Vasculo-metabolic Axis in Type 2 Diabetes Mellitus—Abductive Reasoning from Sodium-glucose Cotransporter 2-inhibitor Evidence

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Abductive reasoning is an unconventional approach to understanding medical science. It can be described as the opposite of the usual 'bench-to-bedside' technique, whereby one applies laboratory-based learning to the treatment of patients. Abductive reasoning reverses this process and applies the observation of unexpected outcomes of therapy in order to further understand the pathophysiology of disease, a 'bedside-to-bench' learning approach. SGLT2 inhibitors act directly on the kidneys, and have demonstrated various unexpected clinical outcomes in T2DM. These agents act as a unifying intervention to improve the macrovascular, microvascular, and metabolic outcomes in T2DM. Observations in SGLT2-inhibitor therapy provide opportunities to revisit the possible role of the kidneys in the pathogenesis of metabolic syndrome. Albuminuria is a unifying marker for kidney disease, and vasculo-metabolic dysfunction. Based on observations with SGLT2 inhibitors, we apply abductive reasoning to emphasize the pathological role of the kidneys in metabolic syndrome. Further, we support the proposition of including albuminuria as a key parameter in the definition of metabolic syndrome.

The clinical connection between metabolic health and vascular disease is well-known.[1–4] While an association between obesity and diabetes has been historically described, the past century has witnessed the evolution of broader understanding in vasculo-metabolic health.[1–4] In 1923, the Swedish physician Kylin described an association between hypertension, hyperglycemia, and gout.[5] Since then, several developments progressively led to the recognition of metabolic syndrome, an entity characterized by clustering of vasculo-metabolic risk factors.[1,4] This clustering of risk factors predisposes to cardiovascular disease (CVD), and patients may develop metabolic syndrome with different combinations of these risk factors. Certain combinations of these risk factors may confer greater risk of CVD events and mortality. The combination of high blood pressure, increased waist circumference, and hyperglycemia, may confer the greatest risk. The combination of high blood pressure, with low high-density lipoprotein (HDL) cholesterol, and raised triglyceride levels, may also carry significant risk. Thus, combinations and trajectories of the component risk factors may influence the outcomes in metabolic syndrome.[6]

The evolving definition of metabolic syndrome

The initial definition of metabolic syndrome was proposed by the World Health Organization (WHO) in 1998, which laid emphasis on dysglycemia, obesity, lipid disorders, albuminuria, or hypertension.[7] Since then, several definitions have been proposed by various scientific groups, none of which has been accepted as incontrovertible.[1–3] Of note, WHO had placed emphasis on albuminuria, as one of the key criteria to define metabolic syndrome.[7] However, subsequent definitions published by the European Group for Study of Insulin Resistance; the Adult Treatment Panel III; the American Association of Clinical Endocrinology; and the American Heart Association/the National Heart, Lung, and Blood Institute, did not include albuminuria as a defining criterion for metabolic syndrome.[8–11] The International Diabetes Federation (IDF) definition, however, did recognize albuminuria as a supportive factor for diagnosis, and emphasized the need to ascertain its predictive power for metabolic syndrome.[12] Thus, the role of albuminuria in defining the existence of metabolic syndrome remains ambiguous.

Clinical effects of sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated promising effects on several aspects of metabolic syndrome in patients with type 2 diabetes mellitus (T2DM). Apart from glycemic control, these agents have demonstrated reductions in visceral and subcutaneous fat, insulin resistance, uric acid levels, and albuminuria.[13–15]

In terms of clinical outcomes, the SGLT2 inhibitors, empagliflozin, has demonstrated reduction in the risk of mortality in patients with T2DM and established CVD.[16] Further, SGLT2 inhibitors have demonstrated improvements in heart failure as well as renal outcomes in patients with T2DM.[17,18] Additionally, there is growing interest in their possible clinical utility in preventing the worsening of heart failure, chronic kidney disease, and non-alcoholic fatty liver disease in people without diabetes.[19]

Applying therapeutic outcomes to the basics of disease pathophysiology

The classic approach of medical pharmacology begins with knowing the basic pathology of a disease. This knowledge helps in identifying a suitable target for therapy. The next step is the discovery of prospective medicinal agents, which can act on this target. Following thorough research to prove safety and efficacy, a new medicine is then available for clinical use. In this conventional approach of medicinal discovery, deductive reasoning at each step leads to the next step. This is known as the 'bench-to-bedside' approach.

However, not every learning style in medicine follows the classic bench-to-bedside approach. On several occasions, learning can progress in opposite direction, i.e., from 'bedside to bench'. This approach starts with an unexpected clinical observation with any therapy. To explain such unexpected observations, we apply abductive reasoning to arrive at a likely hypothesis. Thus, we progress towards enhancing our basic understanding of a disease, following unexpected therapeutic outcomes.

In this review, we look at the vasculo-metabolic outcomes observed with SGLT2 inhibitors, which have shown largely unexpected and serendipitous findings. Further, we apply the principles of abductive reasoning to these observations, to revisit the role of kidneys in the vasculo-metabolic axis. Thus, we attempt to rationalize certain aspects of metabolic syndrome, based on the evidence of SGLT2 inhibitors.

Sodium-glucose cotransporter 2 inhibitors and metabolic effects

SGLT2 inhibitors have demonstrated consistent effects on glycemia, weight, and blood pressure.[13,14] These agents act on fasting as well as postprandial components of glycemia, and improve the time spent in euglycemic range.[20,21] As a result of the loss of adiposity, peripheral insulin sensitivity is improved. Further, the hyperinsulinemia of T2DM is partly alleviated due to improved insulin sensitivity, combined with reduction in glycemia. SLGT2 inhibitor-associated weight loss plateaus after the initial few months of therapy, due to various adaptive metabolic mechanisms.[22–24] These metabolic adaptions following SGLT2-inhibitor therapy, also result in marginally increased levels of low-density lipoprotein (LDL) cholesterol, as well as HDL cholesterol. These agents may help address nocturnal hypertension in some people with T2DM, when fluid retention is the predominant reason for nocturnal non-dipping.[25] These agents are different from conventional diuretic agents, in that they have a more prominent effect on free-water clearance related to glycosuria. This effect mediates greater loss of interstitial fluid volume, as compared to plasma volume, unlike the conventional diuretic agents.[26] Further, SGLT2-inhibitor therapy mediates a sustained effect of modest hemoconcentration, unlike classic diuretic therapy. SGLT2 inhibitors also mediate improvement in mitochondrial function in the human myocardial cells, which may facilitate improved diastolic relaxation and positive lusitropism.[27] Further research is

needed to characterize the modulation of myocardial energetics, with the use of these agents.

Sodium-glucose cotransporter 2 inhibitors and cardiovascular outcomes

The EMPA-REG OUTCOME study of empagliflozin was the first randomized, controlled cardiovascular (CV) outcomes trial, to demonstrate mortality risk-reduction and CV benefits with any glucose-lowering therapy.[16] Subsequently published CV outcomes trials of SGLT2 inhibitors further enhanced our understanding with these agents.[28,29] Several mechanistic studies of SGLT2 inhibitors are in pursuit of characterizing their CV effects.[30,31]

In EMPA-REG OUTCOME study, 7,020 participants with T2DM with established CVD were randomized to receive either placebo, empagliflozin 10 mg, or empagliflozin 25 mg, on top of standard of care therapies.[16] Empagliflozin therapy demonstrated significant 14% reduced risk of major adverse cardiovascular events (MACE) (hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.74, 0.99; p<0.05). This was driven by a prominent 38% reduction in risk of CV death (HR 0.62; 95% CI 0.49, 0.77; p<0.001). All-cause mortality risk was reduced by 32% (HR 0.68; 95% CI 0.57, 0.82; p<0.001). The CV mortality benefit encompassed all types of CV deaths, and was consistent irrespective of the heart-failure burden in the study participants.[32,33] Further, empagliflozin therapy demonstrated a significant 35% lower risk of hospitalizations for heart failure (HR 0.65; 95% CI 0.50, 0.85; p<0.05).[32] The outcomes for stroke and myocardial infarction were not significantly different from placebo.

Empagliflozin therapy demonstrated consistent CV-mortality benefit across major subgroups of participants, including those with or without chronic kidney disease.[16,34] The CV benefits were consistently observed in patients with moderate renal impairment, up to the estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m². This is unlike the glycemic effects of SGLT2 inhibitors, which are evident only up to an eGFR level of 45 mL/min/1.73 m².[35] Thus, a discordance is observed between the vascular and metabolic effects of SGLT2 inhibitors, based on the renal functioning. These CV and mortality reductions had an early onset, and remained consistent throughout the study; this may suggest diverse vasculo-metabolic mechanisms being effective over the duration of trial.[36]

Around 35% of patients in the EMPA REG OUTCOME study did not have prior event of myocardial infarction or stroke. These patients had established CVD, in the form of coronary or peripheral arterial disease. In these patients without prior events, the risk of CV death increased five-fold across the spectrum of CV risk, and that of heart-failure hospitalizations increased nine-fold. The effects of empagliflozin on mortality and heart failure outcomes, were consistent across this CV risk spectrum, in patients of T2DM with CVD.[34,36]

Further, the likelihood of CV benefits with empagliflozin also extended to patients with adequate glycemic control. Within the EMPA-REG OUTCOME study, a cohort of 424 participants had glycated hemoglobin (HbA1c) values of <7% at baseline. In these patients, empagliflozin therapy consistently reduced the risk of CV death, and heart failure outcomes.[37] This observation suggests that even with controlled glycemia, the CV benefits may be available.[38]

The CANVAS program was a pooled analysis of two randomized controlled trials, CANVAS and CANVAS-renal (CANVAS-R).[28,39] The pooled analysis involved 10,142 participants with T2DM and high CV risk. The CANVAS

program evaluated CV outcomes with the use of canagliflozin, in comparison to a placebo group, on top of standard of care. In this overall study population, 6,656 participants (~66%) had a prior history of symptomatic atherosclerotic CVD. In the pooled analysis, canagliflozin therapy demonstrated a significant 14% lower risk for 3P-MACE (HR 0.86; 95% CI 0.75, 0.97; p<0.05). The MACE benefit was observed predominantly in patients with prior CVD (HR 0.82; 95% CI 0.72, 0.95), whereas it was neutral in patients without CVD (HR 0.98; 95% CI 0.74, 1.30). Canagliflozin therapy did not demonstrate significant reduction in overall mortality (HR 0.87; 95% CI 0.74, 1.01), or in CV death (HR 0.87; 95% CI 0.72, 1.06). In patients of T2DM with prior CVD, canagliflozin therapy did not demonstrate significant reduction in the risks of overall mortality (HR 0.89; 95% CI 0.85, 1.07), and of CV death (HR 0.86, 95% CI 0.70, 1.06).[39] Risk of heart failure hospitalization was significantly reduced with canagliflozin therapy, by 33% (HR 0.67; 95% CI 0.52, 0.87).[28,39]

The DECLARE-TIMI 58 study evaluated the CV outcomes with dapagliflozin 10 mg once daily versus placebo.[29] The study included 17,160 participants with T2DM with high CV risk, who were followed up over median duration of 4.2 years. Of the study participants, 6,974 (~40.6%) had prior established atherosclerotic CVD. The efficacy outcomes included a composite of 3P-MACE, and a composite of CV death or hospitalization for heart failure. The study demonstrated CV safety profile of dapagliflozin, as compared to placebo. However, dapagliflozin therapy did not demonstrate a significant benefit for 3P-MACE as compared to placebo (HR 0.93; 95% CI 0.84, 1.03; p=0.17). In patients with prior established CVD, dapagliflozin therapy did not demonstrate reduced risk of 3P-MACE (HR 0.90; 95% CI 0.79, 1.02). Further, dapagliflozin therapy did not demonstrate reduction in risk of all-cause mortality in the overall study (HR 0.93; 95% CI 0.82, 1.04), or in patients with prior CVD (HR 0.92; 95% CI 0.79, 1.08). Dapagliflozin therapy reduced the risk of composite parameter of CV death or hospitalization for heart failure (HR 0.83; 95% CI 0.73, 0.95); this benefit was due to lower risk of hospitalization for heart failure (HR 0.73; 95% CI 0.61, 0.88), without significant reduction in risk of CV death (HR 0.98; 95% CI 0.82, 1.17). These heart failure outcomes with dapagliflozin were consistently observed, in patients with or without prior history of heart failure.[16,29]

To summarize, published CV outcomes-trial evidence suggests favorable CV outcomes with the use of SGLT2 inhibitors. This also raises the hope for their possible usefulness as CV risk-reducing interventions in people without T2DM. The clinical relevance of SGLT2 inhibitors in T2DM, extends to patients with, or at-risk for, both atherosclerotic CVD and heart failure. All studies consistently demonstrated benefits in heart failure outcomes, in the variously included study populations. However, these CV outcome trials are not primarily designed as dedicated heart-failure trials, and hence the heart-failure outcomes in these studies do not reflect confirmatory evidence of such benefit. Ongoing dedicated heart-failure trials will provide further insights into this scientific opportunity with SGLT2 inhibitors, in patients with heart failure with preserved ejection fraction or reduced ejection fraction, regardless of background T2DM.

Sodium-glucose cotransporter 2 inhibitors and renal outcomes

Renal dysfunction is assessed in two major ways; a decline in eGFR levels, and an increase in albuminuria. SGLT2 inhibitors are known to impact both these parameters.[40–42] They are known to cause modest decline in eGFR levels in the early weeks of therapy in T2DM.[40,42] This occurs due to normalization of the afferent renal vascular tone following SGLT2-inhibitor therapy. In T2DM,

the activity of SGLT2 is upregulated in the proximal tubules. This results in increased sodium reabsorption. As a corollary, lesser amounts of sodium reaches the macula-densa cells. This triggers a tubulo-glomerular feedback mechanism, which causes dilatation of the afferent renal arterioles. The afferent arteriolar dilatation results in increased glomerular blood-flow, intra-glomerular hypertension, and subsequent damage to the nephron. When an SGLT2 inhibitor is used in T2DM, this pathological sequence may be alleviated. As the SGLT2 is blocked, the sodium transport in proximal tubule is corrected. This results in correction of the tubulo-glomerular feedback signal, and constriction of the afferent arteriole. The intra-glomerular pressure is thus reduced. SGLT2 inhibitors have consistently demonstrated 30–50% reductions in albuminuria levels, particularly in diabetic kidney disease. These changes in albuminuria levels are suggestive of intra-renal hemodynamic mechanisms, as they occur irrespective of reductions in blood pressure, weight loss, and glycemic control.[40–42]

In the EMPA-REG OUTCOME study, treatment with empagliflozin significantly reduced the incident or worsening of nephropathy by 39% (HR 0.61; 95% CI 0.53, 0.70; p<0.001).[40,42,43] This parameter was a composite of progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease. The benefit was consistent in all the individual components of this composite parameter. Even when the albuminuria component was excluded from this composite parameter, a significant 46% lower risk (HR 0.54; 95% CI 0.40, 0.75; p<0.001) was observed with empagliflozin. Empagliflozin therapy significantly preserved the renal function, with significant slowing in decline of eGFR levels. This effect of eGFR preservation was increasingly prominent in patients with greater albuminuria levels. The risk of incident albuminuria was not reduced with empagliflozin, whereas progression to macroalbuminuria was reduced by 38% (HR 0.62; 95% CI 0.54, 0.72). Further, in patients with macroalbuminuria at baseline, empagliflozin therapy demonstrated significant 82% greater chances of regression in albuminuria category, as compared to placebo.[44]

In the CANVAS program, a significant 40% reduced risk was observed with canagliflozin therapy for the composite renal endpoint, which suggested renal protection.[28] This composite renal endpoint included the parameters of sustained 40% reduction in eGFR, need for renal replacement therapy, or death from renal causes (HR 0.60; 95% CI 0.47, 0.77).[28] In another analysis using a different composite renal endpoint, canagliflozin therapy similarly demonstrated 47% lower risk of renal events.[45] This composite renal endpoint included robust parameters of sustained doubling of serum creatinine, end-stage kidney disease, and death from renal causes (HR 0.53; 95% CI 0.33, 0.84).[45] Canagliflozin therapy also demonstrated preservation of renal function, with a slower annual rate of decline in eGFR by 1.2 mL/min/1.73 m². Further, the risk of progression in albuminuria category was 27% lower with canagliflozin (HR 0.73; 95% CI 0.67, 0.79). Canagliflozin therapy lowered the risk of new-onset microalbuminuria significantly by 20% (HR 0.80; 95% CI 0.73, 0.87). The risk of macroalbuminuria was also significantly lowered by 42% (HR 0.58; 95% CI 0.50, 0.68) with canagliflozin.[45] The renal benefits demonstrated in EMPA-REG OUTCOME and CANVAS Program are remarkable, as they have been demonstrated in a cohort that was already using the renin-angiotensin system inhibitors.[43]

The DECLARE-TIMI 58 trial evaluated the effect of dapagliflozin on composite renal parameters of 40% decrease in eGFR to <60 mL/min/1.73 m², end-stage renal disease, or death from renal causes. Dapagliflozin therapy

demonstrated significant 47% lower risk (HR 0.53; 95% CI 0.43, 0.66) for this renal outcome.[42] Based on the study design, the majority of patients had baseline eGFR levels of >60 mL/min/1.73 m^2.[2,29,42]

While CV outcomes trials have demonstrated largely consistent benefits in renal outcomes with the SGLT2 inhibitors, these trials were not essentially designed to assess the renal outcomes. Dedicated renal outcome studies of these agents will provide conclusive evidence on the possible renal benefits. The CREDENCE study of canagliflozin has been prematurely terminated due to definitive renal protection observed in patients of diabetic kidney disease with macroalbuminuria.[46] The ongoing DAPA-CKD and EMPA-KIDNEY trials will provide insights into possible benefits of these agents in chronic kidney disease, including non-diabetic kidney disease.[47,48]

Abductive reasoning for metabolic syndrome

The rapidly evolving clinical evidence for SGLT2 inhibitors has provided opportunities to reflect on the pathophysiological mechanisms in T2DM. One such under-recognized aspect is the possible role of kidneys in metabolic syndrome. As a victim of metabolic syndrome or its components, the kidney is well-recognized for diabetic kidney disease, hypertensive kidney disease, and obesity-related glomerulopathy. Chronic hyperglycemia promotes glomerular endothelial dysfunction, resulting in podocyte damage and albuminuria. The underlying pathological processes involving podocyte-endothelial crosstalk mechanisms, and mitochondrial oxidative stress, are being increasingly understood.[49] Podocyte injury contributes to progressive albuminuria in diabetic and nondiabetic glomerular diseases. Emerging evidence also suggests that albuminuria may further enhance podocyte damage, by hampering the limited regenerative mechanisms.[50] As per a recently published large meta-analysis, obesity was associated with reduced eGFR levels and death, regardless of background kidney disease.[51] Further, an association between metabolic syndrome and exercise-induced albuminuria in the absence of microalbuminuria, has also been observed.[52]

However, the kidneys may also play an important causative role in metabolic syndrome. While the role of the kidneys in hypertension is well-known, the contribution of the kidneys in diabetes and vasculo-metabolic outcomes beyond hypertension, has remained understated. Indeed, the first definition of metabolic syndrome included albuminuria as one of the diagnostic components.[7] However, albuminuria was not considered as a key component in defining metabolic syndrome in the subsequent updates; although its possible supportive role was recognized in the IDF definition.[8–12]

SGLT2 inhibitors underline the pathophysiological role of the kidneys, in not only dysglycemia, but also several vasculo-metabolic outcomes. The fact that SGLT2-inhibitor therapy generally does not predispose to hypoglycemia, suggests the pathological upregulation of SGLT2 activity in diabetic kidneys.[53] This upregulated SGLT2 activity also contributes to glycemia levels. Further, the transporter upregulation results in increased activity of the sodium–potassium ATPase pump in the proximal tubule.[54] This leads to increased metabolic stress in the renal cortex, facilitating the progression of chronic kidney disease. Following SGLT2 upregulation, the altered tubulo-glomerular feedback, hyper-filtration, progressive renal function decline, and fluid retention, result in several vasculo-metabolic effects in the body.[42]

SGLT2 inhibitors act directly at the level of the kidneys, and mediate glycemic and vascular effects. These effects are evident by improvements in glycemia, blood pressure, albuminuria, eGFR decline, and CV and renal outcomes, as described earlier.[13–20] Further, the vascular effects of SGLT2 inhibitors extend even at lower eGFR levels, wherein the glycemic effects are insignificant.[43,46] This discordance between the vascular and glycemic effects of SGLT2-inhibitor therapy in patients with lower eGFR levels, suggests a key role of the kidneys in maintaining vascular homeostasis.

The vasculo-protective effects of SGLT2 inhibitors extend to the macrovasculature, the microvasculature, and the myocardium.[16–19,42,46] Additionally, although the microvascular and macrovascular complications of T2DM arise from considerably distinct pathological mechanisms, albuminuria is possibly a unifying link for this vasculo-metabolic axis. Although the two renal markers of albuminuria and eGFR independently predict the risks of renal and vascular outcomes,[55,56] albuminuria remains a key indicator of renal and vascular pathology in metabolic disease.

SGLT2-inhibitor therapy acts as a unifying intervention at the vascular, myocardial, and metabolic axis. This abductive reasoning prompted by the observations with SGLT2 inhibitors, helps in delineating the pathophysiology of metabolic syndrome. Thus, we believe that the presence of albuminuria may have greater implications in recognizing the existence of metabolic syndrome, than presently believed. We support the earlier propositions for considering albuminuria as a key defining component of metabolic syndrome. ❏

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