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Metabolism and Target Organ Damage

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# Glucose transporters in health and disease: from molecular mechanisms to therapeutic applications

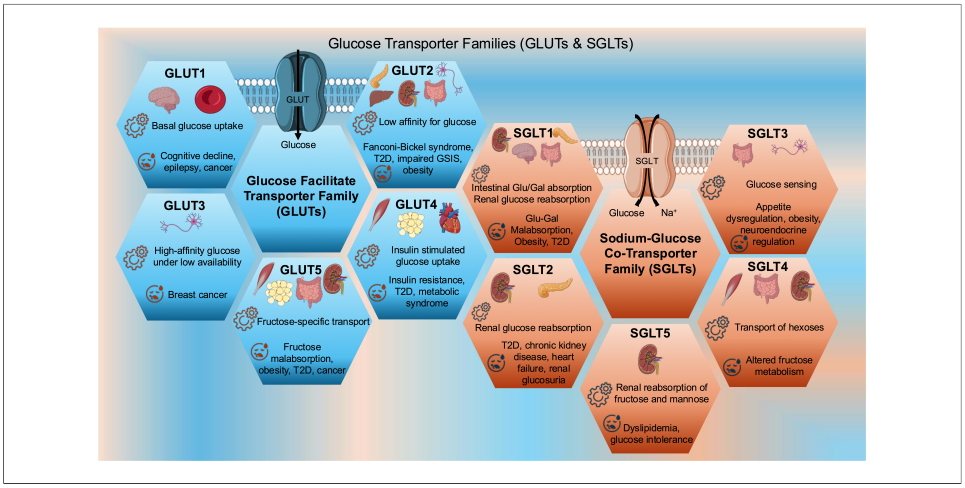
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## Abstract

The purpose of this review is to provide a comprehensive analysis of glucose transporters, integrating molecular mechanisms, physiological roles, and therapeutic applications across health and disease states. Glucose transport across cellular membranes, mediated by facilitative glucose transporters (GLUTs) and sodium-glucose cotransporters (SGLTs), represents a fundamental control point in glucose homeostasis. Since the initial discovery of specific membrane components for glucose transfer in 1948, our understanding has evolved substantially, revealing complex tissue-specific expression patterns and regulatory mechanisms. Recent structural biology advances, genetic studies, and clinical developments, particularly the success of SGLT2 inhibitors in treating type 2 diabetes and their unexpected benefits in heart failure and chronic kidney disease, have transformed our understanding of these essential proteins. This review examines the structural and functional properties of glucose transporters, their tissue-specific distribution and regulation, their roles in metabolic organs, and their dysfunction in various diseases. We specifically address unresolved questions regarding tissue-specific regulation, expanding roles in disease pathogenesis beyond diabetes, and emerging therapeutic strategies. By

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synthesizing recent technological advances, clinical implications, and areas of continuing controversy, this review provides a framework for understanding both the fundamental biology of glucose transporters and their growing therapeutic significance in metabolic diseases.

## INTRODUCTION

Glucose transport across cellular membranes constitutes a fundamental process in human metabolism and acts as a critical control point for energy homeostasis. Since LeFevre's pioneering hypothesis in 1948 that specific membrane components mediate glucose transfer across lipid bilayers[1], research has since uncovered complex, tissue-specific transporter families with distinct regulatory mechanisms and pathophysiological roles. Studies of erythrocyte plasma membranes in the 1970s confirmed protein-mediated transport[2], launching decades of investigation into these essential membrane transport proteins.

Two principal families facilitate cellular glucose transport: facilitative glucose transporters (GLUTs, SLC2 family) and sodium-glucose cotransporters (SGLTs, SLC5 family). GLUTs facilitate passive transport down concentration gradients through ATP-independent mechanisms, while SGLTs actively transport glucose against gradients using sodium-coupling and energy-dependent processes[3]. Both families regulate glucose homeostasis across multiple organ systems, including the brain, liver, kidney, intestine, pancreas, and muscles. Each transporter demonstrates distinct kinetic properties and tissue-specific expression patterns suited to their physiological roles[4]. Later discovery of the SWEET class of glucose uniporters (SLC50) added another dimension, with *SLC50A1* being the sole member in the human genome[5,6]. SWEET homologs are better characterized in plants, where they facilitate glucose efflux particularly in interactions with symbionts and pathogens[7].

Recent therapeutic developments underscore the clinical significance of glucose transporters. SGLT2 inhibitors were initially designed to treat type 2 diabetes (T2D) through enhanced renal glucose excretion[8]. Unexpectedly, large-scale clinical trials revealed substantial cardiovascular and renal protective effects[9,10]. These agents decrease heart failure hospitalizations and decelerate chronic kidney disease progression, transforming treatment paradigms far beyond glycemic control[11,12]. The therapeutic success has sparked a renewed investigation into the molecular mechanisms, tissue-specific regulation, and broader disease applications of glucose transporters.

This review addresses glucose transporter structure, function, and regulation while examining their tissue-specific roles and control mechanisms. We explore how these transporters contribute to disease pathogenesis in metabolic, cardiovascular, renal, and oncological conditions, and assess both established and emerging therapeutic strategies. Our goal is to bridge basic science with clinical applications, offering insights into both fundamental biology of glucose transporters and their expanding therapeutic significance.

## FACILITATIVE GLUCOSE TRANSPORTER FAMILY (GLUTS)

### Structure and general properties

The GLUT family represents the most extensively characterized glucose transporter system. Encoded by *SLC2A* genes, GLUTs belong to the major facilitator superfamily (MFS) and transport monosaccharides, polyols, and other small carbon compounds. These integral membrane proteins span approximately 500 amino acids and share a conserved architecture: 12 hydrophobic transmembrane alpha-helices (TMH), both $NH_2$ and COOH termini facing the cytoplasmic, and a characteristic N-linked oligosaccharide positioned between TMH 1 and 2[13,14]. Fourteen GLUT family members exist in the human genome, classified into three groups by sequence homology: Class 1 (GLUTs 1 - 4), Class 2 (GLUTs 5, 7, 9, and 11), and Class 3 (GLUTs 6,

8, 10, 12, and HMIT)[15,16] [Table 1] adapted from Wright and Thorens[5,17]. Most members operate through facilitative diffusion, though HMIT ($H^+$/myo-inositol transporter, GLUT13) functions as an $H^+$/myo-inositol symporter[18,19]. This structural diversity enables both unidirectional and bidirectional transport with symmetric or asymmetric kinetics[15]. Specific inhibitors, particularly phloretin and cytochalasin B, have proven instrumental in characterizing this family[20-22].

## Class I GLUT transporters

Class I transporters comprise the most well-characterized GLUT family members.

### *GLUT1 and GLUT3: central glucose transporters*

GLUT1 (*SLC2A1*), the first membrane transporter purified and cloned[23,24], serves a vital function in glucose homeostasis. This transporter exhibits moderate glucose affinity (*Km* 1-5 mM) and accepts multiple substrates, including mannose, galactose, glucosamine, and ascorbic acid[13]. Expression levels are particularly high in erythrocytes and at the blood-brain barrier (BBB)[25]. The critical importance of GLUT1 for cerebral energy metabolism becomes evident in GLUT1 deficiency syndrome, a rare genetic disorder marked by seizures, developmental delay, and movement abnormalities[26]. GLUT3 offers higher glucose affinity (*Km* ~ 1.5 mM) and localizes predominantly to neurons[27]. These two transporters work in concert to ensure adequate glucose delivery to metabolically demanding tissues, especially the brain.

**GLUT1 and GLUT3 in cancer metabolism:** Cancer cells commonly upregulate both GLUT1 and GLUT3, driving the enhanced glucose uptake seen in the Warburg effect[28]. Within hypoxic tumor microenvironments, hypoxia-inducible factor-1α (HIF-1α) becomes activated[29] and promotes transcription of both transporters, facilitating metabolic adaptation under oxygen and nutrient stress[30].

Several oncogenic signaling pathways selectively enhance GLUT3 expression. mTORC1 and NF-κB signaling[31,32], loss of p53 function[33], and oncogenic EGFR signaling all enhance GLUT3 levels, sustaining glycolytic metabolism and tumor cell proliferation. GLUT3 thus emerges as a key driver of metabolic plasticity in cancer[34]. Both transporters represent attractive, though technically difficult, therapeutic targets in oncology.

Beyond cancer, disrupted GLUT1 and GLUT3 function contributes to neurodegenerative and neurological disorders[35]. Decreased GLUT1 expression or impaired glucose transport at the BBB correlates with cerebral hypometabolism characteristic of Alzheimer's disease and related conditions[36]. Neuronal GLUT3 expression changes may likewise restrict glucose availability to vulnerable neuronal populations, worsening energy failure, synaptic dysfunction, and neurodegeneration[37]. These metabolic defects appear early in disease progression, pointing to GLUT1 and GLUT3 as promising targets for interventions designed to maintain neuronal energy homeostasis.

### *GLUT2: the low-affinity metabolic sensor*

GLUT2 (*SLC2A2*) displays distinctive kinetic properties, with unusually low glucose affinity (*Km* ~ 17 mM) that renders its activity largely insensitive to normal physiological blood glucose fluctuations[38]. Beyond glucose, this transporter accepts diverse substrates, glucosamine with notably high affinity (*Km* ~ 0.8 mM), alongside fructose (*Km* ~ 76 mM), galactose (*Km* ~ 92 mM), and mannose (*Km* ~ 125 mM)[39]. These kinetic characteristics match GLUT2's tissue distribution in insulin-secreting beta cells, liver, intestine, kidney, and select central nervous system regions, including neurons, astrocytes, and tanycytes[40].

**Tissue distribution and regulation across metabolic organs:** In pancreatic beta cells, GLUT2 works together with glucokinase to create a glucose-sensing apparatus that responds rapidly to blood glucose changes.

**Table 1. SLC2: facilitative GLUT transporter family**

| GLUT classes | GLUT isoforms | Gene | Main tissue expression | Substrate specificity | Physiological function | Disorder involved |
|---|---|---|---|---|---|---|
| I | GLUT1 | *SLC2A1* | Ubiquitous, erythrocytes, brain-barrier[13] | Glucose/Galactose/Mannose/Glucosamine[13] | Basal glucose uptake[306] | GLUT1 deficiency syndrome (epilepsy)[26], cognitive decline[36], gastric cancer[24,28], osteonecrosis[307] |
| I | GLUT2 | *SLC2A2* | Liver, islets, small intestine, kidney[40] | Glucose/ Fructose/ Galactose/ Mannose/ Glucosamine[13,39] | Glucoses absorption in intestine and kidney Glucose sensor[40] | Fanconi-Bickel syndrome[58,59], T2D[43,55] |
| I | GLUT3 | *SLC2A3* | Brain (neuronal), testis[27] | Glucose/Galactose/ Mannose/Xylose[13] | Basal Glucose uptake[27] | Breast cancer[28] |
| I | GLUT4 | *SLC2A4* | Muscle, adipose tissue and heart[4] | Glucose/ Glucosamine[13] | Mediates insulin-stimulated glucose uptake in skeletal, cardiac muscle, and fat cells[60] | Gastric cancer[28], T2D[61] |
| I | GLUT14 | *SLC2A14* | Testis[17] | Glucose/Galactose[3] | Duplicon of GLUT3[13] | - |
| II | GLUT5 | *SLC2A5* | Small intestine, kidney, muscle and adipose tissue[73] | Fructose[73] | Fructose transporter[79,88] | Colon cancer[293], Crohn's disease[73,76] |
| II | GLUT7 | *SLC2A7* | Colon, testis, prostate[35] | Fructose/Glucose[87] | Unknown | - |
| II | GLUT9 | *SLC2A9* | Kidney, liver[90,91] | Urate/Fructose/ Glucose[13,89] | Urate homeostasis[89] | Renal hypouricemia[92] |
| II | GLUT11 | *SLC2A11* | Heart, skeletal muscle, pancreas[94,95] | Glucose/Fructose[65] | Unknown | - |
| III | GLUT6 | *SLC2A6* | Spleen, peripheral leucocytes and brain[6] | Glucose[6] | Lysosomal transporter; modulates glycolysis in macrophages[97] | Endometrial cancer[99] |
| III | GLUT8 | *SLC2A8* | Testes, mammary gland, kidney, intestine epithelia, skeletal muscle, blastocyst, liver, brain and adipose tissue[6,99] | Glucose[99] | Insulin-responsive transport in blastocyst[99] | Hepatic steatosis[101,102] |
| III | GLUT10 | *SLC2A10* | Heart, lung, brain, liver, skeletal muscle, pancreas, placenta and kidney[103] | 2-Deoxy-glucose,dehydroascorbic acid[6,99] | Not determined | Arterial tortuosity syndrome[105,106], Leukemia[99] |
| III | GLUT12 | *SLC2A12* | Spleen, skeletal muscle, kidney, testes, mammary gland, liver, lung and intestine[107-110] | Glucose/Fructose[96] | Insulin-stimulated glucose uptake[108,109] | Breast cancer[112] |
| III | GLUT13 - HMIT | *SLC2A13* | Brain[18] | Myoinositol[13] | $H^+$/myo-inositol transporter | - |

GLUT: Glucose transporter; T2D: type 2 diabetes.

GLUT2-deficient mice demonstrate the vital importance of this system; loss of *Slc2a2* in beta cells impairs glucose-stimulated insulin secretion (GSIS) and causes neonatal death[40,41]. At the molecular level, GLUT2 surface expression requires interaction with galectin 9, a lectin that binds specific N-linked glycan structures

[42]. Glucolipotoxicity destabilizes these N-glycan modifications, triggering transporter internalization and potentially contributing to impaired insulin secretion and T2D progression[43].

**Hepatic** GLUT2 follows distinct regulatory pathways, controlled primarily by the transcription factor hepatic nuclear factor-1alpha (HNF1A)[44,45]. In hepatocytes, GLUT2 acts as the primary glucose transporter in both rodents and humans, proving essential for glucose uptake though not for glucose output[23,41,45].

In **kidney and intestine**, GLUT2 acts with SGLTs to establish an efficient transport system where SGLTs mediate apical uptake while GLUT2 handles basolateral export[46]. Renal expression shows segment-specific patterns, with higher levels in the proximal convoluted tubule (S1/S2) alongside SGLT2, but lower expression in the proximal straight tubule (S3) where SGLT1 predominates[47].

Intestinal GLUT2 localizes predominantly to the duodenum and proximal jejunum, facilitating glucose and fructose absorption from dietary sources into the bloodstream. While GLUT2 absence leads to significant glucosuria, this transporter is not essential for intestinal glucose absorption under normal conditions[35]. GLUT2 displays dynamic trafficking behavior, particularly SGLT1-dependent translocation to the brush-border membrane (BBM) in murine models. Increased SGLT1-mediated glucose uptake depolarizes the membrane, raising cytoplasmic calcium through Cav1.3 channels[48,49]. Elevated calcium activates protein kinase C (PKC) βII in intestine and PKC βI in kidney, phosphorylating myosin II and driving GLUT2 translocation to the apical surface[50,51], allowing rapid adaptation to dietary glucose and fructose loads[52,53]. Chronic dietary patterns modulate this system mainly through SGLT1 regulation[54]. Because apical GLUT2 translocation depends on SGLT1-mediated glucose transport, long-term dietary habits substantially affect glucose absorption capacity[48,49]. In T2D, increased GLUT2 recruitment to the BBM occurs in both intestine and kidney[55]. Insulin normally promotes apical GLUT2 internalization, but insulin resistance disrupts this control, resulting in increased glucose absorption[56].

Loss-of-function mutations in *SLC2A2* cause Fanconi-Bickel syndrome (FBS, OMIM 227810), a rare autosomal recessive disorder[57,58]. Affected individuals develop hepatomegaly from glycogen storage, glucose and galactose intolerance, fasting hypoglycemia, and renal dysfunction manifesting as glucosuria and aminoaciduria, all while maintaining normal insulin secretion[59].

### *GLUT4: the insulin-responsive transporter*

GLUT4 (*SLC2A4*) represents the primary insulin-responsive glucose transporter and controls postprandial glucose homeostasis. This transporter effectively removes glucose ($Km \sim 5$ mM) from the bloodstream in muscle, adipose tissue, and heart[4], functioning as the rate-limiting step in glucose disposal. Unlike other GLUTs, GLUT4 remains sequestered in intracellular storage vesicles under basal conditions[60], translocating to the plasma membrane only following insulin stimulation to enhance glucose uptake and metabolism[61]. Exercise and muscle contraction can also drive GLUT4 translocation through insulin-independent pathways[62].

**Mouse model insights:** GLUT4-null mice develop cardiac hypertrophy, reduced adipose tissue, postprandial hyperinsulinemia, and blunted insulin responsiveness[63]. Compensatory regulation of GLUT2 in the liver or GLUT1 in heart allows survival, though skeletal muscle function suffers[4]. Heterozygous GLUT4$^{+/-}$ mice show peripheral insulin resistance with progression toward hypertension and diabetes, whereas GLUT4 overexpression improves insulin sensitivity and glucose tolerance[64,65].

Tissue-specific knockouts revealed critical inter-organ crosstalk: muscle-specific *Slc2a4* depletion (MG4KO) impairs insulin responsiveness in adipose tissue and liver, while adipose tissue-specific deletion (AG4KO) produces insulin resistance in muscle and liver[66,67]. These cross-tissue effects highlight the metabolic

interdependence of insulin target organs. During obesity and T2D, GLUT4 expression declines in adipose tissue but remains stable in skeletal muscle[68].

## Class II GLUT transporters

Class II GLUTs preferentially transport fructose over glucose, distinguishing them functionally from Class I members.

### *GLUT5: the fructose specialist*

GLUT5 (*SLC2A5*), the first characterized Class 2 member, exhibits the highest fructose transport capacity ($Km$ ~ 6-15 mM) among glucose transporters[69]. This transporter primarily facilitates dietary fructose absorption across the apical membrane of small intestine enterocytes[70] and mediates fructose reabsorption in kidney proximal straight tubule (S3) cells[71].

**Tissue distribution and regulation:** GLUT5 expression predominates in proximal intestinal segments (duodenum and proximal jejunum) compared to distal regions (distal jejunum and ileum) in both humans and rodents[35]. Like GLUT2, GLUT5 localizes to the basolateral membrane of human jejunum and shuttles between membranes with assistance from the cytosolic Ras-related protein-in-brain 11[72].

Intestinal GLUT5 displays remarkable substrate-specific regulation[73]: high-fructose diets elevate mRNA and protein levels, whereas high-glucose diets produce no such increase[74]. Conversely, lipid intake may suppress intestinal GLUT5 expression[75]. Aberrant GLUT5 expression correlates with fructose malabsorption, inflammatory bowel disease, and metabolic disorders including obesity, diabetes, and cancer[76].

Fructose malabsorption (FM, OMIM 229600) represents a common digestive disorder marked by impaired fructose absorption in the small intestine[77]. Paradoxically, adult FM patients show normal GLUT5 levels compared to healthy individuals[78] though *Slc2a5* deletions produce intestinal FM in mice[79]. *Slc2a5* knockout mice absorb 75% less dietary fructose and maintain 90% lower blood fructose concentrations. Under high-fructose feeding, these mice develop hypertension, malabsorption syndrome, and cecal distention[77,79].

The fructose-GLUT5 pathway contributes to cancer progression. Elevated fructose intake promotes colorectal cancer metastasis and enhances nucleotide synthesis in hepatic and pancreatic cancer cells[80]. Since GLUT5 is absent from pancreas[81], other transporters must mediate these effects. Diabetic patients express elevated intestinal GLUT5 levels[75], while Zucker rats (a T2D model) do not[82,83]. In diabetic rats, increased intestinal Glut5 expression does not correlate with enhanced activity, as fructose uptake normalizes[72].

Beyond the intestine, GLUT5 appears in insulin-sensitive tissues including skeletal muscle and adipose tissue[70], particularly in adipocyte membranes and skeletal sarcolemma. Insulin upregulates GLUT5 expression in these tissues, with T2D patients showing substantial increases in skeletal muscle *SLC2A5* mRNA and protein[70]. Obesity-induced adipose tissue hypoxia also drives GLUT5 expression. In streptozotocin-induced diabetic rats, glycemia regulates *SLC2A5* mRNA levels in adipocytes[69,84]. While GLUT5 represents an interesting therapeutic target across multiple pathologies, its complete physiological and pathological roles require further investigation.

### *Additional Class II GLUT Transporters*

**GLUT7** (*SLC2A7*) displays approximately 50% sequence identity with GLUT5 and localizes predominantly to the small intestine and colon[35]. Early reports proposed high-affinity fructose transport[85,86] but mammalian expression systems reveal minimal fructose activity relative to GLUT5[87]. Chimeric protein

studies suggest GLUT7 may recognize distinct substrates or perform alternative functions[88], underscoring the need for deeper structural and functional characterization.

GLUT9 (*SLC2A9*) acts primarily as a urate transporter while retaining glucose transport capacity[89]. Two splice variants, GLUT9a and GLUT9b, show tissue-specific membrane targeting[90]: GLUT9a localizes predominantly to basolateral membranes in liver, kidney, and placenta, whereas GLUT9b targets the apical membrane in kidney proximal tubules[91]. Loss-of-function mutations in *SLC2A9* cause renal hypouricemia type 2 (RHUC2) and modulate serum uric acid concentrations[92], connecting GLUT9 dysfunction to gout and cardiometabolic disorders[93]. Although urate transport is well-characterized, the physiological significance of GLUT9-mediated glucose transport remains unclear, particularly in diabetic tissues. This dual substrate specificity may mechanistically link fructose consumption, hyperuricemia, and metabolic syndrome[4]. GLUT11 (*SLC2A11*) exhibits approximately 42% sequence identity with GLUT5 and generates three splice variants that localize predominantly to skeletal muscle, heart, and pancreas[94,95]. This transporter accepts both glucose and fructose as substrates, with fructose competitively inhibiting glucose transport[65]. Localization to insulin-sensitive tissues implicates GLUT11 in glucose homeostasis, with potential involvement in cancer metabolism[96].

## Class III GLUT transporters

Class III GLUTs display a distinctive structural feature: a large extracellular loop positioned between transmembrane helices 9 and 10, contrasting with the Class I and II arrangement between helices 1 and 2. These transporters also possess unique trafficking motifs that govern intracellular localization and regulation[65].

GLUT6 (*SLC2A6*) exhibits low-glucose affinity and is expressed in brain, spleen, and leukocytes, where an N-terminal dileucine motif drives intracellular retention[6]. Expression increases in pancreatic islets of obese and insulin-resistant mice. Rather than mediating direct glucose uptake, GLUT6 localizes to lysosomes and modulates glycolytic flux in inflammatory macrophages[97]. NF-κB induces its expression, though knockout mice display only modest phenotypic changes during inflammatory challenge[97,98].

GLUT8 (*SLC2A8*) is highly expressed in testis, albeit less in the brain, liver, and adipose tissue[99]. A dileucine motif controls subcellular targeting, and GLUT8 participates in blastocyst development, neuronal function[35] and sperm glucose supply[100]. This transporter proves essential for hepatic fructose metabolism, where it influences insulin[101]. Liver-specific GLUT8 deletion protects female mice from fructose-induced macrosteatosis and inflammation[4,102], linking this transporter to NAFLD-NASH pathogenesis[101].

GLUT10 (*SLC2A10*) targets mitochondria in liver, pancreas, and vascular smooth muscle cells[103] and may transport dehydroascorbic acid[104]. Loss-of-function mutations produce arterial tortuosity syndrome (ATS), characterized by arterial anomalies, ventricular hypertrophy, skin hyperextensibility, and connective tissue abnormalities[105]. Defective monosaccharide transport likely disrupts glycosylation pathways critical for extracellular matrix integrity[106].

GLUT12 (*SLC2A12*) transports D-glucose and 2-deoxy-D-glucose[96] and localizes to insulin-sensitive tissues including heart, skeletal muscle, intestine, and white adipose tissue[107-110]. Insulin stimulates GLUT12 translocation to the plasma membrane in these metabolic organs[108]. Overexpression enhances whole-body insulin sensitivity and glucose clearance[111]. In cancer, GLUT12 sustains glucose uptake under hormonal and hypoxic conditions[96] fueling the Warburg effect and tumor progression[112-114].

**Table 2. SLC5: sodium-glucose co-transporter family**

| SGLT isoforms | Gene | Main tissue expression | Substrate specificity | Physiological function | Disorder involved |
|---|---|---|---|---|---|
| SGLT1 | *SLC5A1* | Small intestine, kidney (proximal convoluted tubule S3)[128,167] | Glucose/Galactose/[35,246] Proposed Urea[199] | Absorption of dietary glucose[144] /Reabsorption in kidney[167] | Glucose-galactose malabsorption (GGM)[163,164] |
| SGLT2 | *SLC5A2* | Kidney (proximal convoluted tubule S1-S2)[187] | Glucose[192] | Reabsorption in proximal tubule of kidney[187] | Familial Renal glucosuria[189] and diabetic nephropathy[170] |
| SGLT3 | *SLC5A4* | Cholinergic neurons of enteric nervous system[219] | - | Glucose sensor only[219] | Attention deficit hyperactivity disorder[14,15] |
| SGLT4 | *SLC5A9* | Small intestine, pancreas[198,227] | Mannose, glucose, fructose, galactose[227] | Intestinal absorption of mannose, fructose and glucose[227] | Diabetic proliferative retinopathy[115] |
| SGLT5 | *SLC5A10* | Kidney cortex[235] | Mannose, fructose, galactose, glucose and 1,5-anhydroglucitol[190,235] | Fructose transporter[190,236] | Neutropenia G6PC3 deficiency-related[190,232] |
| SGLT6 | *SLC5A11* | Proximal convoluted tubule[14] | Myo-inositol and glucose[14] | Not available | Rheumatological disease, Ischemic stroke, and Schizophrenia/bipolar disorder[14] |

SGLT: Sodium-glucose cotransporter.

## SODIUM GLUCOSE-CO-TRANSPORTER FAMILY (SGLTS)

### Structure and general properties

The $Na^+$/glucose co-transporter family (SGLTs, SLC5A) comprises 12 members that transport diverse substances including sugars, anions, vitamins, and short-chain fatty acids[14]. Beyond substrate transport, SGLTs serve additional roles as water and urea channels, glucose sensors, and mediators of coupled water and urea flux[115]. The *SLC5A1-3* genes encode proteins spanning approximately 665 amino acids with 14 transmembrane helices (TMHs). Both $NH_2$ and COOH termini face the extracellular space, and N-linked glycosylation occurs between TMH 6 and 7[116,117]. The most thoroughly characterized members are summarized in Table 2 adapted from Wright and Hediger[5,118].

Building on Crane's 1960 sodium-glucose cotransport hypothesis[119], the sodium gradient across cell membranes powers active glucose transport. $Na^+/K^+$-ATPase in the basolateral membrane maintains this gradient by expelling three sodium ions while importing two potassium ions. The transport mechanism follows a six-state model with mirror symmetry. Under saturating external $Na^+$, two cations bind first, creating an outward-facing open conformation. Glucose binding triggers external gate closure and rapid isomerization, releasing both sugar and ions into cytoplasm through an internal vestibule. The protein then isomerizes back to its ligand-free outward-facing state, completing the cycle. Voltage influences the distribution between conformational states[120].

### SGLT1: high-affinity intestinal and renal transporter

Semeza and Wright first cloned the phlorizin-sensitive SGLT1 in the 1980s[121]. SGLT1 (*SLC5A1*) operates as a high-affinity, low-capacity glucose transporter (Km ~ 0.5 mM) with 2 $Na^+$:1 sugar coupling stoichiometry. This transporter responds to natural sugars, sweet proteins, and certain artificial sweeteners (sucralose, acesulfame K, though not aspartame *in vitro*)[122,123]. Whether artificial sweeteners induce SGLT1 activity *in vivo* remains debated[124-126].

**Intestinal expression and function: SGLT1 localizes** primarily to the BBM of mature enterocytes in intestinal villi, where it mediates glucose and galactose uptake (Km ~ 1 mM) from the lumen[35,46][Figure 1]. Expression predominates in the proximal jejunum compared to distal segments[56,127,128], though SGLT1 also

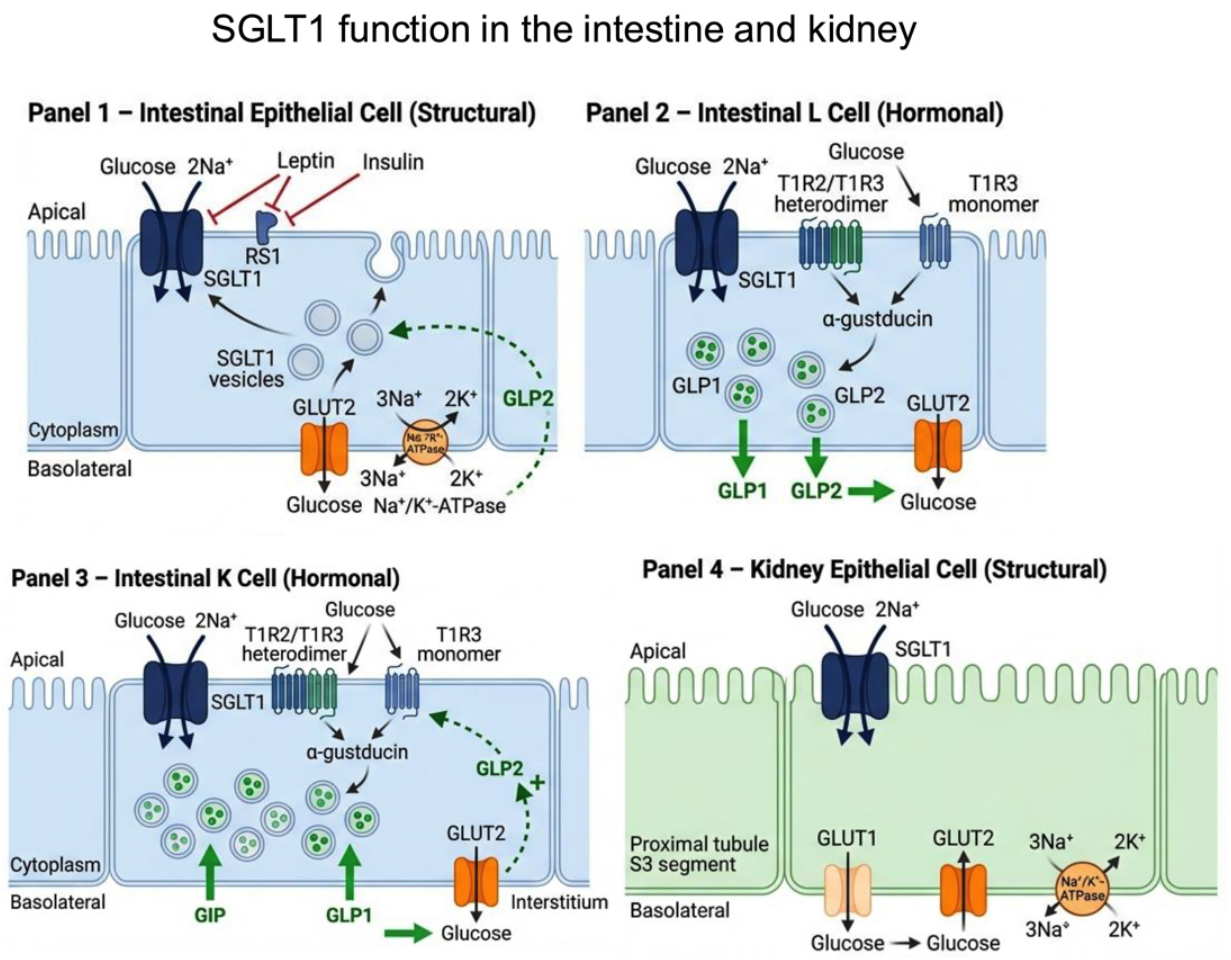



**Figure 1.** SGLT1 function in the intestine and kidney. Four cell types are depicted, separated into structural (glucose transport) and hormonal (incretin secretion) roles. Panel 1 - Intestinal epithelial cell (structural): SGLT1 mediates apical co-transport of glucose with $2Na^+$ from the intestinal lumen. RS1 protein inhibits SGLT1 activity at the apical membrane. Leptin and insulin exert inhibitory regulation of SGLT1 expression and trafficking. Intracellular SGLT1-containing vesicles are recruited to the apical membrane in response to luminal glucose, a process stimulated by GLP2 via a neuro-paracrine feedback loop (dashed arrow). GLUT2 on the basolateral membrane exports glucose to the interstitium. The $Na^+/K^+$-ATPase maintains the electrochemical sodium gradient driving apical SGLT1 activity. Panel 2 - Intestinal L cell (hormonal): SGLT1 on the apical membrane senses and transports luminal glucose. The T1R2/T1R3 heterodimer and T1R3 monomer sweet taste receptors activate α-gustducin, stimulating intracellular synthesis and basolateral secretion of GLP1 and GLP2. GLUT2 mediates basolateral glucose export. Panel 3 - Intestinal K cell (hormonal): Identical apical glucose-sensing machinery (SGLT1, T1R2/T1R3, T1R3, α-gustducin) drives secretion of GIP and GLP1 from the basolateral membrane. GLP2 arriving from L cells provides a positive feedback signal (+) stimulating SGLT1 activity. GLUT2 exports glucose basolaterally. Panel 4 - Kidney epithelial cell (structural): SGLT1 in the proximal tubule S3 segment recovers residual filtered glucose from the tubular lumen with $2Na^+$. The $Na^+/K^+$-ATPase ($3Na^+/2K^+$) maintains the driving gradient. GLUT1 and GLUT2 on the basolateral membrane return glucose to the interstitium. Figure created with FigureLabs. SGLT: sodium-glucose cotransporter; GLUT: facilitative glucose transporter; GIP: gastric inhibitory peptide; GLP: glucagon-like peptide.

appears in crypt cells[127,129]. Immunoreactivity occurs in enteroendocrine K and L cells, which secrete gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP1), respectively[130,131]. These hormones stimulate pancreatic beta cells for insulin release[132,133] while suppressing glucagon secretion and appetite[134,135].

**Regulation of intestinal SGLT1:** Dietary and hormonal factors modulate intestinal SGLT1 expression. Luminal nutrients prove essential for maintaining expression levels[136], with changes occurring independently of how sugars are metabolized[137]. Chronic high-carbohydrate diets increase intestinal glucose transport rates in parallel with Sglt1 expression[56]. Short-term glucose exposure enhances protein levels at the BBM, while sustained exposure drives *SLC5A1* gene translation. Post-transcriptionally, SGLT1 accumulates

in subapical vesicles[35], with glucose accelerating RS1 protein-mediated exocytosis[138]. The sweet taste receptor T1R2+T1R3 complex senses luminal sugar concentrations and activates G protein alpha-gustducin[139], upregulating *SLC5A1* mRNA expression. This sweet receptor also triggers GLP2 expression in L-cells[140], which then regulates SGLT1 activity through neuro-paracrine pathways[140,141]. Deletion of alpha-gustducin, T1R3, or GLP2 receptors prevents dietary monosaccharide-induced Sglt1 upregulation[141,142]. Long-term regulation occurs at the crypt-villus junction, where *SLC5A1* mRNA levels peak[143]. In mice, this heterodimer also appears in endocrine L and K cells. Sglt1$^{-}$/$^{-}$ mice show reduced glucose-triggered GIP and GLP1 secretion[144], though in humans, SGLT1 represents only one contributor to GLP1 and GIP release[145].

Sodium and leptin provide additional regulatory input. In chickens, low-salt diets decrease glucose transport $V_{max}$ by reducing brush-border transporter density, whereas high-salt diets do not affect glucose transport rates or SGLT1 protein levels[146]. Leptin exerts hormonal control over SGLT1[147-149], producing significant downregulation following leptin administration in rats and hyperleptinemic mice, but not in leptin-deficient mice or those with intestine-specific leptin receptor deletion[148,150]. Portal vein insulin can also downregulate Sglt1 via its basolateral membrane receptor[151].

**Pathological alterations:** Several conditions correlate with altered intestinal SGLT1 expression. Overexpression is linked to severe obesity in both murine models and patients with morbid obesity[152]. Diabetes elevates intestinal SGLT1 expression, likely reflecting increased dietary sugar intake, with elevated mRNA detected in STZ-induced diabetic mice and rats, Otsuka Long-Evans Tokushima Fatty rats (a T2D model), and patients with non-insulin-dependent diabetes[82,153-155]. This upregulation probably accelerates postprandial blood glucose spikes by enhancing glucose absorption in proximal intestine and amplifying incretin-glucagon responses, thereby promoting hyperinsulinemia and hyperglycemia.

Studies in subjects with obesity [body mass index (BMI) > 35 kg/m$^2$] reveal intestinal SGLT1 alterations following Roux-en-Y gastric bypass (RYGB), which typically produces approximately 25% weight loss[156,157]. Bariatric surgery profoundly affects T2D, with roughly 60% of patients achieving remission two years post-surgery[158,159]. Glucose control improves dramatically within days, suggesting that rapid diabetic symptom reversal stems primarily from digestive system reorganization rather than weight loss alone[160]. Potential mechanisms include decreased intestinal Sglt1 expression[161,162].

Loss-of-function mutations in *SLC5A1* produce intestinal Glucose Galactose Malabsorption (GGM, OMIM 182380), a rare autosomal recessive disorder characterized by severe neonatal diarrhea and water loss[163-165]. These mutations impair SGLT1 trafficking from the endoplasmic reticulum to the BBM[35]. Dietary exclusion of D-glucose and D-galactose enables normal life for affected individuals[166]. Sglt1-null mice absorb approximately 95% less glucose, developing severe diarrhea and dying within two weeks on standard diet[144].

**Renal, pancreatic, and central nervous system expression:** In the kidney, SGLT1 recovers residual glucose (~ 3% of filtered load) from the lumen in the proximal tubule segment 3 (S3) BBM cells[167]. Murine Sglt1 protein expression predominates in S2 segments versus S3 segments[128] [Figure 1]. This compensatory capacity activates when SGLT2 is absent (through pharmacological blockade or genetic deletion), increasing the glucose load delivered to downstream SGLT1[168-170]. Diabetic rodent models show variable renal Sglt1 protein level, with some studies detecting no change or reductions[171]. SGLT1 deletion ameliorates glomerular hyperfiltration in T2D mice, lowering kidney weight, glomerular size, and albuminuria[172], implicating Sglt1 in renal integrity beyond simple glucose reabsorption.

Bankir and Yang proposed SGLT1 involvement in tubular urea secretion[173]. High-protein feeding in Sglt1 KO mice increased hepatic urea formation and elevated plasma urea levels, likely reflecting enhanced demand for renal excretion[174]. Work in mice and human HK-2 cells indicates that Sglt1-mediated glucose at

the apical membrane inhibits gluconeogenic gene expression (*Pepck* and *G6pase*), mimicking insulin's effect. This mechanism may protect proximal tubular cells against glucose overload[175].

**Pancreatic expression:** SGLT1 is expressed in the luminal membrane of pancreatic intralobular and interlobular ducts[176]. Elevated expression associates with pancreatic ductal adenocarcinoma and may indicate favorable prognosis[177]. SGLT1 is also expressed in pancreatic alpha cells[178], where it potentially influences glucagon secretion[179], though findings diverge. Kuhre *et al.* detected *Slc5a1* mRNA expression in murine beta and delta cells, but not in alpha cells[180]. In rodent models, Sglt1 upregulation was observed in islets from insulin-resistant prediabetic *ob/ob* mice before declining once diabetic phenotype emerges[181]. Mühlemann and colleagues showed Sglt1 maintains murine islet integrity: its absence produced enlarged islets with reduced proliferation and apoptosis rates alongside impaired insulin and glucagon secretion[182]. Human SGLT1 expression shows substantial inter-individual variation[183] yet remains elevated during progression from insulin resistance to diabetes[178].

**Central nervous system expression:** *Slc5a1* (Sglt1) mRNA localizes to diverse neuronal and glial cell types, including cortical neurons, hippocampal pyramidal cells, cerebellar Purkinje cells, and VMH neurons in rats[184]. Glial expression appears likely, evidenced by mRNA detection in primary rat astrocyte cultures and immunoreactivity in VMH glial cells[185]. SGLT1 at the BBB likely helps control glucose concentration in brain interstitium[186]. SGLT1 is expressed widely throughout the brain, with particular high levels in regions governing learning, feeding behavior, energy expenditure, and glucose homeostasis[35].

## SGLT2: the renal glucose reabsorber

SGLT2 (*SLC5A2*) exhibits low-affinity (Km ~ 5 mM), high-capacity transport characteristics with 1:1 sodium-to-glucose coupling stoichiometry. This transporter serves as the primary glucose reabsorber in the BBM of proximal renal tubule S1/S2 segments, recovering approximately 90% of filtered glucose alongside GLUT2[187]. *Slc5a2* deletion preserves roughly 40%-50% of glucose reabsorption, largely through SGLT1 compensation[188]. Patients carrying *SLC5A2* mutations develop Familial Renal Glucosuria (FRG), characterized by urinary glucose excretion ranging from 1 to over 100 g daily without intestinal absorption defects[189]. Affected individuals typically avoid other complications such as kidney dysfunction or urinary tract infections[163,190]. Although rare, these mutations inspired development SGLT2 inhibitors as a potentially safe therapeutic strategy to lower blood glucose.

Expression levels govern SGLT2 glucose transport capacity, responding to glucose and insulin rather than sodium, particularly in diabetes[191]. Primary cultures of human exfoliated proximal tubular epithelial cells from T2D patients showed elevated SGLT2 expression and increased glucose uptake[52], with comparable findings in *db/db* mice and Akita rats[164,192]. Angiotensin II AT1 receptors and HNF1A contribute to SGLT2 upregulation[193]. Mice lacking *Hnf1a* display impaired renal glucose reabsorption from reduced *Sglt2* gene expression[194]. Norton *et al.* detected lower *SGLT2* mRNA in kidneys from T2D patients compared with non-diabetic controls[195].

Insulin acts as an agonist for SGLT2 activity *in vivo*[196], presumably maintaining elevated filtered glucose reabsorption during the postprandial phase. Hyperinsulinemia associated with insulin resistance in obesity and T2D might enhance renal SGLT2 activity. This enhancement likely stems from general proximal tubule growth and hypertrophy in diabetes, which expands the overall glucose transport capacity[197].

**Pancreatic and central nervous system expression:** Despite initial assumptions, SGLT2 shows low-level expression in brain, liver, pancreas, and other tissues[127,178,183,198,199]. Intestinal SGLT2 remains controversial, with immunofluorescence detecting limited enterocyte expression in duodenal mucosa across species[198,200-203]

, though, some studies report no expression in human small intestine[198].

Pancreatic SGLT2 expression generates ongoing debate. While several studies detect no SGLT2 in murine or human islets[179-181,198,204], Vergari *et al.* identified SGLT2 in approximately 40% of delta cells[205], whereas Bonner *et al.* localized *SLC5A2* mRNA and protein specifically to human alpha cells, under HNF4A transcriptional control[178]. SGLT2 inhibition through dapagliflozin or siRNA stimulates glucagon secretion both *in vivo* and *in vitro*[178,183], aligning with elevated plasma glucagon observed in diabetic patients receiving SGLT2 inhibitors[206,207]. Saponaro *et al.* revealed substantial inter-individual variability in pancreatic islet SGLT2 expression[183], potentially explaining conflicting study findings. Like SGLT1, SGLT2 appears functionally active in pancreatic adenocarcinomas, where SGLT2 inhibitors block glucose uptake and reduce tumor growth[208,209].

Brain SGLT2 expression remains substantially lower than SGLT1[198,199,203] and localizes predominantly to the cerebellum[210]. Murine studies detect SGLT2 in cerebellum, amygdala, hypothalamus, periaqueductal gray (PAG), nucleus of the solitary tract, and microvessels comprising the BBB[211]. Like SGLT1, SGLT2-expressing brain regions associate with learning, food intake, energy and glucose homeostasis, and central cardiovascular and autonomic regulation[212]. However, low expression levels and limited immunofluorescence or *in situ* hybridization confirmation fuel ongoing debate about its functional significance in central glucose sensing and energy regulation.

### Additional SGLT family members

SGLT3 (*SLC5A4*), first characterized as a renal amino acid co-transporter (SAAT1) in pigs, operates as a glucose-sensing ion channel rather than a glucose transporter in humans[213]. Mice and rats express two, whereas humans express only one[214,215]. Human SGLT3 and mSglt3a share 79%-80% amino acid sequence identity and conserved ligand-binding sites[216,217], implying distinct functional roles for the rodent isoforms. In fact, mSGLT3b transports glucose similarly to SGLT1, while mSglt3a does not. Both hSGLT3 and mSglt3a produce membrane currents at pH 7.4 when exposed to glucose and either $Na^+$ or $H^+$, supporting the view that SGLT3 operates as a glucose-sensitive ion channel rather than a transporter[218].

Humans mRNA profiling reveals *SLC5A4* expression predominates in small intestine, with markedly lower expression in skeletal muscle and testis, then spleen, liver, and kidney[198]. Immunofluorescence studies localized hSGLT3 to the small intestine submucosa, where it co-localizes with nicotinic acetylcholine receptors in cholinergic neurons[219]. Obesity reduces hSGLT3 protein in jejunal region[220]. Mouse and rat intestine and kidney display similar expression patterns[214,218,221,222]. Both isoforms appear in rat duodenum, with rSglt3b also detected in jejunum and proximal ileum, where it may contribute to GLP1 secretion[185,223,224]. Specifically, mSglt3a/3b localizes to small intestinal epithelial cells, though *ob/ob* mice show markedly lower duodenal and jejunal expression than controls[220]. rSglt3 also localizes to the hepatic portal area and contributes to reducing food intake[222,225].

Sglt3 additionally serves glucose-sensing functions in the brain. Most glucose-excitable cultured hypothalamic neurons increase cytosolic $Ca^{2+}$ levels following alpha-MDG exposure[185]. Sglt3 expression across diverse brain structures supports this observation, including cortex, hypothalamus, hippocampus, midbrain, striatum, medulla, olfactory bulb, and cerebellum. Yamazaki et al. identified a neuroprotective role for Sglt3 in cholinergic neurons[226].

SGLT4 (*SLC5A9*) and SGLT5 (*SLC5A10*) represent poorly understood members of the SGLT family. COS-7 cell studies show SGLT4 transports mannose, glucose, fructose, 1,5-anhydroglucitol (1.5-AG), and galactose with varying affinities[227]. Moreover, recent work has excluded 1.5-AG as a SGLT4 substrate[190]. 1.5-AG acts

as a biomarker for hyperglycemic excursions[228-231], since high concentrations of glucose, fructose, and mannose compete with 1,5-AG for renal absorption. Elevated blood 1,5-AG drives neutropenia in patients with G6PPT/SLC37A4 deficiency and glycogen storage disease type 1b[232,233], underscoring the clinical relevance of this metabolite.

Chen *et al.*[198] and Tazawa *et al.*[227] revealed that SGLT4 shows minimal expression in the kidney, but substantial intestinal expression followed by the pancreas, indicating its physiological role likely diverges from the renal-centric characteristics of other SGLT family members[198,227]. Work by Forester et al. examining SGLT-mediated proximal tubule fructose reabsorption in hypertension supports this non-renal role. Comparing SGLT4 and SGLT5 knockout models, they found SGLT5 deletion prevented hypertension during short-term (7.5-day) fructose high-salt feeding, whereas SGLT4 knockout rats still developed hypertension under identical conditions[234].

SGLT5 is predominantly expressed in the renal cortex, similarly to SGLT2[190], and operates with a 1:2 sodium-to-substrate transport ratio. This transporter exhibits high-capacity transport for mannose and fructose, with reduced efficiency for glucose and galactose[235]. Fructose regulates SGLT5 expression, as Sglt5-deficient mice lose all sodium-dependent fructose uptake in the renal brush border membrane[236]. These findings establish SGLT5 as the principal transporter for renal fructose reabsorption. High-fructose feeding in Sglt5-null mice reduces plasma triglycerides and epididymal fat mass. Paradoxically, these mice develop elevated fasting insulin, glucose intolerance, and worsened hepatic steatosis alongside increased inflammation and tissue damage markers. These metabolic consequences arise not from excessive hepatic fructose uptake but likely from enhanced hepatic de novo lipogenesis and defective mannose-dependent glycosylation[236].

SGLT5 displays 3-4-fold higher transport affinity for 1,5-AG than mannose. Genetic mutations or single-nucleotide polymorphisms (SNPs) in SLC5A10 associate with altered plasma 1,5-AG concentrations[237-239]. Heterozygous SGLT5 mutations produce approximately 50% reduction in circulating 1.5-AG, indicating no alternative transporter compensates for its renal absorption[190]. Overall, SGLT4 and SGLT5 jointly regulate plasma fructose and mannose through intestinal absorption and renal reabsorption, though their complete regulatory mechanisms and physiological significance require further investigation.

## CURRENT SGLT INHIBITORS AND THERAPEUTIC APPLICATIONS

### SGLT1 inhibitors

SGLT inhibitors delay dietary glucose absorption in the small intestine, lowering postprandial glucose levels. These agents elevate plasma GLP1 and potentially GIP levels[188]. SGLT1 inhibitors (SGLT1i) enhance glucose delivery to the distal small intestine and colon, where the microbiome ferments glucose into short-chain fatty acids (SCFAs). SCFAs then stimulate GLP1 release through binding to free fatty acid receptors on L cells[240]. Increased intestinal glucose exposure also enhances microbial propionate production, yielding beneficial metabolic effects in the intestine[241,242].

T2D and diabetic cardiomyopathy upregulate SGLT1 expression in cardiomyocyte membranes, where it serves a critical role in energy production during hypoglycemia or ischemia[243]. SGLT1i may therefore protect cardiac tissue by reducing glycogen accumulation and lowering reactive oxygen species production[244]. Sodium influx through SGLT1 appears to worsen ischemic damage in cerebral neurons and myocardial cells, potentially promoting toxic calcium accumulation and impairing mitochondrial function[245]. This therapeutic approach carries potential side effects, including diarrhea, dehydration, metabolic acidosis, and possibly elevated euglycemic diabetic ketoacidosis risk[246]. Nevertheless, nonclinical

studies (KGA-2727) and clinical trials (GSK-1614235) of highly selective SGLT1i detected no serious gastrointestinal adverse events[245,247]. While these drugs have not yet reached market, several compounds continue advancing through development for diabetes and cardiovascular disease treatment.

## SGLT2 inhibitors

SGLT2 inhibitors (SGLT2i), including dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, and luseogliflozin, are approved to treat T2D[248]. These agents inhibit renal glucose reabsorption, producing insulin-independent glycosuria and lowering glycemic HbA1c by approximately 0.7%-0.8%[249,250]. This mechanism differs from other antidiabetic therapies that target hepatic glucose production (metformin), stimulate insulin secretion (sulfonylureas, GLP1 receptor agonists, DPP4 inhibitors), enhance insulin sensitivity (thiazolidinediones), or provide exogenous insulin[251].

SGLT2i slow T2D progression by reducing glucotoxicity-induced beta-cell dysfunction and improving insulin sensitivity[252]. However, these agents associate with modest increases in LDL and HDL cholesterol[253]. SGLT2i also induce glucagon secretion and endogenous glucose production[206,207,254,255], unlike other glucose-lowering agents such as metformin or GLP1 receptor agonists[256]. This phenomenon may stem partly from SGLT2 expression in human pancreatic alpha cells[178,183].

SGLT2i-induced glycosuria reduces body weight by 1-3 kg, predominantly affecting visceral adiposity[257-259]. Enhanced urinary glucose and sodium excretion promote mild osmotic diuresis and sodium loss, lowering extracellular fluid volume. These hemodynamic changes likely contribute to the cardiovascular and renal benefits observed with SGLT2i therapy. SGLT2i lower glomerular hyperfiltration, glomerular hypertrophy, inflammation markers, and albuminuria[260-262], and decrease systolic blood pressure by 2.6-6 mm Hg[263,264].

**Cardiovascular and renal benefits:** Heart failure coexists with diabetes in approximately 22% of patients over age 65, with diabetic individuals facing more than double the heart failure risk of non-diabetic counterparts. This translates to higher hospitalization rates and worse cardiovascular outcomes[265]. Most traditional antidiabetic therapies show cardiovascular neutrality or may worsen cardiovascular risk factors[266]. In contrast, SGLT2i, particularly empagliflozin, canagliflozin, and dapagliflozin, have shown robust cardiovascular and renal benefits in large-scale clinical trials[267], and are now approved to treat heart failure and chronic kidney disease regardless of baseline T2D status[268].

Empagliflozin benefits patients with existing cardiovascular disease by reducing myocardium interstitial fibrosis, improving aortic stiffness, delivering anti-inflammatory effects, and decreasing pericardial fat accumulation[12,269]. Dapagliflozin protects the heart through vasodilatory effects on thoracic aorta, while canagliflozin reduces myocardial infarct size and protects against cardiac arrest in experimental models[261,262,268,270]. Compensatory upregulation of renal SGLT1 during SGLT2 inhibitor therapy caps glucose excretion to 30%-50% of the filtered load, partially mitigating hypoglycemia risk[271-273].

Beyond cardiovascular and renal outcomes, SGLT2 inhibitors offer additional metabolic benefits, including body weight reduction, improved insulin sensitivity, and potential efficacy in metabolic dysfunction-associated steatotic liver disease (MASLD)[274] and obstructive sleep apnea[275], though further research is needed. Type 1 diabetes represents another investigational application, where sotagliflozin received EMA approval (subsequently withdrawn) for adults with T1DM and BMI ≥ 27 kg/m$^2$, and dapagliflozin has been approved as an adjunct to insulin in some jurisdictions, with demonstrated HbA1c reduction and body weight loss. However, substantially elevated DKA risk constrains their use and demands careful patient selection and monitoring[276,277].

**Table 3. Indications and Food & Drug Administration (FDA) and European Medicines Agency (EMA) approval dates for SGLT2 inhibitor treatment**

| Compound | Indications | Date FDA/EMA approval |
|---|---|---|
| Canagliflozin | 1. As an adjunct to diet and exercise to improve glycemic control in adults with T2D<br>2. To reduce the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease<br>3. To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with T2D and diabetic nephropathy with albuminuria[308,309] | FDA: Mar 29, 2013;<br>EMA: Nov 15, 2013 |
| Dapagliflozin | 1. It is indicated in adults for the treatment of insufficiently controlled T2D as an adjunct to diet and exercise as monotherapy when metformin is considered inappropriate or in addition to other medicinal products for the treatment of T2D<br>2. It is indicated in adults for the treatment of symptomatic chronic heart failure, regardless of ejection fraction<br>3. It is indicated in adults for the treatment of chronic kidney disease[310,311] | FDA: Jan 8, 2014;<br>EMA: Nov 12, 2012 |
| Empagliflozin | 1. It is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, regardless of ejection fraction<br>2. To reduce the risk of cardiovascular death in adults with T2D and established cardiovascular disease<br>3. As an adjunct to diet and exercise to improve glycemic control in adults with T2D<br>4. To reduce the risk of kidney disease progression and cardiovascular death in adults with chronic kidney disease at risk of progression[312,313] | FDA: Aug 1, 2014;<br>EMA: May 22, 2014 |
| Ertugliflozin | It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D[314,315] | FDA: Dec 19, 2017;<br>EMA: Mar 21, 2018 |
| Sotagliflozin | FDA: To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure or T2D, chronic kidney disease, and other cardiovascular risk factors<br>EMA: As an adjunct to insulin to improve glycemic control in adults with type 1 diabetes and BMI ≥ 27 kg/m$^2$[277,316,317] | FDA: May 26, 2023;<br>EMA: Apr 26, 2019<br>(withdrawn Mar 22, 2022) |

T2D: Type 2 diabetes.

SGLT2 inhibitor therapy increases the risk of genital mycotic infections (GMIs) and bacterial urinary tract infections (UTIs), with higher incidence in women than men[262,278]. Diabetic ketoacidosis (DKA) represents another recognized adverse event[279280]. Reduced carbohydrate intake during gastroenteritis, intense exercise, and postoperative stress can trigger DKA, likely through increased glucagon secretion that stimulates lipolysis and ketogenesis[281]. The incidence of DKA has been reported at 55.5 per 1000 person-years in US commercially insured patients with T1D, with substantially lower rates in T2D[282]. The long-term efficacy and safety profile of these interventions requires further definition[283,284].

**Dual SGLT1/SGLT2 inhibitors**: Dual SGLT1/SGLT2 inhibitors address compensatory SGLT1 upregulation. Sotagliflozin, an orally administered dual inhibitor, has undergone extensive phase 3 clinical trial evaluation for T2D and chronic kidney disease treatment. Sotagliflozin demonstrates substantially greater SGLT1 potency than selective SGLT1 inhibitors while maintaining SGLT2 inhibition comparable to dapagliflozin [Table 3][285,286]. Partial SGLT1 inhibition increases urinary glucose excretion through renal mechanisms, delays intestinal glucose reabsorption, and enhances postprandial GLP1 and PYY secretion[241,287].

## OTHER GLUCOSE TRANSPORTERS

Humans express a single SWEET transporter, in contrast to plants which possess numerous SWEET isoforms. Human SWEET1 (*SLC50A1, RAG1AP1*) functions as a glucose uniporter with weak efflux activity and localizes primarily to the Golgi complex[288,289]. SWEET proteins display a distinctive 7-transmembrane domain architecture comprising two triple-helix bundles separated by an inversion linker, generating a 3 + 1 + 3 configuration[5,290]. SWEET1 predominates in oviduct, epididymis, and intestine, with lactation inducing expression in the mouse mammary gland. This transporter may facilitate basolateral glucose exit from enterocytes, potentially contributing to Fanconi-Bickel syndrome pathogenesis[291].

## CONCLUSION

### Integration of current knowledge

Glucose transporters occupy a central position in energy homeostasis, with implications extending across metabolic, cardiovascular, renal, and oncological diseases. This review has synthesized current understanding of molecular mechanisms, tissue-specific regulation, disease pathogenesis, and therapeutic applications spanning the GLUT and SGLT families.

The GLUT and SGLT families employ distinct transport mechanisms that work in concert to maintain glucose homeostasis. Their tissue-specific expression patterns reflect specialized metabolic demands, governed by intricate regulatory networks involving transcriptional control, post-translational modifications, membrane trafficking dynamics, and hormonal signaling. Beyond their established roles in diabetes, these transporters contribute to diverse pathologies. Cancer cells exploit altered transporter expression to fuel metabolic reprogramming, while dysfunction in renal and intestinal glucose handling drives insulin resistance and metabolic complications. Genetic defects in specific transporters produce rare but devastating inherited disorders, underscoring their fundamental physiological importance.

### A paradigm shift in therapeutic strategy

The clinical success of SGLT2 inhibitors exemplifies how deep understanding of transporter biology can revolutionize treatment approaches. Originally designed to improve glycemic control in T2D by promoting renal glucose excretion, these agents unexpectedly improved cardiovascular and renal outcomes in landmark trials[9,10,268]. Empagliflozin, canagliflozin, and dapagliflozin reduce heart failure hospitalizations, cardiovascular mortality, and chronic kidney disease progression through mechanisms that likely involve hemodynamic improvements from natriuresis and osmotic diuresis, metabolic substrate shifts favoring ketone body utilization, reduced inflammation and oxidative stress, and potential direct organ protective effects.

Dual SGLT1/SGLT2 inhibitors such as sotagliflozin advance this therapeutic evolution by combining renal and intestinal glucose transport inhibition, delaying intestinal glucose absorption while enhancing incretin secretion[257,258]. This multi-level intervention addresses different aspects of disease pathophysiology simultaneously, demonstrating how transporter biology informs increasingly sophisticated treatment strategies.

### Persistent questions and critical knowledge gaps

Despite significant progress, several fundamental questions demand resolution. The precise mechanisms underlying SGLT2 inhibitor cardiovascular and renal benefits remain incompletely understood. Clarifying these pathways could reveal additional therapeutic targets and refine treatment strategies. While we understand some regulatory mechanisms, comprehensive knowledge of tissue-specific control remains elusive. Single-cell transcriptomics has revealed unexpected heterogeneity in transporter expression within organs[81], suggesting regulatory complexity beyond current models.

The expanding role of glucose transporters in non-diabetic diseases warrants deeper investigation. Their contribution to cancer metabolism, neurodegenerative disorders, and inflammatory conditions deserves systematic exploration[24,292-294]. Substantial interindividual variability in transporter expression and drug response stems from genetic and environmental factors, raising questions about personalization. Can pharmacogenomics identify which patients will derive maximum benefit from SGLT2 inhibitors or other transporter-targeted therapies?

Newer family members, particularly SGLT4, SGLT5, and SWEET proteins[5], remain poorly characterized in humans[192,198,227,295]. Their physiological roles under normal and pathological conditions need definition, as do their potential therapeutic applications. Although SGLT2 inhibitors demonstrate favorable benefit-risk profiles in trials extending to five years, longer-term safety data beyond ten years remain limited[296]. Rare adverse events including euglycemic ketoacidosis, genital infections, and potential skeletal effects require continued surveillance[297-299].

## Emerging opportunities and future trajectories

Several promising research avenues are now emerging. Advanced structural biology techniques, particularly Cryo-EM and molecular dynamics simulations, continue revealing transporter structure-function relationships, conformational changes during transport cycles, and inhibitor binding mechanisms. High-resolution structures of all major GLUT and SGLT isoforms will enable structure-based drug design for highly selective inhibitors. Artificial intelligence and machine learning can accelerate this discovery process substantially[300,301].

Single-cell RNA sequencing and spatial transcriptomics offer unprecedented resolution of cell-type-specific expression and regulation within heterogeneous tissues. These approaches may illuminate why certain cell populations prove particularly vulnerable to transporter dysfunction and identify cell-specific therapeutic opportunities. Conditional knockout and overexpression models will clarify physiological roles and disease contributions in specific tissues. CRISPR-based genome editing, inducible and cell-type-specific gene modulation, and single-cell multi-omics now permit investigation of previously inaccessible questions regarding transporter function[302,303]. By integrating CRISPR/Cas systems with single-cell transcriptomic readouts, researchers can precisely perturb and comprehensively characterize gene function within defined cell populations. High-content CRISPR screens at single-cell resolution facilitate identification of tissue-specific regulatory networks, providing critical insights into glucose transporter biology.

Therapeutic innovation may take multiple forms. Tissue-specific inhibitors could minimize off-target effects. Allosteric modulators might provide finer control than orthosteric inhibitors. Novel combination therapies could address multiple pathways simultaneously. GLUT-targeted therapies, particularly for cancer where metabolic reprogramming drives proliferation, merit continued development despite selectivity challenges[304]. Emerging evidence linking gut microbiota alterations to changes in intestinal glucose transport suggests that microbial modulation might affect SGLT1 expression and functional outcomes[305].

Pharmacogenomic studies could enable treatment selection based on individual transporter expression profiles, genetic variants affecting drug response, and disease-specific factors. Biomarkers predicting response to SGLT inhibitors or identifying patients at risk for adverse effects would optimize clinical decisions. SGLT2 inhibitors show promise beyond current indications, with ongoing trials evaluating efficacy in heart failure with preserved ejection fraction, acute kidney injury prevention, and polycystic kidney disease. Understanding mechanisms of benefit will identify additional patient populations likely to respond.

## Limitations of the present review and of current research

As a narrative review, this work is subject to inherent limitations. The breadth of the topic necessitated selective coverage of the literature, and the absence of a formal systematic search strategy introduces the possibility of selection bias. At the level of the underlying science, mechanistic insights into the lesser-characterized family members, including Class II and III GLUTs, SGLT3-6, and the SWEET transporter, derive largely from *in vitro* systems or rodent models, with limited human validation. Tissue-specific regulation remains incompletely defined, and single-cell transcriptomic data suggest that existing models will require revision. These gaps collectively define the priorities for the next phase of glucose transporter

research.

### Closing perspective

Glucose transporter research provides a compelling model for translational science. The integration of basic discoveries with clinical application demonstrates that even extensively studied biological systems can yield surprising therapeutic opportunities when examined from fresh perspectives. The journey from membrane transport characterization to blockbuster cardiovascular drugs illustrates how fundamental research ultimately serves patients. Continued investigation of glucose transporter biology promises novel insights and therapies that will improve outcomes across a spectrum of human diseases. As technologies advance and our understanding deepens, these essential proteins will undoubtedly reveal additional secrets, opening new therapeutic frontiers we cannot yet imagine. The field stands poised for its next transformative discoveries.

## DECLARATIONS

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### Authors' contributions

Conceived the idea: Bonner C, Moreno-Lopez M, Saponaro C, Louvet I, Jones JG
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Reviewed and edited the manuscript: Bonner C, Jones JG, Saponaro C
All authors reviewed and edited the manuscript.

### Availability of data and materials

Not applicable.

### AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool FigureLabs (https://www.figurelabs.ai/zh-CN) was used solely to modify and improve the graphic presentation of Figure 1. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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### Conflicts of interest

All authors declare that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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