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Expression of glucose transporters in metabolic syndrome

Expressão de transportadores de glicose na síndrome metabólica

Expresión de transportadores de glucosa en el síndrome metabólico

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ABSTRACT

Objective: To describe the main molecular mechanisms involved in the regulation of glucose transporters during metabolic syndrome. **Literature review:** Metabolic syndrome is a multifactorial metabolic disorder associated with environmental, behavioral, and genetic factors. Understanding the molecular mechanisms that lead to this pathology contributes to understanding the systemic changes observed and aids in the search for new treatments. The expression of glucose transporters (GLUTs) is closely linked to the regulation of glucose homeostasis in tissues. In metabolic syndrome, the regulation of GLUT expression undergoes alterations, leading to changes in glucose fluxes in tissues. Regarding GLUT4, its concentration in the membranes of adipocytes and myocytes decreases as a consequence of obesity and insulin resistance. Regarding GLUT2, its expression occurs differently in hepatocytes and pancreatic cells during metabolic syndrome, with an increase in the former and a decrease in the latter. Regarding GLUT1, its endocytosis occurs in epithelial cells in response to the hyperglycemia generated by metabolic syndrome. **Final considerations:** In metabolic syndrome, the regulation of GLUT expression undergoes alterations, leading to changes in glucose fluxes in tissues. These changes contribute to disturbances in glucose homeostasis and intracellular substrate metabolism, ultimately responsible for the observed functional alterations.

Keywords: Metabolic syndrome, Glucose transport proteins, Hyperglycemia, Insulin resistance, Diabetes mellitus.

RESUMO

Objetivo: Descrever os principais mecanismos moleculares envolvidos na regulação dos transportadores de glicose durante a síndrome metabólica. **Revisão bibliográfica:** A síndrome metabólica é um distúrbio metabólico multifatorial associado a fatores ambientais, comportamentais e genéticos. A compreensão dos mecanismos moleculares que levam a essa patologia contribui para o entendimento das alterações sistêmicas observadas e auxilia na busca por novos tratamentos. A expressão dos transportadores de glicose (GLUTs) está intimamente ligada à regulação da homeostase da glicose nos tecidos. Na síndrome metabólica, a regulação da expressão de GLUT sofre alterações, levando a alterações nos fluxos de glicose nos tecidos. Em relação ao GLUT4, sua concentração nas membranas de adipócitos e miócitos diminui em consequência da obesidade e da resistência à insulina. Em relação ao GLUT2, sua expressão ocorre de forma diferente nos hepatócitos e nas células pancreáticas durante a síndrome metabólica, com aumento no primeiro e diminuição

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no segundo. Em relação ao GLUT1, sua endocitose ocorre nas células epiteliais em resposta à hiperglicemia gerada pela síndrome metabólica. **Considerações finais:** Na síndrome metabólica, a regulação da expressão de GLUT sofre alterações, levando a alterações nos fluxos de glicose nos tecidos. Essas alterações contribuem para distúrbios na homeostase da glicose e no metabolismo do substrato intracelular, responsáveis, em última análise, pelas alterações funcionais observadas.

Palavras-chave: Síndrome metabólica, Proteínas transportadoras de glicose, Hiperglicemia, Resistência à insulina, Diabetes mellitus.

RESUMEN

Objetivo: Describir los principales mecanismos moleculares involucrados en la regulación de los transportadores de glucosa durante el síndrome metabólico**. Revisión de la literatura:** El síndrome metabólico es un trastorno metabólico multifactorial asociado con factores ambientales, conductuales y genéticos. Comprender los mecanismos moleculares que conducen a esta patología contribuye a la comprensión de los cambios sistémicos observados y facilita la búsqueda de nuevos tratamientos. La expresión de transportadores de glucosa (GLUT) está estrechamente relacionada con la regulación de la homeostasis de la glucosa en los tejidos. En el síndrome metabólico, la regulación de la expresión de GLUT sufre alteraciones, lo que conduce a cambios en los flujos de glucosa en los tejidos. Con respecto a GLUT4, su concentración en las membranas de adipocitos y miocitos disminuye como consecuencia de la obesidad y la resistencia a la insulina. Con respecto a GLUT2, su expresión ocurre de manera diferente en hepatocitos y células pancreáticas durante el síndrome metabólico, con un aumento en los primeros y una disminución en las segundas. Con respecto a GLUT1, su endocitosis ocurre en células epiteliales en respuesta a la hiperglucemia generada por el síndrome metabólico. **Consideraciones finales:** En el síndrome metabólico, la regulación de la expresión de GLUT se altera, lo que provoca cambios en los flujos de glucosa en los tejidos. Estos cambios contribuyen a alteraciones en la homeostasis de la glucosa y el metabolismo intracelular de sustratos, responsables en última instancia de las alteraciones funcionales observadas.

Palabras clave: Síndrome metabólico, Proteínas transportadoras de glucosa, Hiperglucemia, Resistencia a la insulina, Diabetes mellitus.

INTRODUCTION

Metabolic syndrome denotes a conjunct of interrelated risk factors that collectively heighten susceptibility to metabolic disease, with insulin resistance as its central hallmark. The syndrome is multifactorial, arising from behavioral determinants, such as unbalanced diet, obesity, and sedentarism, together with genetic predispositions linked to insulin resistance, hypertension, and dyslipidemia. These abnormalities rarely occur in isolation and amplify one another, especially in the context of excess caloric intake and a sedentary lifestyle (FAHED Z, et al., 2022).

A sedentary lifestyle combined with a hypercaloric diet promotes obesity and precipitates insulin resistance. In this network of interacting drivers, insulin resistance functions as the pivotal link among dyslipidemia, adiposity, and impaired glucose regulation (ANDERSON DP, et al., 2023).

Mechanistically, insulin resistance reflects diminished insulin sensitivity in target tissues; pancreatic β-cells initially compensate through hyperinsulinemia but may ultimately fail to sustain secretion. Concomitantly, enhanced lipolysis elevates circulating free fatty acids, fostering intramyocellular lipid deposition that disrupts GLUT4 translocation to the sarcolemma and thereby limits glucose uptake (JIANG H, et al., 2022).

In parallel, hyperactivity of the renin–angiotensin–aldosterone system interferes with insulin signaling, further aggravating insulin resistance. At the molecular level, metabolic syndrome engenders systemic and cellular disturbances that extend to the expression and trafficking of glucose transporters. Because these transporters are essential gatekeepers of glucose homeostasis, alterations in their abundance or localization can reprogram cellular metabolism and exacerbate whole-body dysglycemia (ZAMOLODCHIKOVA TS, et al., 2024).

Although relatively few studies directly interrogate the impact of metabolic syndrome per se on glucose transporter expression, the evidence base expands considerably when individual components of the syndrome are examined. Clarifying how the syndrome reshapes glucose handling is therefore critical for informing preventive strategies and therapeutics aimed at mitigating symptoms and improving quality of life. In this context, the present integrative review synthesizes how metabolic syndrome modulates GLUT1 in the cerebrovascular endothelium, GLUT2 in hepatocytes and pancreatic β-cells, and GLUT4 in adipose and skeletal muscle. Our goal is to delineate the molecular mechanisms governing glucose transporter regulation under the pathophysiological conditions that define metabolic syndrome.

LITERATURE REVIEW

Glucose Transporters

Glucose transporter proteins (GLUTs) comprise a superfamily of facilitative monosaccharide carriers embedded in the plasma membrane. Encoded by the *SLC2A* gene family, these approximately 500 amino-acid proteins contain 12 transmembrane α-helices with cytosolic N- and C-terminals. When expressed at the cell surface, GLUTs mediate the energy-independent transport of hexoses across biological membranes (NAVALE A, 2019).

GLUT1 preferentially transports glucose but can also carry mannose, galactose, and glucosamine. It is widely expressed, with particularly high abundance in the erythrocyte membrane, and is indispensable for cerebral glucose uptake. In the central nervous system, glucose is the primary metabolic fuel, and its delivery is tightly regulated at the blood–brain barrier. GLUT1 also mediates maternal–fetal glucose transfer across the placenta; consequently, alterations in placental GLUT1 expression can have significant implications for fetal development and pathology (PRAGALLAPATI S and MANYAM R, 2019).

The GLUT2 and GLUT4 transporters are in specific and distinct cell types. GLUT2 is expressed predominantly in hepatocytes and is also present in enterocytes, proximal convoluted tubule cells of the kidney, pancreatic β-cells, and, at lower levels, in certain neuronal populations. In pancreatic β-cells, GLUT2-dependent glucose entry is integral to the glucose-sensing pathway that triggers glucose-stimulated insulin secretion. Having outlined the tissue distribution of key GLUT isoforms, we next consider insulin-dependent signaling mechanisms that regulate GLUT4 translocation (VAN GERWEN J, et al., 2023).

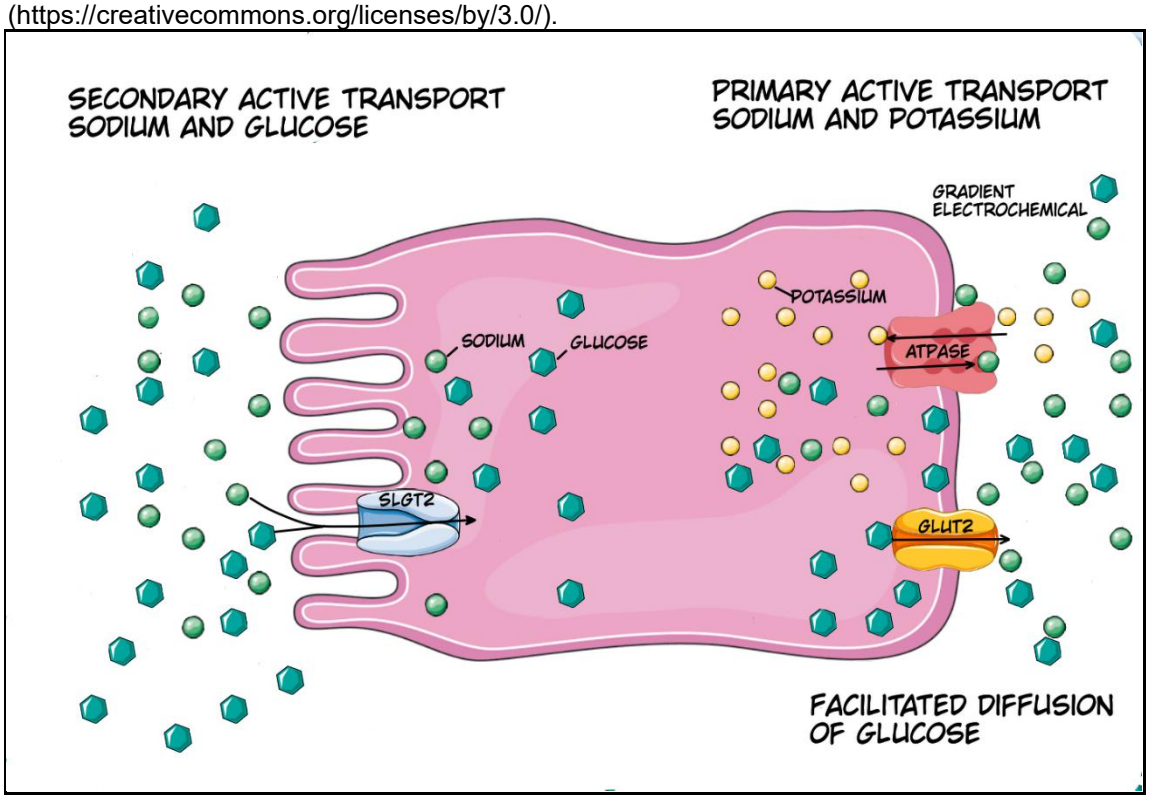
GLUT4 is the principal insulin-responsive glucose transporter in adipocytes and skeletal muscle. In the basal (low-insulin) state, GLUT4 resides predominantly in intracellular storage vesicles. Following a postprandial rise in insulin, GLUT4-containing vesicles translocate to and fuse with the plasma membrane, thereby augmenting glucose uptake and utilization in these tissues and limiting postprandial hyperglycemia. Failure of insulin-mediated GLUT4 translocation underlies peripheral insulin resistance and, together with impaired β-cell function, contributes to the pathogenesis of type 2 diabetes mellitus (T2DM) (WANG T, et al., 2020).

Insulin action on glucose homeostasis

Glucose is a fundamental substrate for cellular energy homeostasis, obtained from the diet and produced endogenously via glycogenolysis and gluconeogenesis. In the small intestine, dietary glucose is absorbed by enterocytes through secondary active transport mediated by the sodium–glucose cotransporter 1 (SGLT1).

The basolateral Na^+/K^+-ATPase maintains a steep transmembrane Na^+ gradient, which furnishes the electrochemical energy that drives apical Na^+-coupled glucose uptake through SGLT1. After entry, glucose exits the cell across the basolateral membrane primarily via GLUT2 to the portal circulation. Beyond intestinal uptake, glucose handling by the endocrine pancreas is a principal determinant of systemic glycemic excursions (KOEPSELL H, 2020) (**Figure 1**).

Figure 1 - Illustrative diagram of the intestinal glucose transport. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).



Source: Silva DG, et al., 2026.

Glucose enters pancreatic β-cells by facilitated diffusion through GLUT transporters, predominantly GLUT2 in rodents (and largely GLUT1/GLUT3 in humans). Once inside, glucose metabolism elevates the ATP/ADP ratio, causing closure of ATP-sensitive K^+ (KATP) channels. Reduced K^+ efflux depolarizes the plasma membrane, which opens voltage-gated Ca^{2+} channels, raises cytosolic Ca^{2+}, and triggers exocytosis of insulin-containing granules (MIAO L, et al., 2026).

Insulin, released in response to rising glycemia, initiates intracellular signaling by binding the insulin receptor (IR), a heterotetrameric receptor tyrosine kinase composed of two extracellular α-subunits and two transmembrane β-subunits. Ligand engagement promotes β-subunit autophosphorylation on tyrosine residues and subsequent phosphorylation of insulin receptor substrates 1 and 2 (IRS-1/IRS-2), which nucleate downstream signaling complexes (MARTÍNEZ BÁEZ A, et al., 2024).

Activated IRS proteins recruit and stimulate class I phosphatidylinositol 3-kinase (PI3K), catalyzing the conversion of phosphatidylinositol-4,5-bisphosphate (PIP_2) to phosphatidylinositol-3,4,5-trisphosphate (PIP_3). PIP_3 then serves as a docking site for pleckstrin-homology–domain proteins, including 3-phosphoinositide–dependent protein kinase-1 (PDK1) and Akt (protein kinase B). PDK1 together with mTORC2 activates Akt, and parallel inputs engage atypical protein kinase C (aPKC), coordinating the signaling required for glucose transporter trafficking (HATAKEYAMA H, et al., 2019).

These pathways converge to mobilize GLUT4 to the plasma membrane. Akt phosphorylates the Rab-GTPase–activating proteins TBC1D1 and TBC1D4 (AS160), inhibiting their GAP activity and thereby permitting Rab-GTP–dependent vesicle trafficking. In concert, aPKC-dependent steps and the Ca^{2+}-sensing effector DOC2B facilitate assembly of the SNARE machinery (e.g., syntaxin-4, SNAP23, VAMP2) that mediates vesicle fusion. The net effect is increased surface GLUT4 and augmented glucose uptake (DROBIOVA H, et al., 2025).

The action of adipose tissue in regulating glucose metabolism

Adipose tissue comprises white and brown depots that store metabolic energy as triacylglycerols while also fulfilling thermoregulatory and mechanical-protective roles (DRAGOO JL, et al., 2023). Beyond passive storage, adipose tissue is an active endocrine organ that expresses and secretes numerous bioactive mediators (adipokines), with local and systemic effects on insulin sensitivity, immune tone, and vascular biology (CLEMENTE-SUÁREZ VJ, et al., 2023).

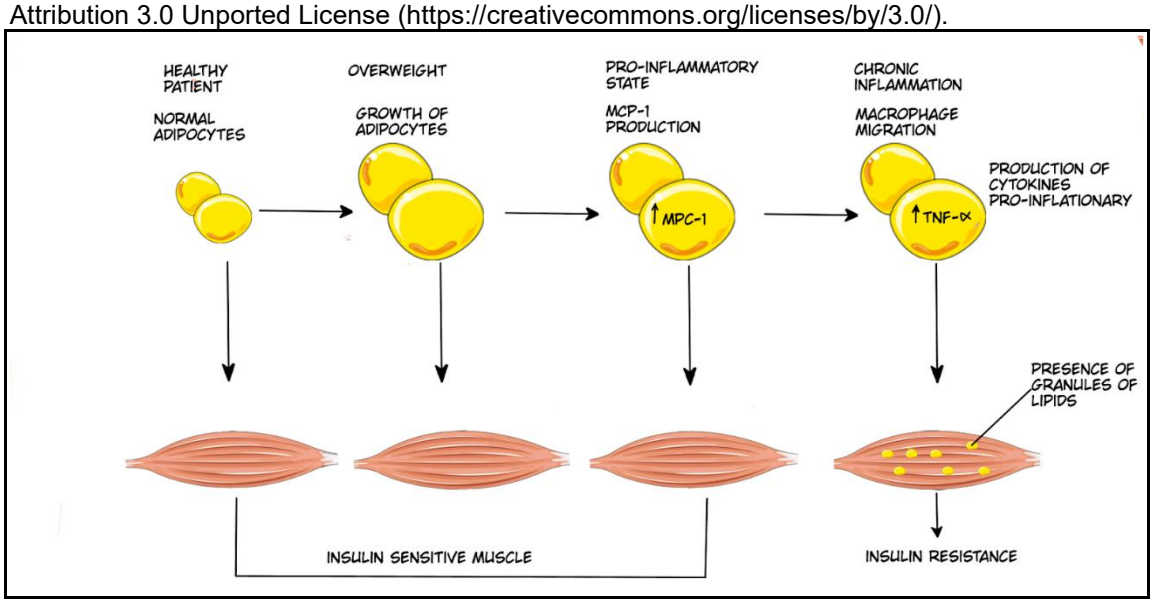
The leptin is a prototypical adipokine, suppresses appetite and increases energy expenditure through hypothalamic actions. Its long signaling isoform receptor (Ob-Rb) dimerizes upon ligand binding and engages Janus kinase 2 (JAK2), which phosphorylates tyrosine residues that recruit downstream effectors, classically STAT3 and, in certain contexts, IRS–PI3K signaling. Through this crosstalk, leptin can potentiate insulin action in metabolic tissues, facilitating pathways that culminate in GLUT4 translocation to the plasma membrane (PEREIRA S, et al., 2021).

Adiponectin enhances insulin sensitivity and exerts anti-inflammatory, antidiabetic, and antiatherogenic effects. It signals via the receptors AdipoR1 and AdipoR2, with the adaptor protein APPL1 coupling receptor activation to the LKB1–AMPK axis. AMPK activation promotes phosphorylation of the Rab-GTPase–activating proteins TBC1D1 and TBC1D4 (AS160), relieving their inhibitory tone on Rab-dependent vesicle trafficking and thereby increasing GLUT4 delivery to the cell surface. In parallel, adiponectin augments lipid catabolism by upregulating PPAR-α activity and downstream targets such as acyl-CoA oxidase and uncoupling proteins (UCPs), collectively supporting fatty-acid oxidation and energy expenditure (PEREIRA S et al., 2021).

Obesity is a principal driver of metabolic syndrome and insulin resistance. In adipose tissue and skeletal muscle, insulin signaling is blunted through reduced insulin-receptor abundance and kinase activity, diminished tyrosine phosphorylation of IRS proteins, and attenuated PI3K activation, defects that impair GLUT4 translocation and glucose uptake (CHOO YN, et al., 2026).

In energy balance, dietary triacylglycerol intake is matched by catabolism, with excess stored in adipocytes. Under chronic caloric excess, adipocytes enlarge (hypertrophy) as triacylglycerol accrues; hypertrophic adipocytes secrete chemokines such as monocyte chemoattractant protein-1 (MCP-1), recruiting monocytes/macrophages into adipose tissue and fostering a pro-inflammatory milieu. This immune infiltration amplifies cytokine signaling that further disrupts insulin action (KOLB H, 2026) (**Figure 2**).

Figure 2 - Insulin resistance in muscles. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).



Source: Silva DG, et al., 2026.

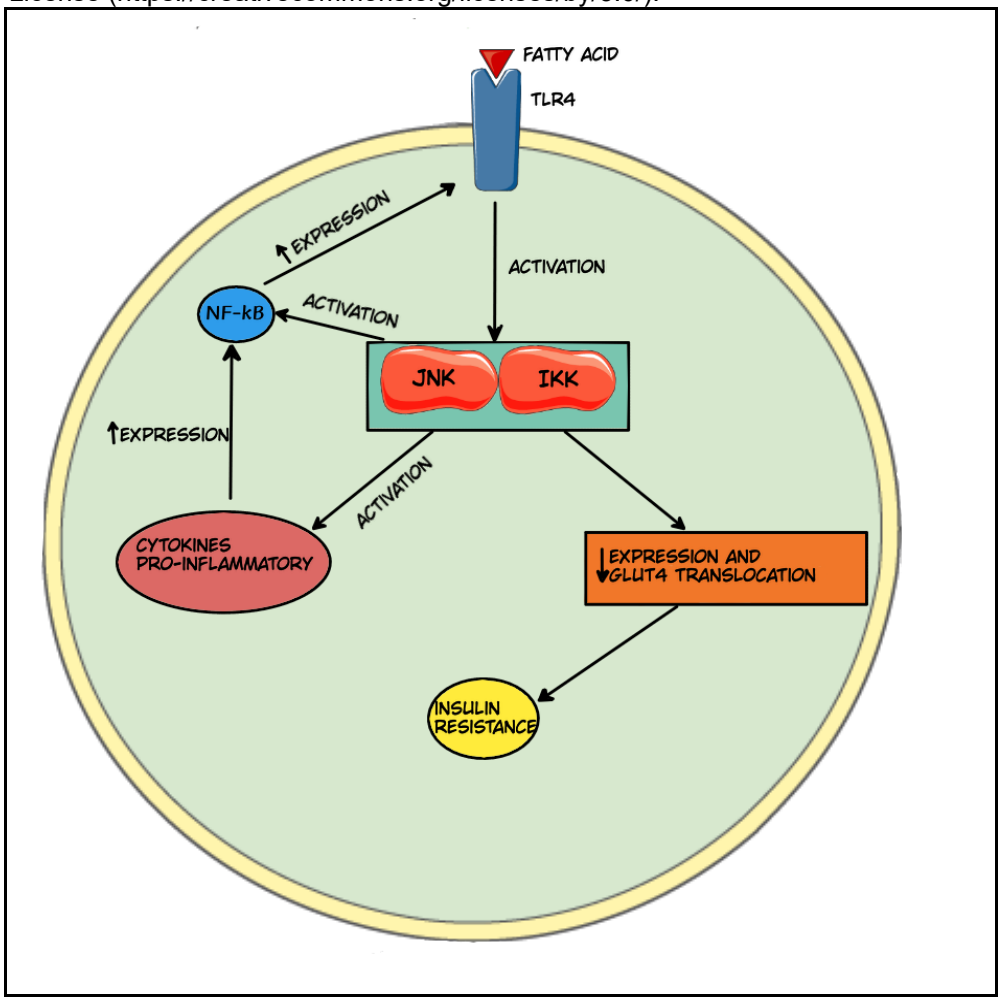
After infiltrating adipose tissue, macrophages secrete pro-inflammatory cytokines, most notably tumor necrosis factor-α (TNF-α), that stimulate adipocyte lipolysis and increase the release of free fatty acids (FFAs) into the circulation.

FFAs are subsequently delivered to skeletal muscle and to the liver via the portal vein, where their accumulation drives ectopic lipid deposition (intramyocellular and hepatic lipid droplets). These lipotoxic stores impair insulin action in part by reducing GLUT4 translocation to the plasma membrane (LAIR B, et al., 2020).

The TNF-α cytokine activates c-Jun N-terminal kinase (JNK), which cooperates with the nuclear factor-κB (NF-κB) pathway to sustain inflammatory signaling. NF-κB activation amplifies cytokine production, which further stimulates JNK activity, establishing a positive feedback loop that promotes chronic, low-grade inflammation.

In parallel, FFAs can engage Toll-like receptor 4 (TLR4) on adipocytes and immune cells, initiating MyD88-dependent cascades that activate both JNK and the IκB kinase (IKK) complex. JNK and IKK target insulin receptor substrates (IRS1/IRS2) for inhibitory serine phosphorylation, which blunts subsequent tyrosine phosphorylation by the insulin receptor. The net effect is attenuation of PI3K–Akt signaling and impaired GLUT4 vesicle trafficking, reinforcing insulin resistance in metabolic tissues (BURHANS MS, et al., 2018) (**Figure 3**).

Figure 3 - The action of inflammation in suppressing GLUT4 expression. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).



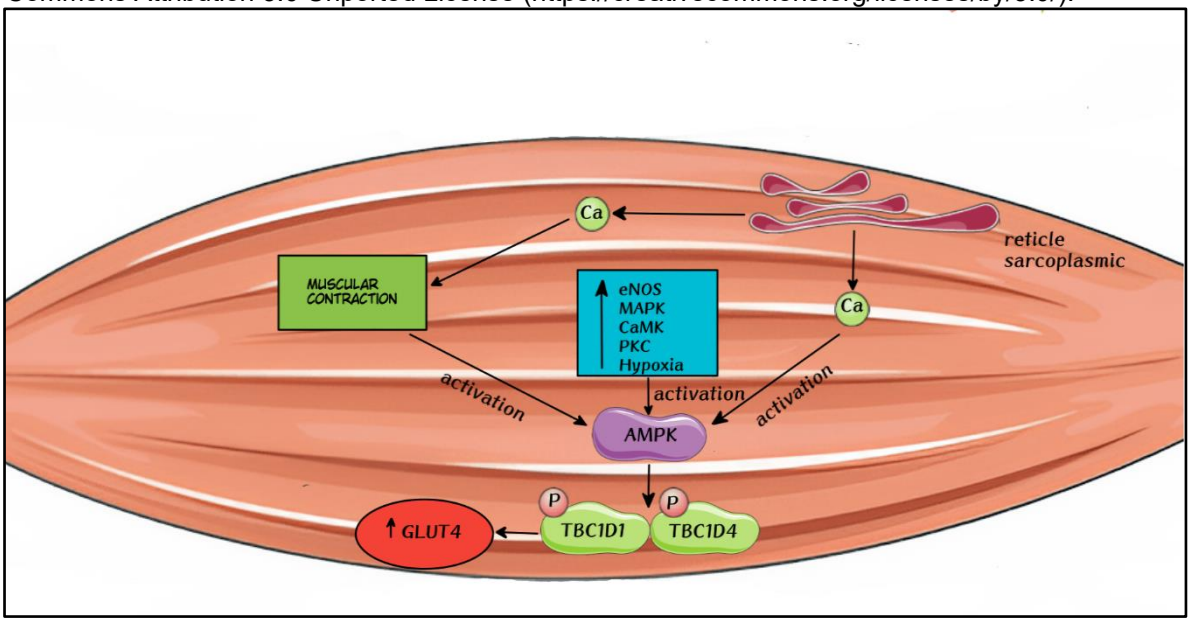
Source: Silva DG, et al., 2026.

The action of muscle contraction in regulating GLUT4 expression

Skeletal muscle uses multiple substrates for ATP production, including phosphocreatine, circulating glucose, glucose derived from intramuscular glycogen, and fatty acids. When lipid availability is high, β-oxidation predominates; conversely, under carbohydrate-rich conditions, glucose/glycogen becomes the principal fuel (ALGHANNAM AF, et al., 2021). During hypoxia or sustained contractile activity, myofibers rapidly increase glucose uptake by promoting GLUT4 translocation via AMP-activated protein kinase (AMPK)–dependent mechanisms (POLLAK N, et al., 2025).

AMPK is activated by a rise in the AMP/ADP:ATP ratio through LKB1, and by elevations in cytosolic Ca^{2+} via Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK). Ca^{2+}-mobilizing stimuli such as bradykinin and enhanced nitric-oxide signaling can further support this response. In parallel, contractile cues engage additional nodes, including atypical protein kinase C (aPKC) and select MAPK modules, that converge with AMPK to facilitate GLUT4 vesicle trafficking and glucose uptake (GARCIA D and SHANW RJ, 2017) (**Figure 4**).

Figure 4 - Influence of muscle contraction on GLUT4 expression. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).



Source: Silva DG, et al., 2026.

In metabolic syndrome, insulin resistance is accompanied by compensatory hyperinsulinemia; PI3K–Akt arm of insulin signaling is selectively impaired, attenuating nitric oxide synthase activation and reducing nitric oxide bioavailability in the microvasculature. Diminished microvascular recruitment, together with a lower drive on AMPK-activating cues (energetic stress and Ca^{2+}-dependent pathways), converges to blunt insulin-independent GLUT4 translocation at the sarcolemma of skeletal muscle fibers, thereby limiting glucose uptake (MIAO R, et al., 2022).

Regulation of GLUT2 transcription factors in hepatocytes

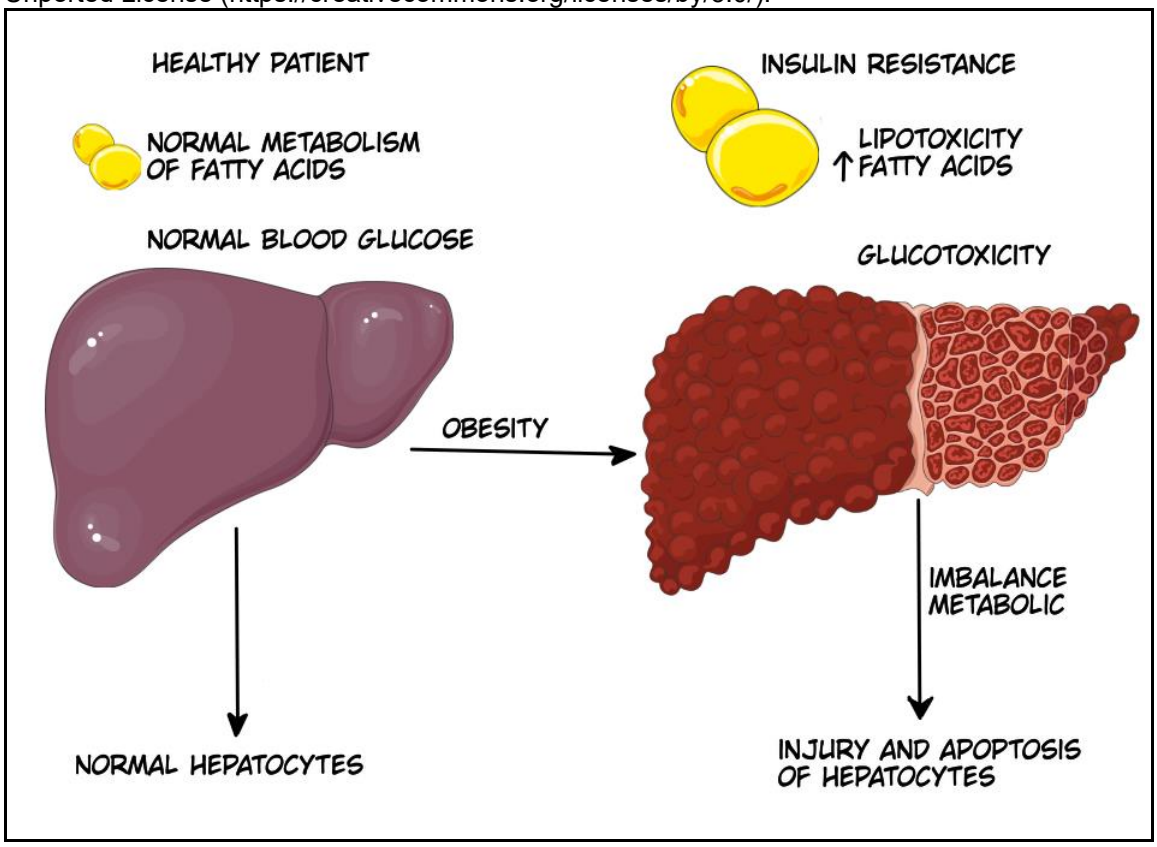
The liver is central to whole-body glucose homeostasis. Hepatocytes take up and release glucose via GLUT2, a high-capacity, low-affinity transporter that operates bidirectionally by facilitated diffusion according to concentration gradients. In hyperglycemia, insulin suppresses hepatic glucose production and promotes glycogen synthesis, establishing an inward gradient that favors glucose influx; in hypoglycemia, hepatocytes curtail glycogenesis and increase glycogenolysis and gluconeogenesis, creating an outward gradient that favors glucose efflux to the circulation (SUN B, et al., 2023).

GLUT2 expression is transcriptionally regulated by glucose-responsive pathways. Hepatocyte nuclear factors (HNF) bind cis-elements within the SLC2A2 locus to stimulate transcription; among these, HNF-3β (FOXA2) is a forkhead transcription factor whose activity is restrained by insulin through Akt-mediated phosphorylation.

Thus, insulin signaling attenuates FOXA2-driven programs controlling GLUT2 and enzymes of gluconeogenesis, glycogenolysis, and glycolysis (SUN B, et al., 2023). In parallel, sterol regulatory element-binding protein-1c (SREBP-1c), a lipogenic transcription factor induced by glucose/insulin, can associate with regulatory regions of SLC2A2, enhancing GLUT2 transcription (LI M, et al., 2022).

In metabolic syndrome, insulin resistance and hyperglycemia dysregulate these transcriptional networks, tending to upregulate SLC2A2 and elevate GLUT2 abundance. Concomitantly, increased flux of free fatty acids in obesity drives hepatic lipotoxicity and glucotoxicity, fostering non-alcoholic fatty liver disease. As FFAs surge, hepatocytes mount adaptive increases in mitochondrial β-oxidation while simultaneously channeling lipids into triacylglycerol and bioactive intermediates; the resulting metabolic stress amplifies inflammation and oxidative injury, culminating in hepatocyte dysfunction and apoptosis (WANG X, et al., 2019) (**Figure 5**).

Figure 5 - Lipotoxicity in hepatocytes. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).



Source: Silva DG, et al., 2026.

Differential regulation of GLUT2 transcription factors in the pancreas

Glucose is indispensable for triggering insulin granule exocytosis in pancreatic β-cells. In rodent β-cells, glucose enters predominantly via GLUT2; chronic hyperglycemia, in contrast to its effects in hepatocytes and renal tubules, downregulates β-cell GLUT2 expression (SHEN Z, et al., 2024). Pancreatic and duodenal homeobox 1 (PDX1) is the principal β-cell transcription factor governing both insulin and β-cell–specific GLUT2 expression. PDX1 binds regulatory elements within the SLC2A2 promoter to drive transcription (ZHANG Y, et al., 2022).

Acutely, rising glucose enhances PDX1 activity and supports GLUT2 expression; however, prolonged hyperglycemia induces a compensatory downregulation of PDX1 and its target genes, a response often interpreted as a protective brake against glucotoxic stress (LEE JH and LEE J, 2022).

Multiple stress pathways converge to suppress PDX1. In β-cells, chronic hyperglycemia activates SREBP-1c, promoting lipid accumulation and attenuating PDX1 expression. Hyperglycemia-induced endoplasmic reticulum stress further compromises β-cell function by fostering oxidative stress and diminishing PDX1 binding to DNA. Elevated free fatty acids exert additional lipotoxic pressure; sustained exposure to palmitate impairs insulin gene transcription by reducing PDX1 occupancy at its promoter (ZHANG M, et al., 2021).

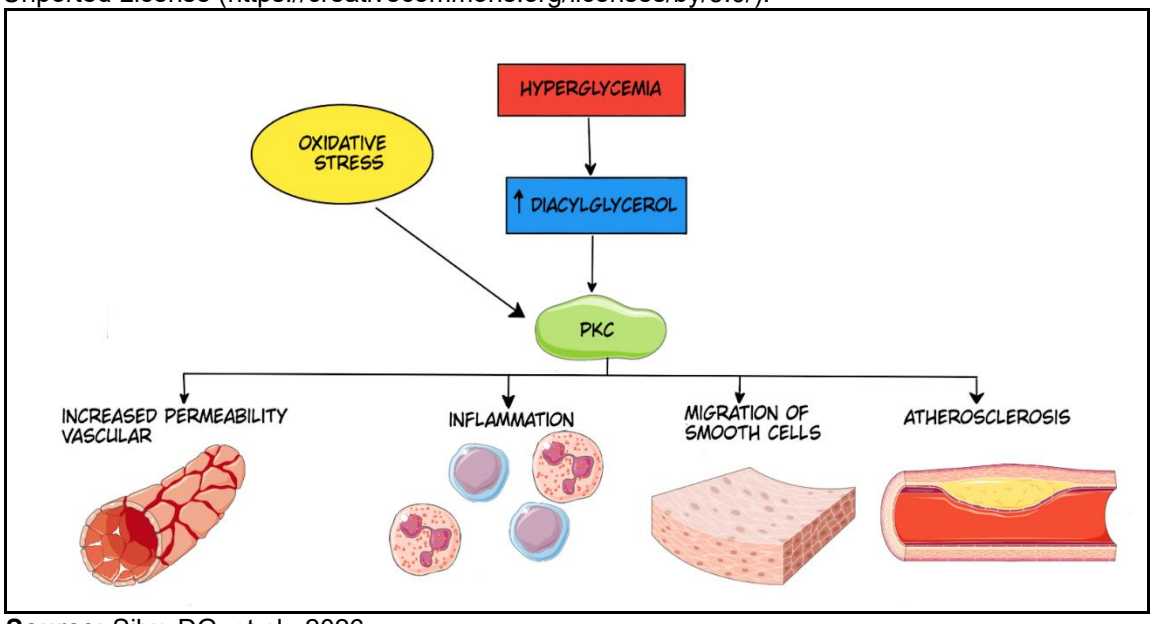
Reactive oxygen species also modulate PDX1 localization and function. Through JNK activation, oxidative stress promotes PDX1 nuclear export to the cytoplasm, thereby weakening its transcriptional control of the insulin gene. Collectively, the decline in PDX1 undermines both SLC2A2 (GLUT2) and insulin expression, providing a mechanistic link between chronic hyperglycemia, β-cell dysfunction, and the reductions observed in metabolic syndrome (BAUMEL-ALTERZON S and SCOTT DK, 2022).

The action of hyperinsulinemia on endothelial cells

GLUT1 is the principal facilitative glucose transporter in brain microvascular endothelial cells that form the blood–brain barrier (BBB). In metabolic syndrome, chronic hyperglycemia can drive a protective reduction in endothelial glucose flux by promoting clathrin-mediated endocytosis of surface GLUT1, thereby limiting glucotoxicity and oxidative stress–induced endothelial dysfunction. A key mediator of this response is thioredoxin-interacting protein (TXNIP), which restrains tissue glucose uptake by orchestrating GLUT1 internalization via the clathrin/AP-2 endocytic machinery (DYKSTRA H, et al., 2021).

Upon glucose- and stress-dependent induction, cytosolic TXNIP engages the cytoplasmic N terminus of GLUT1 and, through its C-terminal interfaces, couples the transporter to clathrin coat components. In canonical clathrin-dependent endocytosis, the N-terminal endocytic motif of GLUT1 serves as a docking signal for the adaptor protein complex AP-2; TXNIP functions as a dual-capture scaffold, binding GLUT1 and the clathrin/AP-2 complex, aiming to accelerate transporter internalization and curb glycolytic influx under hyperglycemic conditions. During insulin stimulation, TXNIP levels/activity are suppressed, disrupting this dual capture and preventing inappropriate GLUT1 endocytosis (WALDHART AN, et al., 2017) (**Figure 6**).

Figure 6 - PKC mechanisms of action. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).



Source: Silva DG, et al., 2026.

Transcription of the *TXNIP* gene is driven by the carbohydrate-responsive element-binding protein ChREBP, which binds regulatory motifs in the TXNIP promoter. ChREBP's subcellular localization and DNA binding are governed by reversible phosphorylation: protein kinase A (PKA) and AMP-activated protein kinase (AMPK) phosphorylate ChREBP to retain it in the cytosol and suppress transcription, whereas dephosphorylation promotes nuclear accumulation and target-gene activation. Under hypoglycemic conditions, glucagon–cAMP signaling activates PKA, which phosphorylates ChREBP on serine/threonine residues and maintains its cytosolic sequestration. Energetic stress likewise engages AMPK, further restraining ChREBP activity. By contrast, sustained hyperglycemia favors ChREBP dephosphorylation and nuclear entry, thereby enhancing TXNIP transcription (WU N, et al., 2013).

In parallel, chronic hyperglycemia activates protein kinase C (PKC) signaling. Excess glucose drives flux through the polyol pathway (glucose; sorbitol; fructose), shifting the NADH/NAD^+ redox balance and fostering diacylglycerol (DAG) accumulation, a direct activator of PKC isoforms. PKC exerts multiple vasculopathy effects, including inhibitory threonine phosphorylation of endothelial nitric-oxide synthase (eNOS), reduced nitric-oxide bioavailability, heightened expression of chemokines and inflammatory cytokines, vascular smooth-muscle cell migration into the intima, and foam-cell formation-events that collectively promote atherogenesis (WALDHART, et al., 2017).

FINAL CONSIDERATIONS

The expression and trafficking of GLUTs, governed by tissue-specific transcriptional programs, are integral to glucose homeostasis. In metabolic syndrome, chronic hyperglycemia, lipotoxicity, and inflammation disrupt these programs, redirecting glucose fluxes and altering intracellular substrate metabolism. In adipose tissue and skeletal muscle, defects along the IR–IRS–PI3K–Akt axis reduce insulin-stimulated GLUT4 translocation (and, in some contexts, expression), driving peripheral insulin resistance and loss of glycemic control. In pancreatic β-cells, prolonged gluco lipotoxic stress diminishes PDX1 activity and lowers GLUT2, impairing glucose-stimulated insulin secretion. At the blood–brain barrier, TXNIP-dependent, clathrin/AP-2–mediated endocytosis reduces surface GLUT1 as a compensatory brake on glucotoxicity, while hyperglycemia-PKC signaling promotes endothelial dysfunction and atherogenesis. Collectively, these GLUT-centered alterations help explain the organ-specific dysfunctions that characterize metabolic syndrome.

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