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Review

The Impact of Sodium–Glucose Co-Transporter 2 Inhibitors on Systemic and Cardiac Cellular Metabolism: A Comprehensive Review

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Abstract

Sodium–glucose co-transporter 2 (SGLT2) inhibitors have emerged as major therapeutic agents for cardiometabolic disease, demonstrating cardiovascular and renal protection that extends beyond glucose lowering. Although the primary mechanism of these inhibitors is to block renal glucose reabsorption, increasing evidence suggests that systemic and cellular metabolic adaptations may underpin many of their pleiotropic benefits. Proposed mechanisms include altered substrate utilisation, increased ketone body production, reduced adiposity, and modulation of nutrient-sensing pathways. In addition, emerging data indicate that microRNAs (miRNAs) may contribute to SGLT2 inhibitor-mediated metabolic reprogramming and cardioprotection. This narrative review synthesises clinical and pre-clinical evidence on the metabolic effects of SGLT2 inhibitors and their potential contribution to cardiovascular protection. Clinical studies assessing body weight, body composition, and adipose tissue distribution were reviewed, and the evidence consistently showed modest weight reduction, with preferential reductions in fat mass and visceral adiposity. These changes have been linked to improvements in insulin sensitivity, inflammatory signalling, and overall metabolic homeostasis. Mechanistic hypotheses linking SGLT2 inhibition to cardiovascular benefit were explored, including the "fuel shift" hypothesis, whereby increased circulating ketone bodies may improve myocardial energy efficiency and mitochondrial function, as well as fasting-mimetic and nutrient-deprivation signalling pathways involving adenosine monophosphate (AMP)-activated protein kinase activation, autophagy, and altered insulin/glucagon balance. Pre-clinical studies involving animal and cellular models further demonstrated tissue-specific metabolic adaptations affecting cardiac, hepatic, renal, and adipose tissue metabolism, including modulation of mitochondrial energetics, oxidative stress, and substrate utilisation. Finally, the review examines the emerging role of miRNAs in regulating nutrient metabolism, mitochondrial function, fibrosis, and inflammatory signalling, with growing evidence identifying several metabolically relevant miRNAs that are modulated by SGLT2 inhibitors. Current evidence supports metabolic reprogramming as a central, potentially key mechanism that can explain the cardiovascular benefits of SGLT2 inhibitors. Clinical and experimental findings collectively demonstrate that SGLT2 inhibition induces coordinated systemic and cellular metabolic adaptations that extend beyond glycaemic control. Further translational studies integrating metabolic phenotyping, molecular signalling, and miRNA profiling are needed to clarify causal mechanisms and identify novel therapeutic targets within these pathways.

Keywords: sodium-glucose transporter 2 inhibitors; metabolism; biomarkers; adiposity; body composition; microRNAs; inflammation

1. Introduction

The global burden of type 2 diabetes mellitus (T2DM) continues to rise and is strongly associated with an increased risk of cardiovascular disease, heart failure (HF), and chronic kidney disease (CKD), which collectively account for most morbidity and mortality in this population [1]. Historically, therapeutic strategies have focused primarily on glycaemic control, but recent advances have prioritised mitigating cardiovascular and renal risks by addressing the broader pathophysiological processes underpinning cardiometabolic disease. In this context, sodium–glucose co-transporter 2 (SGLT2) inhibitors emerged and have since transformed the management of not only T2DM, but also HF and CKD. Initially developed to lower blood glucose by promoting glycosuria through inhibition of SGLT2 in the proximal tubule, these agents soon demonstrated robust and reproducible benefits in cardiovascular and renal outcomes. Among the earliest and most influential studies, the EMPA-REG OUTCOME trial [2] demonstrated that empagliflozin significantly reduced cardiovascular mortality and hospitalisation for HF in patients with established cardiovascular disease and T2DM. Notably, the reduction in HF hospitalisation was rapid in onset and sustained over time, suggesting mechanisms that extend beyond structural vascular changes or long-term glycaemic control. Subsequently, the DAPA-HF [3], EMPEROR-

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Reduced [4], DELIVER [5] and EMPEROR-Preserved [6] trials consistently demonstrated that these benefits extended to patients without T2DM, with substantial reductions in major adverse cardiovascular events (MACE), cardiovascular death and HF hospitalisations across the entire spectrum of HF irrespective of left ventricular ejection fraction. A recent retrospective analysis of whole-exome sequencing data from the DECLARE-TIMI 58 trial [7] even suggests that carriers of a pathological cardiomyopathy genetic variant responded better to dapagliflozin, raising the possibility of SGLT2 inhibitor therapy as a preventive measure to delay the onset of clinical HF [8].

A striking feature of these observations is the apparent dissociation between glycaemic control and clinical benefit. Cardiovascular improvements after SGLT2 inhibition often emerge early after treatment initiation and appear disproportionately large relative to modest reductions in glycated haemoglobin (HbA1c). Furthermore, beneficial effects have been reported in populations without significant hyperglycaemia, suggesting that the protective mechanisms are independent of glucose reduction. This paradox has driven considerable interest in identifying alternative pathways through which SGLT2 inhibitors exert their protective effects. Proposed mechanisms include haemodynamic improvements via natriuresis and mild diuresis (reducing preload and afterload) [9], suppression of inflammation and oxidative stress [10], modulation of autonomic function [11], and favourable effects on endothelial function [12]. Despite extensive investigation, the exact mechanisms underlying the full spectrum of cardiovascular benefits remain incompletely understood and are likely multifactorial.

Among the leading hypotheses, those centred on metabolic changes, both systemic and at the cardiac cellular level, carry particular credibility because these changes align with observed clinical timelines, the primary action of the drug class on renal glucose and sodium handling, and downstream effects on energy substrate utilisation and tissue remodelling. From a systemic perspective, SGLT2 inhibition induces a negative energy balance through glycosuria, accompanied by shifts in substrate utilisation, including increased lipid oxidation and enhanced ketone body production. At the cardiac cellular level, metabolic hypotheses primarily focus on reprogramming myocardial energy utilisation and modulating ion channels. Insights into these processes are derived from both clinical and preclinical studies, each offering complementary perspectives. Clinical investigations provide evidence of phenotypic changes, including reductions in body weight, modifications in body composition, and alterations in circulating metabolic substrates. In contrast, preclinical models allow detailed interrogation of tissue-specific and cellular mechanisms that are not readily accessible in human studies.

The following sections review the clinical evidence on the metabolic effects of SGLT2 inhibitors, beginning with changes in body weight and body mass index (BMI), followed by an in-depth examination of body composition metrics, including fat mass (FM), fat percentage, fat-free/lean mass, visceral and subcutaneous adiposity, and epicardial fat, assessed via dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), computed tomography (CT) or magnetic resonance imaging (MRI), and related non-invasive methodologies. This review also examines the preclinical evidence regarding the cellular signalling and energy metabolic changes induced by SGLT2 inhibitors. An additional, emerging layer of complexity is provided by microRNAs (miRNAs), which function as key post-transcriptional regulators of gene expression and play critical roles in metabolic homeostasis. This review then explores the metabolic effects of SGLT2 inhibitors across multiple levels of biological organisation and the emerging role of miRNAs as potential mediators of these effects. This evidence will form a critical foundation for evaluating how metabolic reprogramming may contribute to the cardiovascular protection and pleiotropic effects observed with SGLT2 inhibitors.

2. SGLT2 Inhibitors and Systemic Metabolism

There is a well-established association between diabetes and sarcopenic obesity [13]. Sarcopenic obesity is a syndrome characterised by the coexistence of low muscle mass (sarcopenia) and excess fat (obesity) [14]. Obesity is also an independent risk factor for cardiovascular disease and its adverse outcomes [15]. Body composition analysis provides a more detailed understanding of physical health by breaking down body weight into metrics such as FM, fat-free mass (FFM), muscle mass and fat percentage [16]. SGLT2 inhibitors have been shown to cause direct weight loss through their glycosuric effect, as well as a beneficial reduction in adiposity via adipocyte dysfunction [17].

The “insulin–glucagon axis” hypothesis emphasises that endocrine regulation is the primary driver of metabolic reprogramming. SGLT2 inhibition in the kidneys induces glycosuria, lowering plasma glucose levels and, in turn, reducing insulin secretion and circulating insulin levels. The resulting reduction in insulin lifts inhibition of glucagon secretion by pancreatic α-islet cells, thereby lowering the plasma insulin–glucagon ratio. This relative hypoinsulinaemia relaxes inhibition of lipolysis in adipose tissue, thereby releasing free fatty acids (FFAs) into the circulation as an alternative energy source to glucose [18]. This supports the “fuel shift” hypothesis, which proposes that SGLT2 inhibition drives a transition from glucose-dependent metabolism to increased reliance on fatty acids and ketone bodies. Increased lipolysis and lipid oxidation in the liver lead to ketogenesis, raising circulating levels of ketone bodies, particularly β-hydroxybutyrate, which yields more adenosine triphosphate (ATP) than glycolysis [19]. This metabolic shift from glycolysis towards FFA oxidation and ketone body utilisation as a more efficient

energy source, may contribute to the reduction in FM and the overall cardiovascular protection seen with SGLT2 inhibitor therapy.

Furthermore, the myocardium is metabolically flexible, preferentially oxidising ketones, which are a more oxygen-efficient fuel than fatty acids [20]. In conditions where energetic efficiency is impaired, such as HF, this metabolic shift could improve myocardial work output per unit of oxygen consumed. Importantly, this hypothesis does not suggest that ketones are simply an alternative fuel, but rather that ketones represent a metabolically advantageous substrate under stress conditions, potentially enhancing mitochondrial efficiency and reducing oxidative stress. The "adiposity reduction" hypothesis is similar but conceptually distinct, and centres on changes in body composition and adipose tissue biology. SGLT2 inhibitors consistently produce modest weight loss, but, more importantly, these inhibitors have been shown to produce preferential reductions in visceral adiposity [21]. Visceral fat is metabolically active and strongly linked to systemic inflammation, insulin resistance, and adverse cardiovascular outcomes [22]. Thus, a reduction in visceral fat may be associated with downstream improvements in cardiometabolic risk, independent of total weight loss. In addition to simple FM reduction, there is growing interest in qualitative changes within adipose tissue, including improved adipokine profiles, reduced inflammatory signalling, and possible induction of "browning" in white adipose depots [23]. Collectively, these changes may help create a more favourable systemic metabolic environment, with reductions in lipotoxicity and improved substrate delivery to the heart.

2.1 SGLT2 Inhibitors on Body Weight and BMI

In major cardiovascular outcome trials such as EMPA-REG OUTCOME [2] (empagliflozin) and DECLARE-TIMI 58 [24] (dapagliflozin), mean weight loss typically ranged from ~2–3 kg over 6–12 months, with early reductions observed within weeks of initiation. In 2021, a meta-analysis of five randomised controlled trials (RCTs) focused on weight reduction with SGLT2 inhibitors in overweight and obese populations without T2DM and reported a mean weight reduction of –1.62 kg (95% confidence interval (CI): –2.38 to –0.85 kg) with SGLT2 inhibitors compared with placebo [25]. A 2022 meta-analysis of 116 RCTs included patients using either sodium–glucose co-transporter 1 (SGLT1) or SGLT2 inhibitors irrespective of diabetic status and reported a reduction in mean weight of –1.79 kg (95% CI: –1.93 to –1.66 kg) and a reduction in BMI of –0.71 kg/m^2 (95% CI: –0.94 to –0.47 kg/m^2) versus placebo [26]. These effects were consistent across diabetes status, follow-up duration, comorbidities, and individual agents, with some dose-response relationships noted. SGLT1/2 dual inhibitors were associated with slightly greater weight reduction than selective SGLT2 inhibitors. A 2023 systematic review and meta-analysis of 25 RCTs (n = 2286) in T2DM with sarcopenia reported a weighted mean difference (WMD) for body weight of –2.74 kg (95% CI: –3.26 to –2.23 kg) and for BMI of –0.72 kg/m^2 (95% CI: –0.95 to –0.49 kg/m^2) with SGLT2 inhibitor therapy [27]. Weight loss has also been observed with SGLT2 inhibitor therapy in HF, with greater reductions seen with higher baseline BMIs [28]. Weight loss followed a biphasic pattern, with an initial rapid, largely fluid-related phase, followed by a more gradual, sustained phase driven by fat loss [29]. Hence, SGLT2 inhibitors may not be suitable as exclusive weight-loss medications due to their relatively modest effects on body weight; however, the impact on weight and BMI is consistent across different disease spectra. A summary of the clinical evidence is shown in Table 1 (Ref. [3,21,24,25,26,27,30,31,32]).

2.2 SGLT2 Inhibitors and Body Composition

As mentioned in the previous section, the observed reduction in weight with SGLT2 inhibitors is modest and less than predicted from caloric loss alone, suggesting compensatory mechanisms such as increased energy intake and metabolic adaptation, may be involved [33]. Furthermore, the maintenance of body weight reduction over the first few months of therapy suggests that these changes may reflect more sustained alterations in peripheral and visceral composition. Importantly, changes in body composition are more relevant than absolute weight loss. Clinical studies employing DEXA and MRI have demonstrated that weight reduction is predominantly attributable to loss of FM rather than lean tissue. A 2012 study demonstrated that weight loss observed with the addition of dapagliflozin to standard therapy in T2DM was primarily attributable to a reduction in overall FM, with a preferential reduction in visceral rather than subcutaneous adiposity [30]. In 2014, a double-blind, placebo-controlled RCT involving 140 patients with T2DM concluded that SGLT2 inhibitor therapy resulted in an average reduction in FM of 2.80 kg, out of a total weight reduction of 4.54 kg, measured by DEXA, with the reduction maintained consistently over the 102-week follow-up period [34]. Similar results were reported for canagliflozin over 104 weeks by Blonde et al. [35] in 2016, with a large fraction of the weight loss attributable to a reduction in FM. In 2019, a Japanese RCT on ipragliflozin employed both DEXA and BIA for composition analysis and demonstrated sustained reduction in total FM, with preservation of muscle mass and bone mineral content after 24 weeks of therapy [31]. A meta-analysis in 2022 reviewing 18 RCTs concluded that alongside a statistically significant reduction in FM, SGLT2 inhibitors specifically led to reductions in visceral fat area (VFA) [–14.79 cm^2, 95% CI: –24.65 to –4.93; p = 0.003] and subcutaneous fat area (SFA) [–23.27 cm^2, 95% CI: –46.44 to –0.11; p = 0.05] [36]. This was corroborated again in 2023 by Zhang et al. [27], who reported statistically significant reductions in FM, fat percentage, VFA, and SFA across 25 RCTs involving patients

Table 1. Clinical evidence of key trials and meta-analyses on the effect of SGLT2 inhibitor therapy on body weight.

References	Design and SGLT2 inhibitors	Key findings
Bolinder et al. (2012) [30]	RCT, n = 182; dapagliflozin	Mean difference –2.08 kg (95% CI: –2.84 to –1.31; $p < 0.0001$)
CANVAS Programme Neal et al. (2017) [32]	RCT, n = 10,142; canagliflozin	Mean difference ~ –1.6 kg (95% CI: –1.7 to –1.51; $p < 0.001$)
DECLARE-TIMI 58 Oyama et al. (2022) [24]	RCT, n = 17,160; dapagliflozin	Pooled mean difference ~ –1.8 kg (95% CI: –2.04 to –1.58) calculated by random-effects (DerSimonian-Laird) inverse variance pooling of the reported BMI-subgroup estimates
DAPA-HF McMurray et al. (2019) [3]	RCT, n = 4744; dapagliflozin	Mean difference ~ –0.87 kg (95% CI: –1.11 to –0.62) at 8 months, $p < 0.001$
Inoue et al. (2019) [31]	RCT, n = 49; ipragliflozin vs. control	Mean difference –2.56 kg (95% CI: –3.67 to –1.45; $p < 0.0001$)
Cho et al. (2021) [25] meta-analysis	5 RCTs, n = 692; overweight and obese patients without T2DM	–1.62 kg (95% CI: –2.38 to –0.85)
Cheong et al. (2022) [26] meta-analysis	116 RCTs, n = 98,497; heterogeneous population with and without T2DM	–1.79 kg (95% CI: –1.93 to –1.66; $p < 0.001$)
Wang et al. (2023) [21]	18 RCTs, n = 1063, patients with T2DM	Mean difference –2.60 kg (95% CI: –3.30 to –1.89; $p < 0.0001$)
Zhang et al. (2023) [27] meta-analysis	25 RCTs, n = 2286; patients with T2DM and sarcopenia	Mean difference –2.74 kg (95% CI: –3.26 to –2.23; $p < 0.01$)

SGLT2, sodium–glucose co-transporter 2; RCT, randomised controlled trial; BMI, body mass index; T2DM, type 2 diabetes mellitus; CI, confidence interval.

with T2DM and sarcopenia. Both meta-analyses reported a minor reduction in lean mass, highlighting the potential risk of muscle loss with SGLT2 inhibitors. However, a more recent meta-analysis from 2025 demonstrated preservation of FFM when the follow-up period was extended to 12 months, indicating stabilisation of metabolism over time [37].

In addition to overall adiposity, SGLT2 inhibitors influence ectopic fat stores, which are closely linked to insulin resistance and cardiovascular disease. A small-scale RCT in 2018 demonstrated that adding empagliflozin to standard therapy in 50 patients with T2DM and metabolic dysfunction-associated steatotic liver disease (MASLD) reduced hepatic fat content measured by MRI, with a significant reduction from 16.2% to 11.3% ($p < 0.0001$) in the empagliflozin group compared with the control group [38]. These findings were replicated by another group using dapagliflozin, which attenuated liver fibrosis [39]. Another 2021 study used hepatic fibroscans to assess hepatic steatosis and reported significant reductions in hepatic fat content and VFA with empagliflozin compared with pioglitazone and placebo [40]. Clinical evidence also indicates that this benefit extends to epicardial adiposity, which has been reported as an independent predictor of coronary artery disease [41]. Sato et al. [42] reported a significant reduction in epicardial adipose tissue (EAT) measured by CT with dapagliflozin at 6 months compared with conventional therapy for T2DM. Recently, a sub-study reported a short-term reduction in EAT on positron emission tomography (PET)/CT at 13 weeks with empagliflozin 25 mg/day in patients with T2DM compared with placebo, along with favourable changes in FM and left ventricular mass [43]. A list of clinical evidence pertinent to changes in body composition and adiposity is summarised in Table 2 (Ref. [21,27,30,31,34,35,36,38,42,43,44]).

2.3 SGLT2 Inhibitors on Adipose Tissue Function

These changes in adiposity are accompanied by alterations in adipose tissue function and endocrine signalling. Treatment with SGLT2 inhibitors has been associated with increases in circulating adiponectin and reductions in leptin concentrations, resulting in an improved adiponectin-to-leptin ratio, a biomarker of enhanced metabolic health [23]. Over 52 weeks, 300 mg/day of canagliflozin significantly lowered serum leptin by ~25% and increased adiponectin by ~17% compared with glimepiride [45]. A subsequent 2019 meta-analysis of 10 RCTs in patients with T2DM demonstrated that SGLT2 inhibitor treatment significantly decreased circulating leptin levels and increased circulating adiponectin levels compared with placebo or other comparators [46]. Adipokines are a heterogeneous group of proteins comprising hormones and cytokines, including, but not limited to, leptin, adiponectin, interleukins (IL-1β and IL-6), tumour necrosis factor alpha (TNFα), fibroblast growth factor 21 (FGF21), and monocyte chemoattractant protein-1 (MCP-1) [47]. Adiponectin is an insulin-sensitising, anti-inflammatory adipokine that promotes fatty acid oxidation, reduces ectopic fat accumu-

Table 2. Clinical evidence from key trials and meta-analyses on the effect of SGLT2 inhibitor therapy on body composition and adiposity.

References	Design and SGLT2 inhibitors	Key findings
Bolinder et al. (2012) [30]	RCT, n = 182; dapagliflozin	FM: –1.48 kg (95% CI: –2.22 to –0.74; $p = 0.0001$) VAT volume: –258.4 cm^3 (95% CI: –448.1 to –68.6; $p = 0.0084$) SAT volume: –184.9 cm^3 (95% CI: –359.7 to –10.1; $p = 0.0385$)
Bolinder et al. (2014) [34]	RCT, n = 182 (140 completed) dapagliflozin	FM reduction: –2.80 kg out of a total body weight reduction of –4.54 kg
Blonde et al. (2016) [35]	RCT, n = 211; canagliflozin vs. placebo	FM reduction of ~ –2.5 to-3.2 kg at 26 weeks; greater relative reduction in VAT over SAT
Inoue et al. (2019) [31]	RCT, n = 49; ipragliflozin in T2DM	FM: –2.06 kg (95% CI: –2.85 to –1.26; $p < 0.0001$) by DEXA –1.94 kg (–3.28 to –0.60; $p = 0.0056$) by BIA
Pan et al. (2022) [36] meta-analysis	18 RCTs, n = 1430; patients with T2DM	FM: –1.16 to –1.49 kg FP: –1.28 to –1.50% VAT area: –14.79 cm^2 (95% CI: –24.65 to –4.93, $p = 0.003$) SAT area: –23.27 cm^2 (95% CI: –46.44 to –0.11, $p = 0.05$)
Wang et al. (2023) [21] meta-analysis	18 RCTs, n = 1063; patients with T2DM	Standard mean differences: VAT: –1.42 (95% CI: –2.02 to –0.82; $p < 0.0001$) SAT: –1.21 (95% CI: –1.99 to –0.42; $p = 0.003$) Hepatic fat: –0.70 (95% CI: –1.20 to –0.20; $p = 0.006$)
Zhang et al. (2023) [27] meta-analysis	25 RCTs, n = 2286; patients with T2DM and sarcopenia	FM –1.49 kg (95% CI: –2.18 to –0.80; $p < 0.01$) FP: –1.28% (95% CI: –1.83 to –0.74; $p < 0.01$) VAT area: –19.52 cm^2 (95% CI: –25.90 to –13.14; $p < 0.01$) SAT area: –19.11 cm^2 (95% CI: –31.18 to –7.03; $p = 0.002$)
Masson et al. (2021) [44] meta-analysis	3 RCTs, n = 64 (SGLT2i) vs n = 62 (standard therapy)	EAT: SMD –0.82 (95% CI: –1.49 to –0.15; $p < 0.0001$)
Kuchay et al. (2018) [38]	RCT, n = 50; T2DM and NAFLD, empagliflozin vs. control	Hepatic FP reduction: –4.9% vs. –0.9%; $p < 0.0001$
Sato et al. (2018) [42]	RCT, n = 40; T2DM and CAD, dapagliflozin vs. control	Change in EAT volume: –16.4 cm^3 vs. 4.7 cm^3; $p = 0.01$
Brandt-Jacobsen et al. (2023) [43]	RCT, n = 90; T2DM with high CV risk, empagliflozin vs. placebo	Change in cardiac adipose tissue: –5.4 mL vs. +7.0 mL; between-group treatment effect: −12.41 mL (95% CI: −23.83 to −0.99; $p = 0.034$)

FM, fat mass; FP, fat percentage; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; EAT, epicardial adipose tissue; CV, cardiovascular; DEXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; SMD, standard mean difference; NAFLD, non-alcoholic fatty liver disease; CAD, coronary artery disease.

lation, and exerts direct cardioprotective effects [48]. In contrast, elevated leptin in obesity reflects leptin resistance and is associated with increased sympathetic activity, inflammation, and cardiovascular remodelling [49]. Therefore, the shift towards higher adiponectin and lower leptin levels indicates a transition towards less-inflamed, more metabolically favourable adipose tissue.

In parallel, reductions in pro-inflammatory cytokines such as TNFα and IL-6 have been reported, suggesting attenuation of chronic low-grade inflammation within adipose tissue. The CANVAS trial reported decreased plasma concentrations of TNF receptors (TNFR1 and TNFR2) following treatment with canagliflozin [50]. In another small-scale trial involving patients with both T2DM and HF with reduced ejection fraction (HFrEF), empagliflozin was associated with a significant reduction in IL-6 after 3 months [51]. A 2023 meta-analysis reported significant decreases in circulating IL-6 levels with dapagliflozin, empagliflozin, and canagliflozin, with dapagliflozin showing greater potency and a larger reduction than the other two formulations [52]. A 2019 preclinical study in diseased mice demonstrated that canagliflozin also increased hepatic and plasma levels of FGF21, a fasting-induced, peroxisome proliferator-activated receptor alpha (PPARα)-regulated hepatokine that serves as a major metabolic regulator by stimulating glucose uptake in an insulin-

independent manner and activating hepatic lipid oxidation and ketogenesis [53]. The anti-inflammatory properties of SGLT2 inhibitors have been suggested to be mediated by macrophages. Notably, macrophages can respond to cytokines and hormones to adopt either proinflammatory (M1) or anti-inflammatory (M2) phenotypes *in vitro*; however, *in vivo*, their properties are more malleable, and macrophages may not conform to any single phenotype [54]. Preclinical models, *e.g.*, in Zucker diabetic fatty rats [55] or high-fat diet mice [56], show that empagliflozin and other SGLT2 inhibitors reduce expression of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), associated with a decrease in proinflammatory M1 macrophage markers, and promote a shift to anti-inflammatory M2 macrophages, which are stimulated by IL-4 and IL-13 and release IL-10 and transforming growth factor beta (TGF-β), aiding tissue repair [57]. These findings suggest that the systemic anti-inflammatory effects of SGLT2 inhibitors independently contribute to adipose tissue metabolism and improved energy utilisation, thereby resulting in measurable changes in body composition.

Overall, clinical evidence supports modest, sustained reductions in weight and BMI with SGLT2 inhibitors, driven primarily by FM and visceral/ectopic fat loss, with relative preservation (or only modest reduction) of fat-free/lean mass in many analyses. SGLT2 inhibitors produce favourable changes in body weight and composition primarily through caloric loss from glycosuria and associated osmotic diuresis, with downstream effects on fat metabolism and energy balance. However, the evidence is limited by small sample sizes, short and variable follow-up durations, heterogeneity in the methodologies used for composition assessment, and the fact that the reported results are largely secondary outcome measures or subgroup analyses. Furthermore, disentangling the direct pharmacological effects of SGLT2 inhibition from indirect effects related to caloric loss, changes in dietary intake, and behavioural adaptation remains challenging. Nevertheless, these systemic metabolic effects provide a plausible mechanistic link between SGLT2 inhibition and cardiovascular protection, although definitive translational evidence establishing causality remains sparse.

3. SGLT2 Inhibitors and Cellular Metabolism

Perhaps the most integrative concept is the "nutrient deprivation mimicry" hypothesis, which frames SGLT2 inhibition as a pharmacological analogue of caloric restriction or intermittent fasting. Despite adequate caloric intake, the glycosuria creates a perceived energy deficit at the cellular level. This triggers conserved nutrient-sensing pathways, including the signal transducer and activator of transcription 3 (STAT3) signalling pathway, up-regulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), inhibition of mechanistic target of rapamycin complex 1 (mTORC1) signalling, and promotion of autophagy. These pathways are central to cellular homeostasis, promoting mitochondrial biogenesis, improving protein quality control, and enhancing resistance to oxidative and metabolic stress. These adaptations can potentially improve injury resilience in cardiomyocytes, thus slowing the progression of HF. Importantly, this hypothesis provides a unifying framework that links systemic metabolic changes (*e.g.*, weight loss, ketogenesis) to intracellular processes (*e.g.*, autophagy, mitochondrial function), suggesting that the benefits of SGLT2 inhibitors arise from coordinated multi-level reprogramming rather than a single dominant mechanism.

In general, cardiac myocytes rely more on FFA metabolism than on glucose as their primary energy source, with evidence of impaired FFA uptake and increased ketone body metabolism in failing hearts [58]. In the failing or diabetic heart, inefficient substrate utilisation is often characterised by uncoupled glycolysis, impaired fatty acid oxidation, and reduced ATP production, which contribute to contractile dysfunction. Ketone bodies provide an alternative, oxygen-efficient fuel source for cardiac myocytes, with a direct relationship between circulating ketone levels and the degree of ketone body uptake and oxidation [20]. In rodent models of diabetes and HF, treatment with empagliflozin or dapagliflozin induced a shift in myocardial substrate utilisation away from glucose towards fatty acids and ketone bodies, particularly β-hydroxybutyrate [59,60]. Santos-Gallego et al. [61] used a porcine model of HF and demonstrated that empagliflozin increased myocardial ketone uptake and oxidation, accompanied by reverse myocardial remodelling and improved left ventricular function. Similarly, Verma et al. [62] reported enhanced myocardial energetics and ATP production in diabetic mice treated with empagliflozin. Likewise, other animal model studies have demonstrated an association between a range of SGLT2 inhibitors and increased ketone body levels and utilisation (Table 3, Ref. [60,61,62,63,64,65]).

At the mitochondrial level, SGLT2 inhibitors have been shown to enhance oxidative phosphorylation, reduce reactive oxygen species (ROS) generation [66], and activate several key nutrient-signalling pathways [67,68]. Mitochondrial dysfunction, characterised by reduced ATP synthesis, is strongly associated with T2DM, metabolic syndrome, and cardiovascular disease [69,70,71,72]. The STAT pathway plays an integral role in inflammation, tissue damage, and fibrosis. STAT3 activation has been shown to confer protective effects on the heart and is associated with various cardiac pathologies, ranging from post-myocardial infarction (MI) recovery [73,74] to protection against doxorubicin-induced cardiomyopathy [75]. STAT3 deletion in cardiac myocytes in pregnant mice resulted in a form of peripartum cardiomyopathy [76]. In macrophages, STAT factors play a crucial role in driving polarisation to the M2 phenotype and in controlling the expression and

Table 3. Animal studies demonstrating increased ketone body production and utilisation associated with SGLT2 inhibitor therapy.

References	Design and SGLT2 inhibitors	Key findings
Verma et al. [62]	Diabetic mice; empagliflozin	Increased systemic FFA oxidation; increased KB utilisation; increased cardiac ATP production
Santos-Gallego et al. [61]	Ischaemic HF in non-diabetic pigs; empagliflozin	Increased circulating KB levels; increased KB oxidation; enhanced mitochondrial energetics
Yurista et al. [60]	Non-diabetic Sprague-Dawley rats with induced MI; empagliflozin	Increased circulating KB levels; increased mitochondrial KB transporter expression; increased cardiac ATP production
Wallenius et al. [63]	Obese Zucker rats; dapagliflozin	Increased systemic FFA mobilisation; enhanced hepatic β-oxidation and ketogenesis; increased plasma β-hydroxybutyrate (BHB) levels
Goedeke et al. [64]	Chow-fed Sprague-Dawley rats and ischaemic HFrEF models; dapagliflozin	Improved KB oxidation; marked increase in KB levels after dapagliflozin exposure; improved substrate oxidation and cardiac function with chronic dapagliflozin therapy
Umezawa et al. [65]	Five healthy beagles; dapagliflozin	Marked increase in plasma KB levels

FFAs, free fatty acids; KBs, ketone bodies; ATP, adenosine triphosphate; HF, heart failure; HFrEF, HF with reduced ejection fraction; KB, ketone body; MI, myocardial infarction.

release of various cytokines. In infarcted rat hearts, dapagliflozin was shown to decrease circulating levels of the proinflammatory cytokines IL-1β, IL-6, and TNF-α and to inhibit the differentiation of macrophages into the proinflammatory M1 phenotype via STAT3 activation [77]. In another study on Coxsackie virus B3-induced myocarditis in mice, administration of dapagliflozin attenuated the severity of myocarditis and cardiac dysfunction, and shifted macrophage polarisation towards M2 at the expense of M1, via STAT3 signalling [78]. This was confirmed by observing the opposite effect with a specifically synthesised STAT3 inhibitor. SGLT2 inhibitor therapy was also strongly associated with suppression of nucleotide-binding domain, leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasome activity. NLRP3 is a protein predominantly expressed in macrophages that controls the release of IL-1β [79]. β-hydroxybutyrate has been shown to block NLRP3 inflammasome activity in mice [80]. Kim et al. [81] demonstrated in their prospective study that empagliflozin treatment was associated with increased β-hydroxybutyrate levels and concomitant reductions in IL-1β and TNF-α, consistent with attenuation of NLRP3 inflammasome activity.

SGLT2 inhibitors have also been shown to target the sirtuin family of proteins. Sirtuins are a family of seven signalling deacetylases (SIRT1–7) in human cells that regulate cellular health, metabolism, and ageing [82]. Intracellularly, sirtuins play a key role in regulating nuclear and mitochondrial activity and in attenuating oxidative stress [82]. In mice with streptozocin-induced diabetes, ischaemic renal injury was associated with reduced SIRT3 expression, and treatment with dapagliflozin induced favourable metabolic reprogramming and reduced cell death, accompanied by a restoration of SIRT3 expression [83]. Zhao et al. [84] observed improvement in SIRT3-mediated mitochondrial function with canagliflozin in salt-induced cardiac hypertrophy in Dahl salt-sensitive rats. Luo et al. [85] reported that SIRT3 activated autophagy, mediated by AMPK/Beclin1, following empagliflozin administration in mice with obesity-induced diastolic cardiac dysfunction. While SIRT3 is located in the mitochondrial matrix, SIRT1 is located in the cell's nucleus and is an integral part of the SIRT1/AMPK signalling pathway that drives cellular homeostasis and triggers mitochondrial function [86]. SIRT1 is down-regulated in cells with high insulin resistance, and increased SIRT1 expression correspondingly improves insulin sensitivity [87]. A leading hypothesis is that SGLT2 inhibitors activate SIRT1 and engage the SIRT1/AMPK signalling pathway. Evidence from preclinical models indicates that SGLT2 inhibitors activate AMPK, which suppresses anabolic processes such as lipogenesis and protein synthesis; promotes catabolic pathways such as glucose uptake, FFA, and ketone body oxidation [88,89]; and up-regulates peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 alpha (PGC-1α), widely regarded as the master regulator of mitochondrial biogenesis [90]. PPARγ is a transcription factor expressed primarily in adipose tissue that has been shown to induce FGF21, increase adiponectin levels and promote M2 polarisation in macrophages, all of which contribute to suppressing inflammation, improving energy generation and promoting repair [91].

Alongside AMPK activation, SGLT2 inhibitors also inhibit mTORC1 activation; mTORC1 acts as a master molecular switch linking nutrient signals to intracellular metabolic processes, promoting cell growth, tissue repair, and the synthesis of lipids and proteins [92]. mTORC1 dysregulation and hyperactivation have been implicated in a wide range of disease processes, including the development of diabetes, lipotoxicity and renal injury [92]. Thus, mTORC1 inhibition promotes autophagy, which is crucial for tissue survival during periods of stress, particularly in

dynamic organs such as the heart and kidney. In the absence of autophagy, damaged cellular components and dysfunctional organelles accumulate in the cytoplasm, exacerbating oxidative stress and leading to progressive organ damage [93]. Indeed, by promoting a metabolic shift towards ketone body oxidation, SGLT2 inhibitors can alter the AMP/ATP ratio and modulate the balance between the SIRT1/AMPK and mTORC1 signalling pathways.

Conversely, two recent murine studies have shown that the cardioprotective effects of SGLT2 inhibitors may not require the SGLT2 protein at all, thereby challenging the ketone hypothesis. Wu et al. [94] demonstrated that in global SGLT2 knockout mice, dapagliflozin still inhibited macrophage-mediated inflammation and alleviated cardiac fibrosis in MI and HF, despite no accompanying changes in systemic glucose and ketone levels. Berger et al. [95] corroborated this SGLT2-independence, demonstrating that empagliflozin improved cardiac function in SGLT2-null mice, with comparable changes in other systemic metabolic parameters in both wild-type and SGLT2-knockout mice. Recently, Chen et al. [96] demonstrated that the cardioprotective effects of empagliflozin were observed irrespective of SGLT2 status and were associated with improved cardiac energetics, up-regulated gene expression of mitochondrial metabolic pathways, and increased SIRT3 and GLUT4 protein expression. However, unlike previous studies with canagliflozin [88], Chen et al. [96] failed to demonstrate AMPK activation with empagliflozin, thereby concluding that modulation of the AMPK pathway may not be a mandatory mechanism underlying SGLT2 inhibitor-mediated cardioprotection and alluding to inter-drug differences within the SGLT2 inhibitor class. Therefore, while the nutrient-deprivation hypothesis, centred on ketone body oxidation and downstream pathway modification, offers an elegant and coherent explanation for the cardioprotective effects of SGLT2 inhibitors, these studies actively challenge that theory and instead point towards an off-target, and potentially direct, metabolic effect of these drugs. This scepticism is reinforced by the fact that systemic ketone levels follow a circadian pattern [97], with periods of prolonged fasting or starvation actively affecting the observed degree of ketonemia [98]. Chu et al. [99] hypothesised that a therapeutic β-hydroxybutyrate concentration of 1–3 mmol/L could be achieved with SGLT2 inhibitor therapy; however, an RCT by Pietschner et al. [100] demonstrated a markedly muted increase in β-hydroxybutyrate levels within the empagliflozin arm at 12 weeks (from 0.12 ± 0.22 mmol/L to 0.16 ± 0.18 mmol/L; $p = 0.017$). Furthermore, there was no statistically significant difference in the change in β-hydroxybutyrate levels between the empagliflozin and placebo groups ($p = 0.321$) [100].

In summary, these findings suggest that although the ketone hypothesis is compelling, this theory is unlikely to be the sole or even the dominant explanation for the cardioprotective effects of SGLT2 inhibitors. Emerging evidence of SGLT2-independent, off-target metabolic actions indicates that these drugs likely exert their benefits through a convergence of multiple overlapping mechanistic pathways.

4. SGLT2 Inhibitors and miRNAs in Metabolism

miRNAs are small non-coding RNAs with important gene-regulatory roles in many diseases and are considered among the most promising biomarkers for non-invasive diagnosis due to their high stability in body fluids and their role as “molecular fingerprints” of specific disease states [101]. miRNAs have been implicated in regulating lipid metabolism, insulin signalling, mitochondrial function and inflammatory pathways, all of which are relevant to cardiometabolic disease [102,103]. Recent preclinical evidence indicates that SGLT2 inhibitors can modulate the expression of specific miRNAs, raising the possibility that these molecules contribute to the metabolic reprogramming associated with this drug class.

Dysregulation of miRNA expression is a hallmark of metabolic diseases, including T2DM, obesity, and HF [104]. Interest in miRNAs in cardiology has grown in recent years, and differential regulation of miRNA expression has been identified and implicated in atrial and ventricular arrhythmias, cardiomyopathy and HF, valvular heart disease, atherosclerosis and coronary artery disease, hypertension, and systemic inflammation [104,105,106]. In diabetes, altered miRNA expression contributes to insulin resistance, β-cell dysfunction, and chronic inflammation. For instance, miR-29 has been shown to impair insulin signalling by targeting insulin receptor substrate-1 (IRS-1). In contrast, miR-33a targets insulin receptor substrate 2 (IRS-2) and triggers lipogenesis by suppressing SIRT6 expression [107,108]. Moreover, miR-33 is a well-characterised regulator of cholesterol transport and fatty acid oxidation, targeting the AMPK pathway [108]. Up-regulated miR-103 and miR-107 have been implicated in obesity and insulin resistance through modulation of caveolin-1 and insulin receptor signalling pathways [109]. Additionally, miR-34a has been shown to promote inflammation by suppressing SIRT1, mediated by the proinflammatory transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [110]. Furthermore, miR-34a is up-regulated in MI along with miR-92a, which inhibits angiogenesis and repair. Thus, deficiencies or inhibition of these miRNAs have been linked with reduced infarct size and improved survival of cardiac myocytes [111,112]. The miR-30 family has also been strongly linked to cardiovascular disease, with miRNA arrays in patients with HF demonstrating down-regulation of miR-30, and lower levels correlating with poorer one-year outcomes [113]. Meanwhile, miRNAs such as miR-21, miR-126, and miR-133 regulate processes including fibrosis, angiogenesis, and cardiomyocyte hypertrophy [114,115,116]. These molecules are not

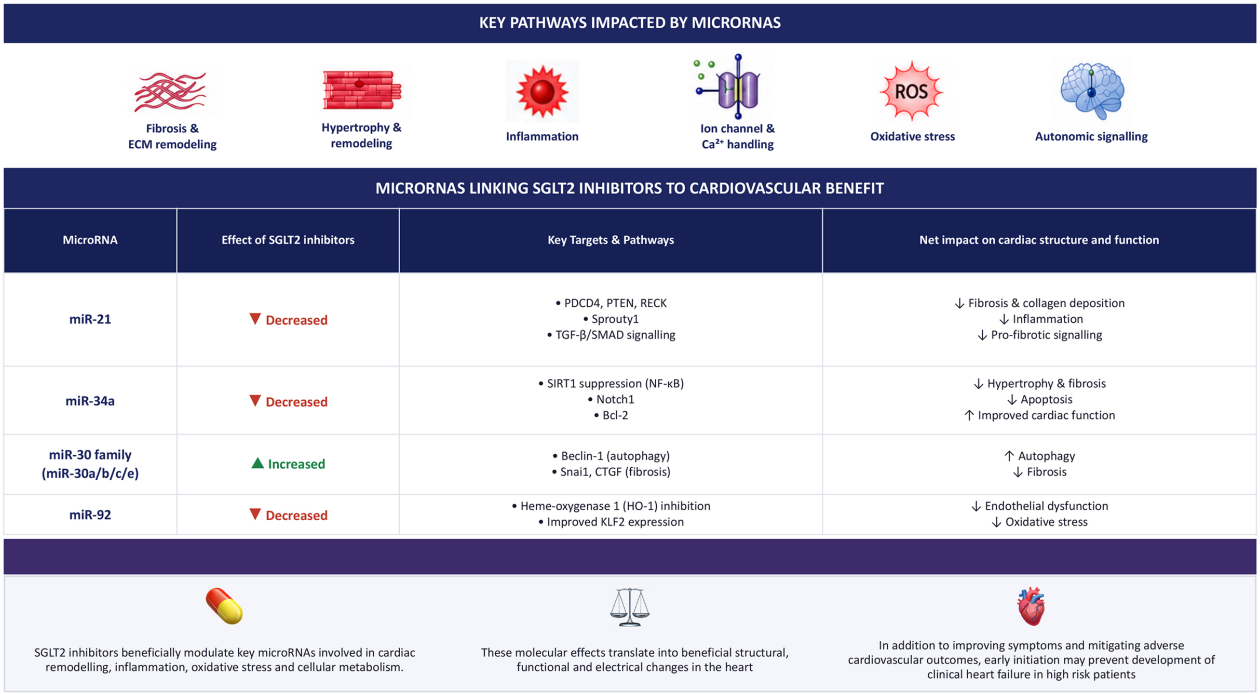


Fig. 1. MicroRNAs (miRNAs) linking SGLT2 inhibitors to cardiac epigenetics and cellular metabolism. Bcl-2, B-cell lymphoma 2; CTGF, connective tissue growth factor; ECM, extracellular matrix; KLF2, Krüppel-like factor 2; miRNAs, microRNAs; NF-κB, nuclear factor kappa B; Notch1, Notch receptor 1; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homolog; RECK, reversion-inducing cysteine-rich protein with kazal motifs; ROS, reactive oxygen species; SGLT2, sodium–glucose cotransporter 2; SIRT1, sirtuin 1; SMAD, SMAD family proteins; SNAI1, snail family transcriptional repressor 1; TGF-β, transforming growth factor beta.

only intracellular regulators but can also be secreted in extracellular vesicles, acting as endocrine-like mediators of inter-organ communication. This is particularly relevant in the context of metabolic therapies that exert systemic effects, such as SGLT2 inhibitors.

Empagliflozin has been shown to improve the miRNA signature of endothelial dysfunction in patients with heart failure with preserved ejection fraction (HFpEF) and diabetes [117]. Preclinical studies in hyperglycaemic mice by Ridwan et al. [118] in 2024 showed decreased relative expression of miR-21 and reduced expression of TGF-β1 and matrix metalloproteinase-2 (MMP-2) in the empagliflozin-treated group. An earlier preclinical study in Japan in 2022 demonstrated a similar alteration in the miRNA profile in rats treated with ipragliflozin [119]. A study comparing the effects of dapagliflozin versus hydrochlorothiazide noted up-regulation of miR-30 in the dapagliflozin arm, which would correlate with the positive HF outcomes observed with dapagliflozin [120]. A sub-study analysis of samples collected from the EMMY trial evaluating the effect of empagliflozin in acute MI, examined the impact on a select panel of miRNAs in relation to sirtuin expression [121]. Empagliflozin significantly altered sirtuin and miRNA expression, and miR-34a was associated with the largest number of sirtuin subtypes. Given that miR-34a suppresses SIRT1 and promotes apoptosis, cardiomyocyte survival and mitochondrial function can be improved by modulating miR-34a expression which may in part explain the protective effects of empagliflozin in an acute MI and HF setting [122]. While circulating miR-34a in this study by Nowak-Szwed et al [122] rose over 26 weeks in both empagliflozin-treated and placebo-treated post-AMI patients, there was no between-arm difference at follow-up ($p = 0.898$), suggesting that the change in miR-34a levels was in keeping with post-infarct convalescence (or other non-treatment factors) rather than an empagliflozin effect. Shen et al. [123] had previously demonstrated more conclusively in rodent models that treatment with empagliflozin resulted in noticeable reduction in inflammation and hepatic fibrosis through down-regulation in miR-34a expression.

The modulation of miRNAs by SGLT2 inhibitors provides a plausible mechanism for the coordinated metabolic reprogramming observed across tissues (Fig. 1). Meanwhile, by targeting key nodes in metabolic and signalling pathways, miRNAs can amplify or fine-tune the effects of upstream changes in nutrient availability on downstream hormonal signalling. For instance, the glycosuria-induced energy deficit and ketone shift created by SGLT2 inhibition activate SIRT1/AMPK and suppress mTOR signalling, leading to downstream changes in miRNA expression. These miRNAs, in turn, regulate genes involved in mitochondrial biogenesis, lipid oxidation, and autophagy,

reinforcing the shift towards a more oxidative and energy-efficient cellular state. Despite promising insights, several challenges limit current understanding of miRNA involvement in the action of SGLT2 inhibitors. First, most data are derived from animal models or small-scale human studies, limiting generalisability. Second, the pleiotropic nature of miRNAs, where a single miRNA can target multiple genes and a single gene can be targeted by multiple miRNAs, complicates mechanistic interpretation. Third, differences in tissue-specific expression and methodological variability in miRNA detection may pose additional hurdles. Future research should adopt an integrative translational approach that combines transcriptomics, metabolomics, and miRNA profiling in well-characterised human cohorts. Longitudinal studies assessing changes in miRNA expression alongside metabolic and clinical endpoints will be particularly valuable.

5. Conclusion

The hypotheses outlined throughout this review are not mutually exclusive; rather, each reflects overlapping components of a broader metabolic shift induced by SGLT2 inhibition. The fuel shift towards ketone utilisation, modulation of the insulin–glucagon axis, reduction in visceral and epicardial adiposity, and activation of nutrient-sensing pathways act in concert to improve cardiac energetics, reduce metabolic stress, and enhance cellular resilience. The integrated evidence supports the concept that SGLT2 inhibitors induce multi-level metabolic reprogramming, spanning systemic fuel utilisation to intracellular gene regulatory networks. Nonetheless, defining the relative contribution of each pathway remains a major challenge for future translational research and will be critical to further refining mechanistic understanding and identifying novel therapeutic targets.

Author Contributions

VA designed the study. VGL, SMZR, HS, MSD, DR, HM and FO reviewed and analyzed the literature. VA wrote the manuscript. VGL, SMZR, HS, MSD, DR, HM and FO contributed to the preparation and implementation of editorial changes to the manuscript. All authors have contributed to the preparation and implementation of editorial changes to the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Claude AI (Anthropic, USA) in order to edit and optimise the figures. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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