1DM [100]. Doria and colleagues found no evidence of clinically meaningful serum urate reduction benefits with allopurinol on kidney outcomes in persons with T1DM and early-to-moderate diabetic kidney disease [100]. It has also been shown that urate-lowering treatment with allopurinol did not slow the decline in eGFR as compared with placebo in persons with CKD [101]. However, while this concludes that uric acid lowering alone does not provide the desired effects on DKD, it does not exclude that in a multifactorial mechanism of action as for SGLT-inhibition, lowering of serum uric acid may have additional impact. This may rather be reflected in a contribution to a reduction of arterial stiffness [102] which was proposed to be associated with renal function in T1DM, as well as to be an independent predictor of mortality in individuals with ESRD and T1DM [103]. Furthermore, elevated uric acid has been suggested to play a role in systemic hypertension as well as for low-grade inflammation [104] – again, while the effects of lowering uric acid alone may be not be strong enough to have a clinically meaningful impact on the progression of DKD, a combined effect with reduction of BP, stress and inflammatory processes by e.g. also reducing hyperglycaemia may be worthwhile considering and has not been thoroughly investigated in T1DM yet.

In summary, SGLT-2 inhibitors have been shown to impact a multitude of factors related to systemic and glomerular hypertension. So far, it is unclear if there is one dominant mechanism responsible for the clinical outcomes, or if it is a form of interconnectedness of several effects with the potential to improve renal outcomes in T1DM or T2DM.

3.3 Renal hypoxia, inflammation, and SGLT-inhibition

It has been elucidated above (in paragraph 1.2 and 3.2) that SGLT-inhibition has the potential to reduce excess renal energy expenditure, and as such also local renal oxygen consumption, diminishing renal hypoxia induced by chronic hyperglycaemia. In addition, all SGLT-2 inhibitors have demonstrated a modest increase of haematocrit in their respective CVOTs which cannot be explained solely by their diuretic effect [105]. It has been proposed that concomitant to hyperglycaemia-induced stress erythropoietin-producing fibroblasts in the kidney may transform into myo-fibroblasts to produce fibrogenic molecules, resulting in decreased serum erythropoietin levels [105]. Upon treatment with SGLT-inhibitors, renal metabolic stress is reduced and myo-fibroblasts may revert back to

erythropoietin-producing fibroblasts, thereby increasing serum erythropoietin and haemoglobin, further enhancing renal oxygen delivery [105]. Another mechanism of increased haematocrit has been suggested by a study in T2DM: treatment with dapagliflozin resulted in a reduction of hepcidin – a peptide which has been found increased in pro-inflammatory conditions and a recognised suppressor of erythropoiesis [106].

Additional and subsequent to ischaemia, inflammation has been postulated to further play a major role in the decline of renal function in DKD: pathological changes of renal vascular structures directly affect renal oxygen homeostasis, resulting in renal medullar hypoxia and renal tubular dysfunction [32]. In combination with disturbed mitochondrial function, increased reactive oxygen species (ROS), AGEs, and toxic metabolite production, this may lead to an activation of an inflammatory response, which is thought to ultimately promote renal (tubulointerstitial) fibrosis [32,107,108]. In a recent animal model and *in vitro* study, dapagliflozin significantly attenuated renal STAT1 and TGF-beta 1 expression – both factors associated with tubulointerstitial fibrosis in DKD [109]. If also demonstrated *in vivo*, it may be a first step into direct, rather than only indirect regulation of cellular pro-inflammatory signalling cascades.

3.4 Increased prevalence of obesity, renal impact, and SGLT-inhibition in T1DM

As discussed above, obesity also in T1DM strongly relates to IR, the metabolic syndrome and its individual components, and is increasingly prevalent in persons with T1DM. It has been demonstrated that in T1DM a BMI ≥27.5 kg/m^2 is associated with increased rates of hypertension, dyslipidaemia, microalbuminuria, and increased insulin demand, without affecting glycaemic control [110]. Furthermore, an increased BMI is associated with an increased risk of DKD [111] and has been demonstrated as a potentially independent risk factor for ESRD [112,113]. The pathological effects of obesity on renal function cycle around RAAS activation, an increase in intra-abdominal pressure affecting GFR and kidney function, sympathetic nervous system activation, IR, and dyslipidaemia resulting in low-grade inflammation, oxidative stress, glomerular hypertension and other factors [114,115].

The effects of SGLT-inhibition on hypertension and inflammation have already been discussed above. In the respective trials, SGLT-2is caused a loss of mean total body weight between ≈2kg and ≈4kg in T1DM [6-9]. These small body weight changes are unlikely to be responsible for any direct renoprotective effects of SGLT-2is – generally speaking, it has been proposed that SGLT-2i monotherapy is insufficient for the treatment of obesity [116]. However, SGLT-2i-mediated weight loss may still contribute to the overall picture of renal- and cardiovascular protection in persons with T1DM and obesity. There are first indications on how SGLT-2is may aid the treatment of IR, obesity and its associated low-grade inflammation by several mechanisms: for example, carbohydrate-related calorie loss by glycosuria, partially responsible for the observed weight losses [117], may cause the observed SGLT-2 mediated shift

of substrate utilization to fatty-acid and ketone body oxidation, contributing to further weight loss, a reduction of pro-inflammatory signalling and improvements in insulin sensitivity [118]. Thus, temporary metabolic reprogramming may be facilitated by SGLT-inhibition – first indications come from animal models, in which SGLT-2 inhibition was proposed to induce metabolic reprogramming related to a reduction of obesity, improved glucose tolerance despite reduced plasma insulin, increased plasma ketones, and improved plasma lipid profiles [119]. Overall, the animal model demonstrated that SGLT-2 inhibition may trigger a fasting-like transcriptional and metabolic paradigm and may reduce obesity in a fibroblast growth factor 21 (FGF21)-signalling-dependent manner [119]. In addition, other animal studies suggested that SGLT-inhibition may improve inflammatory signalling particularly in the liver and the kidneys, and concomitantly improve IR by reducing inflammatory signalling and modified macrophage polarization [120]. On the other hand, it has been shown that obese individuals have increased kidney sizes, glomerulomegaly and increased renal blood flow with concomitant glomerular hyperfiltration, which may lead to, similar to diabetes, increased proximal tubular sodium reabsorption [121]. While combined effects of T1DM and obesity again may be detrimental in this sense, SGLT-inhibition may act in a preserving manner by restoring the tubulo-glomerular feedback as discussed above.

3.4.1. NALFD, T1DM and SGLT-inhibition

It has been considered above the metabolic syndrome, IR and NALFD become increasingly prevalent also in T1DM. A study using magnetic resonance imaging estimated a prevalence of NALFD of around 5% in T1DM [122]. This study also concluded that, while NAFLD and T1DM seem to share some underlying mechanisms like increased inflammation and oxidative stress, T1DM *per se* does not seem to increase the risk to develop hepatic steatosis [122]. However, if persons with T1DM develop the metabolic syndrome, IR and NALFD, SGLT-2is may become a similarly interesting treatment consideration as in T2DM, particularly since NALFD can be considered a multisystem disease with additional detrimental impact on cardiovascular and renal function [123]. Various studies in T2DM have provided a lot of evidence that all available SGLT-2is seem to exert (significant) positive effects on the development of NAFLD/non-alcoholic steatohepatitis (NASH) and improvement of existing NAFLD/NASH [123-125]. Improvements in biomarkers like aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, ferritin, and gamma-glutamyltransferase (γGT) were consistently demonstrated, as reviewed elsewhere [123,124]. Similarly, effects like decreased intrahepatic triglycerides, hepatic fat fraction or content, improved liver/spleen attenuation ratio, reduced liver fibrosis, and attenuated hepatic inflammation were observed [123,124]. Liver biopsies in very small cohorts of persons with T2DM and NAFLD confirmed that SGLT-2is have the potential to reduce stage scores of steatosis, lobular inflammation, ballooning and fibrosis [126-128]. Mechanisms by which SGLT-2is cause these improvements

have to be further investigated. Current suggestions mainly circle around improvements in visceral fat mass, body weight and glycaemic control (by glycosuria), also positively impacting insulin sensitivity (or IR) and the glucagon-to-insulin ratio, as well as a general metabolic shift also relevant to the cardiovascular system like increased ketogenesis and increased fatty-acid oxidation (beta-oxidation). Tightly linked are other effects like improvement of inflammation and oxidative stress [123-125].

SGLT-inhibition is connected with a considerable risk of diabetic ketoacidosis in T1DM, as observed in respective trials [6-9]. However, the risk for DKA may be decreased in individuals with elevated BMI (BMI >27 kg/m^2) [129], for which reason SGLT-inhibition as an adjunct to insulin therapy in T1DM is only in-label in persons with a BMI ≥27 kg/m^2. Thus, SGLT-inhibition may prove a highly viable option in obese individuals with T1DM.

4. Conclusion and Clinical Implications

Diabetic kidney disease, the strongest risk factor for CV disease and mortality in T1DM, still develops in a considerable number of individuals with T1DM, despite access to intensive insulin therapy and technological improvements such as continuous glucose monitoring and (hybrid) closed-loop systems. Several pharmacological interventions failed to significantly reduce DKD progression since RAAS blockade entered international guidelines of DKD treatment. Although the possible renoprotective effect of empagliflozin in individuals with type 1 diabetes was already described[93], randomized controlled trials (RCT's) with this class of antidiabetic drugs thereafter mainly focused on investigating safety and efficacy in persons with T2DM. Several large RCT's in individuals with T2DM have shown, beside cardiovascular benefits, also protective properties of SGLT2 inhibitors against DKD progression. Several hypotheses are developed to explain how SGLT2 inhibitors exert their salutary effects on eGFR and albuminuria in T2DM, and probably different pathways exist in parallel.

The question, whether renoprotection is also present in T1DM is still unanswered. For that, large scale renal trials investigating the effects of SGLT2 inhibitors in T1DM are required, but it remains uncertain whether these trials will ever be performed. Since DKD pathogenesis shows differences between T1DM and T2DM, caution should be taken when extrapolating results from T2DM trials. On the other hand, both diseases often share DKD risk factors such as hyperglycemia, albuminuria, (glomerular) hypertension, overweight, hyperuricemia, NAFLD, and increased inflammation. Several studies with SGLT1/2 inhibition in T1DM showed improvement of these common risk factors, thereby targeting essential pathophysiological pathways leading to DKD. Therefore, the presence of a real renoprotective effect of SGLT inhibition in T1DM would not be unexpected. In fact, data from clinical trials are already emerging showing that inhibition of SGLT might also be renoprotective in T1DM. Both for Sotagliflozin and Dapagliflozin, post-hoc analyses of the InTandem and Depict1/2 trials point towards a decrease in albuminuria after initiation of SGLT-blockade.

An important caveat in the use of SGLT1/2 in T1DM is the well documented increased DKA risk. Health-care providers should very carefully weigh risk and benefits before prescribing SGLT1/2 inhibitors to individuals with T1DM. In case clear renoprotection would be demonstrated in T1DM, the risk-benefit assessment of SGLT1/2 inhibitors in people with T1DM could become clearer. But even then, there will still be a strong need for proper individuals' selection and education on DKA risk and management. Besides data on renal benefits from RCT's, also real-world evidence concerning DKA will deliver essential information on the actual risk and will help both health-care providers and health authorities in deciding on the place of SGLT1/2 inhibitors in the treatment of individuals with T1DM.

5. Bibliography

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. In. Brussels, Belgium2019.

2. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *The New England journal of medicine.* 2019;380(24):2295-2306.

3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *The New England journal of medicine.* 2019;380(4):347-357.

4. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England journal of medicine.* 2017;377(7):644-657.

5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine.* 2015;373(22):2117-2128.

6. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. *Diabetes Care.* 2018;41(12):2560-2569.

7. Dandona P, Mathieu C, Phillip M, et al. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes: The DEPICT-1 52-Week Study. *Diabetes Care.* 2018;41(12):2552-2559.

8. Mathieu C, Dandona P, Gillard P, et al. Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes—DEPICT-2 Study. *Diabetes.* 2018;67(Supplement 1):213-OR.

9. Dandona P, Mathieu C, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *The lancet Diabetes & endocrinology.* 2017;5(11):864-876.

10. Garg SK, Henry RR, Banks P, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. *The New England journal of medicine.* 2017;377(24):2337-2348.

11. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. *Diabetes Care.* 2018:dc180343.

12. Danne T, Cariou B, Banks P, et al. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. *Diabetes Care.* 2018;41(9):1981-1990.

13. First oral add-on treatment to insulin for treatment of certain patients with type 1 diabetes [press release]. European Medicines Agency, 01/02/2019; EMA/CHMP/46542/2019 2019.

14. New add-on treatment to insulin for treatment of certain patients with type 1 diabetes [press release]. European Medicines Agency, 01/03/2019.

15. Costacou T, Orchard TJ. Cumulative Kidney Complication Risk by 50 Years of Type 1 Diabetes: The Effects of Sex, Age, and Calendar Year at Onset. *Diabetes Care.* 2018;41(3):426-433.

16. Perkins BA, Bebu I, de Boer IH, et al. Risk Factors for Kidney Disease in Type 1 Diabetes. *Diabetes Care.* 2019;42(5):883-890.

17. Zelnick LR, Weiss NS, Kestenbaum BR, et al. Diabetes and CKD in the United States Population, 2009-2014. *Clinical journal of the American Society of Nephrology : CJASN.* 2017;12(12):1984-1990.

18. Papadopoulou-Marketou N, Paschou SA, Marketos N, Adamidi S, Adamidis S, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes. *Minerva medica.* 2018;109(3):218-228.

19. Groop PH, Thomas MC, Moran JL, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes.* 2009;58(7):1651-1658.

20. Bjornstad P, Cherney D, Maahs DM. Early diabetic nephropathy in type 1 diabetes: new insights. *Curr Opin Endocrinol Diabetes Obes.* 2014;21(4):279-286.

21. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *The New England journal of medicine.* 2003;348(23):2285-2293.

22. Anders HJ, Huber TB, Isermann B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nature reviews Nephrology.* 2018;14(6):361-377.

23. Gagnum V, Saeed M, Stene LC, Leivestad T, Joner G, Skrivarhaug T. Low Incidence of End-Stage Renal Disease in Childhood-Onset Type 1 Diabetes Followed for Up to 42 Years. *Diabetes Care.* 2018;41(3):420-425.

24. Nishimura R, Dorman JS, Bosnyak Z, et al. Incidence of ESRD and survival after renal replacement therapy in patients with type 1 diabetes: a report from the Allegheny County Registry. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2003;42(1):117-124.

25. Lecaire TJ, Klein BE, Howard KP, Lee KE, Klein R. Risk for end-stage renal disease over 25 years in the population-based WESDR cohort. *Diabetes Care.* 2014;37(2):381-388.

26. Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. *Jama.* 2005;294(14):1782-1787.

27. Helve J, Sund R, Arffman M, et al. Incidence of End-Stage Renal Disease in Patients With Type 1 Diabetes. *Diabetes Care.* 2018;41(3):434-439.

28. Toppe C, Mollsten A, Waernbaum I, et al. Decreasing Cumulative Incidence of End-Stage Renal Disease in Young Patients With Type 1 Diabetes in Sweden: A 38-Year Prospective Nationwide Study. *Diabetes Care.* 2019;42(1):27-31.

29. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. *Clinical journal of the American Society of Nephrology : CJASN.* 2017;12(12):2032-2045.

30. Thorn LM, Gordin D, Harjutsalo V, et al. The Presence and Consequence of Nonalbuminuric Chronic Kidney Disease in Patients With Type 1 Diabetes. *Diabetes Care.* 2015;38(11):2128-2133.

31. Barrett EJ, Liu Z, Khamaisi M, et al. Diabetic Microvascular Disease: An Endocrine Society Scientific Statement. *The Journal of clinical endocrinology and metabolism.* 2017;102(12):4343-4410.

32. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. *Journal of the Formosan Medical Association = Taiwan yi zhi.* 2018;117(8):662-675.

33. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, Group US. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes.* 2006;55(6):1832-1839.

34. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes.* 1983;32 Suppl 2:64-78.

35. Möllsten A, Svensson M, Waernbaum I, et al. Cumulative Risk, Age at Onset, and Sex-Specific Differences for Developing End-Stage Renal Disease in Young Patients With Type 1 Diabetes: A Nationwide Population-Based Cohort Study. In: *Diabetes.* Vol 59.2010:1803-1808.

36. Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. *Kidney Int Suppl (2011).* 2018;8(1):2-7.

37. Molitch ME, Gao X, Bebu I, et al. Early Glomerular Hyperfiltration and Long-Term Kidney Outcomes in Type 1 Diabetes: The DCCT/EDIC Experience. *Clinical journal of the American Society of Nephrology : CJASN.* 2019;14(6):854-861.

38. Sano R, Shinozaki Y, Ohta T. Sodium-glucose Co-transporters: Functional Properties and Pharmaceutical Potential. *J Diabetes Investig.* 2020.

39. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med.* 2015;66(1):255-270.

40. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation.* 2016;134(10):752-772.

41. Cherney DZ, Kanbay M, Lovshin JA. Renal physiology of glucose handling and therapeutic implications. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2020;35(Supplement_1):i3-i12.

42. Takiyama Y, Haneda M. Hypoxia in diabetic kidneys. *Biomed Res Int.* 2014;2014:837421-837421.

43. Dominguez Rieg JA, Rieg T. What does sodium-glucose co-transporter 1 inhibition add: Prospects for dual inhibition. *Diabetes, obesity & metabolism.* 2019;21 Suppl 2(S2):43-52.

44. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet (London, England).* 2013;382(9888):260-272.

45. Collins AJ, Foley RN, Herzog C, et al. US Renal Data System 2010 Annual Data Report. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2011;57(1 Suppl 1):A8, e1-526.

46. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function-Even Without Albuminuria. *Diabetes Care.* 2019;42(10):1886-1894.

47. MacIsaac RJ, Ekinci EI. Progression of Diabetic Kidney Disease in the Absence of Albuminuria. *Diabetes Care.* 2019;42(10):1842-1844.

48. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *The New England journal of medicine.* 2009;361(1):40-51.

49. Marcovecchio ML, Chiesa ST, Bond S, et al. ACE Inhibitors and Statins in Adolescents with Type 1 Diabetes. *The New England journal of medicine.* 2017;377(18):1733-1745.

50. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *The New England journal of medicine.* 2008;358(15):1547-1559.

51. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes. *New England Journal of Medicine.* 2012;367(23):2204-2213.

52. Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet (London, England).* 2019;393(10184):1937-1947.

53. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *The New England journal of medicine.* 2013;369(26):2492-2503.

54. Yin WL, Bain SC, Min T. The Effect of Glucagon-Like Peptide-1 Receptor Agonists on Renal Outcomes in Type 2 Diabetes. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* 2020;11(4):835-844.

55. Bakris GL, Agarwal R, Anker SD, et al. Design and Baseline Characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. *Am J Nephrol.* 2019;50(5):333-344.

56. Ruilope LM, Agarwal R, Anker SD, et al. Design and Baseline Characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. *American Journal of Nephrology.* 2019;50(5):345-356.

57. Ito S, Shikata K, Nangaku M, Okuda Y, Sawanobori T. Efficacy and Safety of Esaxerenone (CS-3150) for the Treatment of Type 2 Diabetes with Microalbuminuria: A Randomized, Double-Blind, Placebo-Controlled, Phase II Trial. *Clinical journal of the American Society of Nephrology : CJASN.* 2019;14(8):1161-1172.

58. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *The Cochrane database of systematic reviews.* 2014(4):Cd007004.

59. Epstein M, Williams GH, Weinberger M, et al. Selective Aldosterone Blockade with Eplerenone Reduces Albuminuria in Patients with Type 2 Diabetes. *Clinical Journal of the American Society of Nephrology.* 2006;1(5):940-951.

60. Gembillo G, Cernaro V, Salvo A, et al. Role of Vitamin D Status in Diabetic Patients with Renal Disease. *Medicina (Kaunas).* 2019;55(6):273.

61. Liyanage P, Lekamwasam S, Weerarathna TP, Liyanage C. Effect of Vitamin D therapy on urinary albumin excretion, renal functions, and plasma renin among patients with diabetic nephropathy: A randomized, double-blind clinical trial. *J Postgrad Med.* 2018;64(1):10-15.

62. Tiryaki Ö, Usalan C, Sayiner ZA. Vitamin D receptor activation with calcitriol for reducing urinary angiotensinogen in patients with type 2 diabetic chronic kidney disease. *Ren Fail.* 2016;38(2):222-227.

63. Cleland SJ, Fisher BM, Colhoun HM, Sattar N, Petrie JR. Insulin resistance in type 1 diabetes: what is 'double diabetes' and what are the risks? *Diabetologia.* 2013;56(7):1462-1470.

64. Bjornstad P, Maahs DM, Duca LM, et al. Estimated insulin sensitivity predicts incident micro- and macrovascular complications in adults with type 1 diabetes over 6 years: the coronary artery calcification in type 1 diabetes study. *Journal of diabetes and its complications.* 2016;30(4):586-590.

65. Maffeis C, Birkebaek NH, Konstantinova M, et al. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: Data from the international SWEET registry. *Pediatric diabetes.* 2018;19(7):1211-1220.

66. Corbin KD, Driscoll KA, Pratley RE, et al. Obesity in Type 1 Diabetes: Pathophysiology, Clinical Impact, and Mechanisms. *Endocrine reviews.* 2018;39(5):629-663.

67. DuBose SN, Hermann JM, Tamborlane WV, et al. Obesity in Youth with Type 1 Diabetes in Germany, Austria, and the United States. *J Pediatr.* 2015;167(3):627-632 e621-624.

68. Melin EO, Thulesius HO, Hillman M, Landin-Olsson M, Thunander M. Abdominal obesity in type 1 diabetes associated with gender, cardiovascular risk factors and complications, and difficulties achieving treatment targets: a cross sectional study at a secondary care diabetes clinic. *BMC Obes.* 2018;5(1):15.

69. Thorn LM, Forsblom C, Fagerudd J, et al. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care.* 2005;28(8):2019-2024.

70. Merger SR, Kerner W, Stadler M, et al. Prevalence and comorbidities of double diabetes. *Diabetes research and clinical practice.* 2016;119:48-56.

71. Pambianco G, Costacou T, Orchard TJ. The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and

estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes Care.* 2007;30(5):1248-1254.

72. Pieber TR, Famulla S, Eilbracht J, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes, obesity & metabolism.* 2015;17(10):928-935.

73. Mathieu C, Dandona P, Gillard P, et al. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial. *Diabetes Care.* 2018;41(9):1938-1946.

74. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients With Type 1 Diabetes. *Diabetes Care.* 2015;38(12):2258-2265.

75. Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clinical Kidney Journal.* 2018;11(6):749-761.

76. Lahtela JT, Edelman S, Jendle J, et al. Effect of adding dapagliflozin as an adjunct to insulin on urinary albumin-to-creatinine ratio over 52 weeks in adults with type 1 diabetes. Paper presented at: 55th Annual Meeting of the European Association for the Study of Diabetes (EASD), September 16-20, 2019, Barcelona, Spain2019.

77. van Raalte DH, Bjornstad P, Persson F, et al. The Impact of Sotagliflozin on Renal Function, Albuminuria, Blood Pressure, and Hematocrit in Adults With Type 1 Diabetes. *Diabetes Care.* 2019;42(10):1921-1929.

78. Roberts TM, Johnson JF, Vaughan AG. Canagliflozin in Type 1 Diabetes: A Case Series of Patient Outcomes in a Diabetes Clinic. *Diabetes Spectrum.* 2019;32(1):47-51.

79. Schnell O, Valensi P, Standl E, Ceriello A. Comparison of mechanisms and transferability of outcomes of SGLT2 inhibition between type 1 and type 2 diabetes. *Endocrinology, Diabetes & Metabolism.* 2020;n/a(n/a):e00129.

80. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes.* 2005;54(6):1615-1625.

81. Intine RV, Sarras MP, Jr. Metabolic memory and chronic diabetes complications: potential role for epigenetic mechanisms. *Current diabetes reports.* 2012;12(5):551-559.

82. Sarafidis P, Ferro CJ, Morales E, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2019;34(2):208-230.

83. Edelman S, Jendle J, Dandona P, et al. Effect of Adding Dapagliflozin as an Adjunct to Insulin on Urinary Albumin-to-Creatinine Ratio over 52 Weeks in Adults with Type 1 Diabetes. In. h*ttps://www.asn-online.org/education/kidneyweek/2018/program-abstract.aspx?controlId=3064879,* 23-28 October 2018, San Diego, CA: ASN Kidney Week 2018. Abstract TH-PO1156; 2018.

84. Nakamura A, Miyoshi H, Kameda H, Yamashita K, Kurihara Y. Impact of sodium-glucose cotransporter 2 inhibitors on renal function in participants with type 2 diabetes and chronic kidney disease with normoalbuminuria. *Diabetology & metabolic syndrome.* 2020;12:4-4.

85. Biester T, Nieswandt A, Biester S, et al. DAPADream: improved postprandial glucose control with dapagliflozin as add-on to full closed loop in type 1 diabetes | https://www.morressier.com/article/dapadream-improved-postprandial-glucose-control-dapagliflozin-addon-full-closed-loop-type-1-diabetes/59d51845d462b80296ca39ea. Published 2019. Updated 2019/02/12/. Accessed.

86. Wadén J, Forsblom C, Thorn LM, Gordin D, Saraheimo M, Groop PH. A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. *Diabetes.* 2009;58(11):2649-2655.

87. Tong L, Chi C, Zhang Z. Association of various glycemic variability indices and vascular outcomes in type-2 diabetes patients: A retrospective study. *Medicine.* 2018;97(21):e10860-e10860.

88. Subramanian S, Hirsch IB. Diabetic Kidney Disease: Is There a Role for Glycemic Variability? *Current diabetes reports.* 2018;18(3):13.

89. Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease. *Diabetes & metabolism.* 2018;44(6):457-464.

90. Chen CM, Juan SH, Chou HC. Hyperglycemia activates the renin-angiotensin system and induces epithelial-mesenchymal transition in streptozotocin-induced diabetic kidneys. *Journal of the renin-angiotensin-aldosterone system : JRAAS.* 2018;19(3):1470320318803009.

91. Tuttle KR. Back to the Future: Glomerular Hyperfiltration and the Diabetic Kidney. *Diabetes.* 2017;66(1):14-16.

92. de Boer IH, Rue TC, Cleary PA, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Archives of internal medicine.* 2011;171(5):412-420.

93. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation.* 2014;129(5):587-597.

94. Kopecky C, Lytvyn Y, Domenig O, et al. Molecular regulation of the renin-angiotensin system by sodium-glucose cotransporter 2 inhibition in type 1 diabetes mellitus. *Diabetologia.* 2019;62(6):1090-1093.

95. Lytvyn Y, Skrtic M, Yang GK, Yip PM, Perkins BA, Cherney DZ. Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated type 1 diabetes mellitus. *American journal of physiology Renal physiology.* 2015;308(2):F77-83.

96. Pizarro MH, Santos DC, Barros BSV, de Melo LGN, Gomes MB. Serum uric acid and renal function in patients with type 1 diabetes: a nationwide study in Brazil. *Diabetology & metabolic syndrome.* 2018;10:22-22.

97. Jalal DI, Maahs DM, Hovind P, Nakagawa T. Uric acid as a mediator of diabetic nephropathy. *Semin Nephrol.* 2011;31(5):459-465.

98. Ahola AJ, Sandholm N, Forsblom C, Harjutsalo V, Dahlström E, Groop PH. The serum uric acid concentration is not causally linked to diabetic nephropathy in type 1 diabetes. *Kidney international.* 2017;91(5):1178-1185.

99. Afkarian M, Polsky S, Parsa A, et al. Preventing Early Renal Loss in Diabetes (PERL) Study: A Randomized Double-Blinded Trial of Allopurinol—Rationale, Design, and Baseline Data. *Diabetes Care.* 2019;42(8):1454-1463.

100. Doria A, Galecki AT, Spino C, et al. Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes. *The New England journal of medicine.* 2020;382(26):2493-2503.

101. Badve SV, Pascoe EM, Tiku A, et al. Effects of Allopurinol on the Progression of Chronic Kidney Disease. *New England Journal of Medicine.* 2020;382(26):2504-2513.

102. Cherney DZ, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovascular diabetology.* 2014;13:28.

103. Theilade S, Lajer M, Persson F, Joergensen C, Rossing P. Arterial stiffness is associated with cardiovascular, renal, retinal, and autonomic disease in type 1 diabetes. *Diabetes Care.* 2013;36(3):715-721.

104. Lytvyn Y, Perkins BA, Cherney DZ. Uric acid as a biomarker and a therapeutic target in diabetes. *Canadian journal of diabetes.* 2015;39(3):239-246.

105. Sano M, Goto S. Possible Mechanism of Hematocrit Elevation by Sodium Glucose Cotransporter 2 Inhibitors and Associated Beneficial Renal and Cardiovascular Effects. *Circulation.* 2019;139(17):1985-1987.

106. Ghanim H, Hejna JM, Abuaysheh S, et al. Dapagliflozin Suppresses Plasma Hepcidin Concentrations. *Diabetes.* 2018;67(Supplement 1):1116-P.

107. Dellamea BS, Leitao CB, Friedman R, Canani LH. Nitric oxide system and diabetic nephropathy. *Diabetology & metabolic syndrome.* 2014;6(1):17.

108. Lahnwong S, Chattipakorn SC, Chattipakorn N. Potential mechanisms responsible for cardioprotective effects of sodium-glucose co-transporter 2 inhibitors. *Cardiovascular diabetology.* 2018;17(1):101.

109. Huang F, Zhao Y, Wang Q, et al. Dapagliflozin Attenuates Renal Tubulointerstitial Fibrosis Associated With Type 1 Diabetes by Regulating STAT1/TGFbeta1 Signaling. *Frontiers in Endocrinology.* 2019;10:441.

110. Fellinger P, Fuchs D, Wolf P, et al. Overweight and obesity in type 1 diabetes equal those of the general population. *Wiener klinische Wochenschrift.* 2019;131(3):55-60.

111. Foster MC, Hwang SJ, Larson MG, et al. Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2008;52(1):39-48.

112. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Annals of internal medicine.* 2006;144(1):21-28.

113. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. *Journal of the American Society of Nephrology : JASN.* 2006;17(6):1695-1702.

114. Tonneijck L, Muskiet MH, Smits MM, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. *Journal of the American Society of Nephrology : JASN.* 2017;28(4):1023-1039.

115. Maric-Bilkan C. Obesity and diabetic kidney disease. *Med Clin North Am.* 2013;97(1):59-74.

116. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. *Drugs.* 2019;79(3):219-230.

117. Seufert J. SGLT2 inhibitors - an insulin-independent therapeutic approach for treatment of type 2 diabetes: focus on canagliflozin. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2015;8:543-554.

118. Ferrannini E, Baldi S, Frascerra S, et al. Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. *Diabetes.* 2016;65(5):1190-1195.

119. Osataphan S, Macchi C, Singhal G, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -independent mechanisms. *JCI Insight.* 2019;4(5).

120. Xu L, Ota T. Emerging roles of SGLT2 inhibitors in obesity and insulin resistance: Focus on fat browning and macrophage polarization. *Adipocyte.* 2018;7(2):121-128.

121. Chagnac A, Herman M, Zingerman B, et al. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2008;23(12):3946-3952.

122. Petit JM, Pedro L, Guiu B, et al. Type 1 diabetes is not associated with an increased prevalence of hepatic steatosis. *Diabetic medicine : a journal of the British Diabetic Association.* 2015;32(12):1648-1651.

123. Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: A common comorbidity associated with severe complications. *Diabetes & metabolism.* 2019;45(3):213-223.

124. Jung C-H, Mok J-O. The Effects of Hypoglycemic Agents on Non-alcoholic Fatty Liver Disease: Focused on Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists. *J Obes Metab Syndr.* 2019;28(1):18-29.

125. Wanner C, Marx N. SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. *Diabetologia.* 2018;61(10):2134-2139.

126. Akuta N, Kawamura Y, Watanabe C, et al. Impact of sodium glucose cotransporter 2 inhibitor on histological features and glucose metabolism of non-alcoholic fatty liver disease complicated by diabetes mellitus. *Hepatology Research.* 2019;49(5):531-539.

127. Akuta N, Watanabe C, Kawamura Y, et al. Effects of a sodium-glucose cotransporter 2 inhibitor in nonalcoholic fatty liver disease complicated by diabetes mellitus: Preliminary prospective study based on serial liver biopsies. *Hepatology Communications.* 2017;1(1):46-52.

128. Seko Y, Nishikawa T, Umemura A, et al. Efficacy and safety of canagliflozin in type 2 diabetes mellitus patients with biopsy-proven nonalcoholic steatohepatitis classified as stage 1–3 fibrosis. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2018;11:835-843.

129. Mathieu C, Dandona P, Phillip M, et al. SAT-LB025 Analysis of Benefit/Risk in the Subgroup of Patients with BMI of equal or larger than 27 kg/m2 in the Dapagliflozin DEPICT-1 and -2 Trials in Type 1 Diabetes. *Journal of the Endocrine Society.* 2019;3(Supplement_1).