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Metabolic reprogramming in diabetes and other endocrine and metabolic disorders: exploring the Warburg effect, ketones, and SGLT2 inhibitors

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Abstract

The "Warburg effect", a metabolic adaptation observed in dividing cells, involves a shift from mitochondrial oxidative phosphorylation to cytoplasmic glucose metabolism. This metabolic process is characterized by increased cellular uptake of glucose and glutamine, elevated intracellular pH and sodium levels, enhanced protection against oxidative stress, altered autophagy, and increased lactate production. Initially identified by Otto Warburg in cancer cells, the Warburg effect is now recognized as a common feature of all dividing cells, prioritizing biomass production for cell proliferation over energy generation for specialized cellular functions. Indeed, the Warburg effect is emerging as an important feature not only in cancer but also in a range of metabolic, endocrine, and neurological chronic disorders, including type 2 diabetes, heart and kidney failure, therapy-refractory epilepsy, Alzheimer's and Parkinson's diseases, chronic fatigue syndrome, and post-viral syndromes. The prevailing notion that "dysfunctional mitochondria" are the primary cause of the "energy deficit" observed in these conditions may be misleading. Instead, this "energy deficit" can result from cells reprogramming their metabolism to support cell division. Additionally, in these disorders, senescent cells are abundant, exhibiting a Warburg-like metabolism with cell cycle arrest and enhanced anabolic activity. This review explores the multifaceted role of the Warburg effect in type 2 diabetes and other metabolic and endocrine chronic disorders and examines the therapeutic potential of different interventions such as intermittent fasting, ketogenic diets, ketone supplements, and sodium/glucose co-transporter 2 inhibitors. Through a comprehensive analysis of existing literature, we aim to shed light on the mechanisms underlying these interventions and their potential impact on disease progression and patient outcomes.

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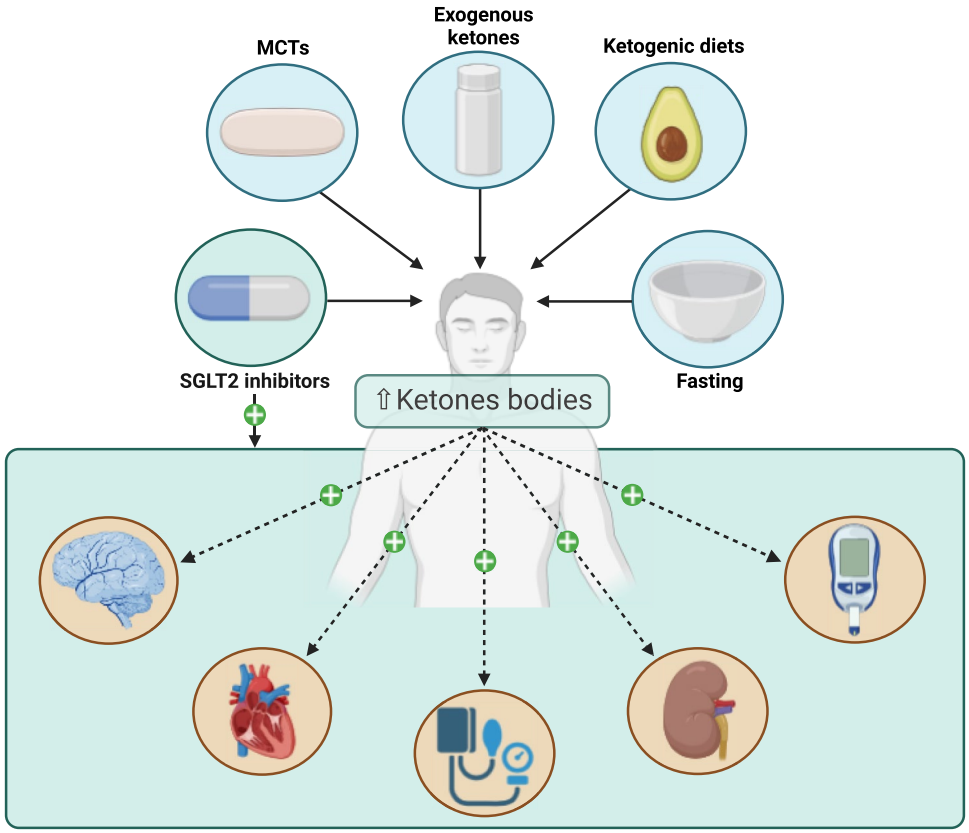
Graphical Abstract



Keywords Warburg effect · Sodium/glucose cotransporter · Ketones · Diabetes · Heart failure · Senescent cells

Abbreviations

GFR	Glomerular filtration rate
GLP	Glucagon-like peptide
mTOR	Mechanistic target of rapamycin
MCTs	Medium-chain triglycerides
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3
NMN	Nicotinamide mononucleotide
NR	Nicotinamide riboside
OXPHOS	Oxidative phosphorylation
SASP	Senescence-associated secretory phenotype
SGLT	Sodium/glucose cotransporter
T2D	Type 2 diabetes
TCA	Tricarboxylic acid

1 Introduction

The "Warburg effect", a metabolic adaptation initially observed in cancer cells by Otto Warburg [1, 2], reflects a fundamental shift in cellular energy production [3, 4]. This change, from mitochondrial oxidative phosphorylation to cytoplasmic glucose metabolism [3], also known as "aerobic glycolysis" or "aerobic fermentation" [4], is not exclusively associated with cancer cells but is increasingly recognized as a common feature of all dividing cells [5–8]. It comprises several key metabolic alterations including increased cellular uptake and utilization of glucose and glutamine, elevated intracellular pH and sodium levels, enhanced protection against oxidative stress, altered autophagy, and increased lactate production [3, 7, 9–17].

During cell division, cellular functions are predominantly focused on producing essential components such as DNA, cell membranes, and proteins [5, 6, 11]. Dividing cells are typically undifferentiated and do not exhibit the specialized functions of their differentiated, post-mitotic counterparts. Instead, they prioritize using glucose to synthesize these building blocks, rather than generating energy, which is crucial for supporting primary functions of mature, specialized cells [9, 11, 18, 19]. While it may seem that mitochondria, often regarded solely as energy generators, are "dysfunctional" in dividing cells, this does not appear to be the case [2, 4, 6, 7, 11]. Driven by mitogenic signals, mitochondria in dividing cells actively engage in anaplerosis [4, 9, 20,

21], synthesizing intermediates [e.g., of the tricarboxylic acid (TCA) cycle] needed for critical biological reactions [9]. This is achieved mainly through the uptake and utilization of glucose and glutamine [9, 22]. Importantly, pyruvate derived from cytoplasmic glycolysis is minimally utilized by the mitochondria in dividing cells. The transport of pyruvate into the mitochondria and its conversion to acetyl-CoA, the usual substrate for the TCA cycle, is severely reduced [23–26]. Instead, intermediates from both glycolysis and the TCA cycle are redirected toward the synthesis of key molecules, such as ribose, glycerol, fatty acids, heme, NADPH, non-essential amino acids, and new glucose via gluconeogenesis [3, 5, 9, 25, 27] (Fig. 1).

These molecules play critical roles as building blocks for nucleic acids, membrane lipids, proteins, and peptides (such as the antioxidant glutathione), among other components that are needed for the formation of daughter cells and for pathogen replication during intracellular infection [35]. The aforementioned metabolic shifts define the main features of the "Warburg effect in cellular metabolism", where increased cellular glucose uptake leads to elevated lactate production, despite aerobic conditions [3–6, 9, 11, 19, 36–40]. As detailed in subsequent Section 3, Section 4, Section 5, and Section 7, the reprogramming of cellular metabolism toward the Warburg effect is increasingly recognized as a common mechanism underlying various seemingly unrelated conditions [6, 34, 38, 39, 41, 42].

This review explores the therapeutic potential of targeting metabolic alterations associated with the Warburg effect, with a focus on interventions such as ketogenic strategies and sodium/glucose cotransporter 2 (SGLT2) inhibitors. Our discussion spans diverse contexts, from cancer to chronic endocrine, metabolic, and neurodegenerative disorders, highlighting the broad impact of these interventions on disease progression and patient outcomes.

2 SGLT2 inhibitors and the Warburg effect

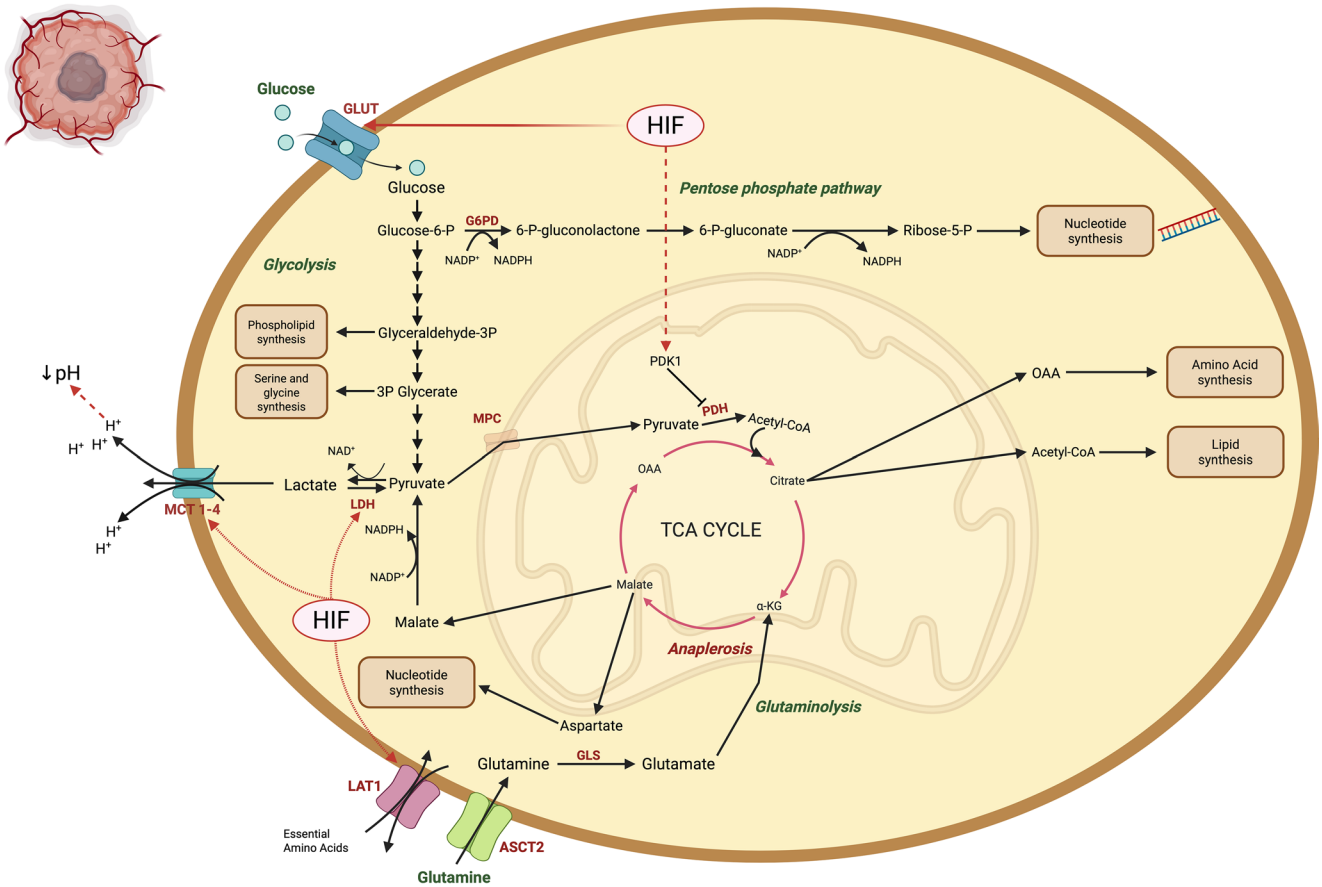
2.1 The rise of SGLT2 inhibitors

The discovery that SGLT2 inhibitors not only improve glucose homeostasis in patients with type 2 diabetes (T2D) but also provide protection against late-stage diabetes complications such as kidney failure, heart failure, and major adverse cardiovascular events has expanded the clinical utility of these drugs [43–48]. Indeed, landmark clinical trials and subsequent detailed analyses have shown that the benefits of SGLT2 inhibitors extend across various patient subgroups, including individuals with and without T2D, those at different stages of chronic kidney disease, and patients with heart failure, whether they have preserved or reduced ejection fraction [46–49]. Importantly, the cardiorenal protection offered by SGLT2 inhibitors extends beyond improved glucose control, as evidenced by the benefits observed in patients without T2D [46, 49, 50]. Moreover, SGLT2 inhibitors were found to exert several effects on the heart that are independent of glucose control [45, 51], underscoring their multifaceted therapeutic potential. However, despite these significant findings, the precise mechanisms underlying the cardiovascular benefits of SGLT2 inhibitors remain incompletely understood. Several explanations have been proposed, including a modest reduction in body weight and blood pressure, decreased renal sodium reabsorption leading to early natriuresis, and sustained osmotic diuresis driven by increased urinary glucose excretion, resulting in lower plasma volume [45]. Additional proposed effects include increased erythropoietin production and erythropoiesis, suppression of sympathetic nervous system activity, upregulation of endogenous antioxidant capacity, reduction of endoplasmic reticulum stress, promotion of mitochondrial biogenesis, attenuation of inflammatory responses (through the inhibition of nuclear factor kappa B and the NOD-, LRR-, and pyrin domain-containing protein 3 [NLRP3] inflammasome), improved vascular function, and shifts in energy-producing substrates [45, 51–53], which will be explored further in Section 2.3.

The primary renoprotective effects of SGLT2 inhibitors are thought to arise from a reduction in glomerular capillary hypertension and hyperfiltration. This decrease, partly mediated by "tubulo-glomerular feedback" (discussed in Section 2.2), alleviates physical stress on the filtration barrier, reduces albuminuria, and lowers oxygen demand for tubular reabsorption [53].

2.2 Renoprotective effects of SGLT2 inhibitors

Within the kidney's smallest functional unit, the nephron, intrarenal autoregulatory mechanisms protect the kidney from elevations in blood pressure that would otherwise be transmitted to the sensitive glomerular capillaries and cause injury. Such autoregulation allows the kidney to maintain a relatively constant glomerular filtration rate (GFR), which is necessary for the clearance of metabolic wastes while efficiently recovering filtered nutrients and electrolytes by the renal tubules [54]. Tubulo-glomerular feedback is one of these autoregulatory mechanisms and, since the seminal work by Kidokoro et al. [55], has gained much interest as an important mediator of the renal benefits of SGLT2 inhibitors [56, 57]. This feedback mechanism senses the concentration of sodium chloride in the tubular fluid reaching the macula densa cells in the distal tubule and adjusts the diameters of the afferent arteriole accordingly [57–60].



As blood flows through the kidneys, circulating glucose is filtered by the renal glomeruli. The kidneys efficiently recover about 99% of filtered glucose in the proximal tubule under normal blood glucose levels [61]. Glucose entry into proximal tubular cells is insulin-independent and is facilitated by both glucose transporters on the basolateral membrane and SGLTs on the apical membrane [62]. The majority of tubular glucose reabsorption (80–90%) occurs in the early proximal tubule via SGLT2, with SGLT1 handling most of the remaining luminal glucose in the later sections of the proximal tubule [62].

The SGLT2 system reabsorbs glucose and sodium simultaneously at the cost of energy (ATP). Glucose molecules are absorbed against the concentration gradient using energy provided by the sodium gradient across the brush-border membrane, which is maintained by the Na^+/K^+ ATPase [57]. As blood glucose levels rise, more glucose and sodium are filtered and reabsorbed through SGLT2 and SGLT1, requiring additional energy and oxygen [57]. Consequently, more sodium is reabsorbed at the level of the proximal tubule, which is followed by chloride and water [63]. This reduces luminal sodium chloride concentration and its delivery to the macula densa [63], triggering tubulo-glomerular feedback to increase the single-nephron GFR and partially restore water and sodium chloride excretion [60, 62–64]. The result is "glomerular hyperfiltration" [63], which leads to an increase in kidney size (hypertrophy) and is believed to predispose to irreversible nephron damage, thereby playing a role in the onset and progression of kidney disease in diabetes [65]. SGLT2 inhibitors reduce the excessive glucose and sodium reabsorption activity in the proximal tubule that typically occurs in the diabetic kidney, thereby lowering glomerular hyperfiltration and aiding in long-term kidney function preservation [58].

2.3 Metabolic reprogramming by SGLT2 inhibitors

When SGLT2 is inhibited in a healthy individual, about 60 g of glucose (equivalent to approximately 250 kilocalories) are excreted per day [66]. This energy loss stimulates adipose tissue lipolysis and hepatic fatty acid oxidation, leading to an increase in circulating ketone bodies, particularly acetoacetate and β-hydroxybutyrate [67, 68]. The resulting metabolic state resembles fasting, being often referred to as "fasting mimicry" [69]. Initially, ketone production was viewed mostly as a mere "side effect" of SGLT2 inhibitors. Indeed, in very rare cases, excessive ketogenesis may contribute to diabetic ketoacidosis, similar to what is observed in type 1 diabetes and occasionally in patients with T2D [70]. However, circulating ketones can be easily taken up and used by

Fig. 1 The Warburg effect and the role of hypoxia-inducible factor (HIF)-1. *Abbreviations:* α-KG, α-ketoglutarate; ASCT2, alanine-serine-cysteine-type amino acid transporter 2; G6PD, glucose-6-phosphate dehydrogenase; GLUT, glucose transporter; GLS, glutaminase; HIF, hypoxia-inducible factor; LAT1, L-type amino acid transporter 1; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; OAA, oxaloacetate; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; ROS, reactive oxygen species; TCA, tricarboxylic acid. *Note*. This figure is adapted from a figure originally published in the Journal of Molecular Medicine ("Hypoxia, cancer metabolism and the therapeutic benefit of targeting lactate/H(+) symporters" by Marchiq I, Pouysségur J, 2016) [25]. The original figure is available at 10.1007/s00109-015–1307-x (Accessed on 06 December 2023). This adaptation is reproduced under the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium. Recreated using BioRender.com. In the resting state (G0), glucose enters the cell via specific glucose transporters (GLUTs) and is primarily converted to pyruvate through glycolysis, with minimal pentose phosphate pathway activity. Anabolic pathways, including the synthesis of non-essential amino acids (Ala, Ser, Asp, Asn, Glu, Gln, Pro), nucleotides, fatty acids, phospholipids, and sterols, are either inactive or occur at low levels. Pyruvate is transported into the mitochondria via the mitochondrial pyruvate carrier (MPC), where it is converted into acetyl-CoA, which then enters the tricarboxylic acid (TCA) cycle to generate reductive potential (NADH and FADH2), fueling oxidative phosphorylation. This process yields 33.45 ATP per glucose molecule (a revision of the previously estimated 36 ATP) [28], though this is not depicted in the figure. When cells are stimulated to divide (e.g., by growth factors, cytokines, or oncogenic signals), their metabolism shifts to the "Warburg effect". Hypoxia-inducible factor (HIF), a transcription factor, is a central activator of this process [25, 27]. Under these conditions, glucose uptake is enhanced via HIF-1-induced GLUT1, and glucose is primarily used to generate "biomass" needed for cell division, including DNA, RNA, and lipid components. Instead of mitochondrial oxidation, pyruvate derived from glycolysis is largely converted into lactate by the lactate dehydrogenase (LDH), facilitating the recycling of NADH to NAD^+, which is essential for sustaining glycolytic flux. This shift is reinforced by HIF-1-induced pyruvate dehydrogenase kinase 1 (PDK1), which inhibits pyruvate dehydrogenase (PDH), thereby limiting pyruvate conversion to acetyl-CoA at the mitochondria. Additionally, pyruvate transport across the mitochondrial inner membrane is restricted by the inhibition of the mitochondrial pyruvate carrier (MPC) [26, 29]. As a result, dividing cells produce only 2 ATP molecules per glucose molecule compared to the 33.45 produced via oxidative phosphorylation [5, 28]. Energy-rich lactate is exported from the cell by the ubiquitous monocarboxylate transporter (MCT)1 and HIF-1-induced MCT4. The Warburg effect also involves a rise in intracellular pH, optimal for cell division [12, 13] and regulated by HIF-1 [25]. This is achieved through the Na^+/H^+ exchanger (not shown in figure), which pumps H^+ out of the cell while importing Na^+. While energy production is reduced, glycolytic intermediates, such as glucose-6-phosphate (glucose-6-P), are diverted into the pentose phosphate pathway, generating NADPH, which supports fatty acid synthesis and glutathione reduction, and ribose-5-phosphate, a precursor for nucleic acid (DNA and RNA) synthesis. By producing NADPH, the pentose phosphate pathway promotes a reductive metabolism that protects DNA from damage caused by reactive oxygen species (ROS) during replication. Additionally, the reduced reliance on oxidative phosphorylation in dividing cells further safeguards DNA integrity by minimizing mitochondrial ROS generation. In addition to glycolysis, glutaminolysis provides another crucial pathway supporting cell division. Cytosolic glutamine is converted to glutamate by glutaminase (GLS) and enters the mitochondria, where it sustains the TCA cycle as α-ketoglutarate (α-KG). This pathway (anaplerosis) supports the synthesis of lipids, amino acids, nucleotides, and lactate, which is subsequently exported by MCT transporters. In summary, dividing cells prioritize biomass synthesis over energy production. This reprogramming involves enhanced glycolysis, pentose phosphate pathway activity, and glutaminolysis, with mitochondria repurposed for biosynthesis rather than oxidative phosphorylation. Importantly, mitochondria are not dysfunctional but are instead actively supporting anabolic metabolism [2, 4, 6, 7, 11]. Metabolic reprogramming associated with the Warburg effect is observed in various diseases. In these contexts, cells face challenges in generating acetyl-CoA from pyruvate and oxidizing fatty acids. Ketones (acetoacetate and β-hydroxybutyrate) offer an alternative energy source, as they readily enter mitochondria (not shown in figure) and are converted into acetyl-CoA for energy production [30]. This ability to bypass the Warburg-induced metabolic bottlenecks is especially relevant in cells where fatty acid oxidation and mitochondrial pyruvate metabolism are downregulated, such as in the heart [31, 32]. Moreover, autophagy, which is critical for clearing cellular debris, is suppressed during cell division [31, 33], reflecting the prioritization of anabolism (building) over catabolism (breakdown) [34].

virtually every cell, particularly in the brain, heart, kidneys, and skeletal muscle tissue [71–74], providing an abundant and readily available energy source upon their activation to an oxidizable form [30]. This conversion is catalyzed by the enzyme succinyl-coenzyme A (CoA):3-oxoacid CoA transferase, which facilitates the transfer of CoA from succinyl-CoA to acetoacetate [71]. Notable exceptions include hepatocytes (which are the primary source of ketones but lack the necessary enzyme, preventing their own utilization of ketones), and erythrocytes (due to their lack of mitochondria) [75]. At low to moderate concentrations, the uptake of ketones by cells correlates directly with their blood levels [76, 77]. Once in the mitochondria, wherein they can easily enter, ketones are unidirectionally converted into acetyl-CoA [30]. This is of particular significance as ketones not only yield significantly more ATP per gram than glucose but also use less oxygen during combustion per unit of ATP generated compared to fatty acids [78, 79].

SGLT2 inhibitors induce this fasting-mimicking metabolic state through mechanisms that, although not completely understood, reduce mechanistic target of rapamycin (mTOR) signaling, which is associated with an upregulation of autophagy [52, 69]. The fasting-mimicking metabolic state may be particularly beneficial for managing chronic kidney disease and heart failure, conditions where excessive mTOR signaling and impaired autophagy are known to contribute to, or exacerbate, disease progression in animal studies [52]. In the context of heart failure, SGLT2 inhibitors induce a metabolic shift in fuel utilization, moving away from energy-inefficient glucose toward free fatty acids and ketones, thereby enhancing myocardial energetics. This metabolic adaptation has been demonstrated both in animal models of heart failure [80] and in patients with this condition [81, 82]. Moreover, the increase in lipolysis associated with SGLT2 inhibitors has been confirmed by a reduction in epicardial adipose tissue in nondiabetic patients

with heart failure enrolled in the EMPA-TROPISM clinical trial, which also showed a significant decrease in interstitial myocardial fibrosis, aortic stiffness, and inflammatory biomarkers [83], illustrating the broad metabolic impacts of SGLT2 inhibition beyond glucose-lowering.

Further supporting the cardiac benefits of SGLT2 inhibitors, ketones have been shown to improve both systolic and diastolic function in heart failure. Specifically, in an experimental nondiabetic porcine model of heart failure, improvements in diastolic function induced by SGLT2 inhibitors were directly correlated with increased ketonemia [80]. Furthermore, the administration of ketones has been observed to enhance left ventricular systolic function in patients suffering from heart failure with reduced ejection fraction [84], as well as in those with cardiogenic shock [85]. Additionally, ketones and SGLT2 inhibitors have been shown to ameliorate ischemia–reperfusion injury and reduce infarction size in the previously mentioned experimental animal model of heart failure [86], underscoring their protective effects on the heart.

In summary, the beneficial effects of SGLT2 inhibition can be classified into hemodynamic and non-hemodynamic (metabolic). The hemodynamic explanation relates to the reduced reabsorption of sodium, resulting in lower blood pressure and restoration of tubulo-glomerular feedback. This leads to a reduction in glomerular hyperfiltration and glomerular pressure. The non-hemodynamic effects include decreased uric acid levels and reduced glucose reabsorption, which in turn leads to a decrease in body weight, body fat, blood glucose, inflammation, and glycolysis, coupled with an increase in circulating ketones [52, 53, 87].

3 The metabolism of a dividing cell

Cell division is driven by growth factors and progresses through distinct phases collectively known as the cell cycle: G0 (resting phase), G1 (preparation, characterized by the doubling of the cytoplasm), S (DNA duplication), G2 (synthesis of new cell components such as proteins and lipids), and finally M (mitosis) [88–90]. Rapidly dividing cells complete this cycle in approximately 24 h [90]. Throughout each phase, growth factors and cyclins (proteins regulating the cell cycle) orchestrate the activation or expression of specific enzymes and other proteins [88]. The composition of this molecular ensemble changes rapidly during the cell cycle to ensure the timely production of required components, culminating in the division of a mother cell into two daughter cells [40, 88]. Importantly, this ensemble includes enzymes that are conventionally involved in energy generation via glycolysis (in the cytoplasm) and the TCA cycle (in the mitochondria) (Fig. 2) [40].

These activations induce metabolic shifts that synchronize with the cell cycle's different phases:

- G1 phase—The Warburg effect (also termed "aerobic glycolysis") supports active protein synthesis, particularly with glycolytic enzymes (hexokinase 2 [HK2], pyruvate kinase M2 [PKM2 inactive form], and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase [PFKFB3]). HATs also play a significant role in protein synthesis in this phase. PKM2 deactivation enhances transcription.
- G1/S transition—Increased glycolysis and oxidative metabolism can temporarily boost ATP supply, as needed (e.g., during the G1/S transition and chromosome segregation in the M phase). PFKFB3 increases ATP production at the G1 restriction checkpoint and promotes activation of cyclins D and E.
- S phase—Aldolase (ALDO) promotes progression.
- S/G2 transition—Glutamine metabolism is critical for DNA replication in the S phase and lipid synthesis in the G2 phase. Key metabolic enzymes (PKM2, PFKFB3, glyceraldehyde-3-phosphate dehydrogenase [GAPDH]) periodically relocate to the nucleus to regulate cell cycle determinants or oncogene expression (e.g., c-Myc). The PKM2 dimer is instrumental in cyclin D1 cellular expression and biosynthesis. Glutaminolysis, regulated by glutaminase 1 (GLS1), and the PPP, driven by glucose-6-phosphate dehydrogenase (G6PDH) and transketolase 1 (TKL), are pivotal for DNA replication and lipid synthesis.
- G2 phase – In this phase, the active form of PKM2 (PKM2a) and GAPDH become activated.

However, during cell division, these enzymes primarily support biosynthetic pathways required for the synthesis of cellular components rather than energy production [40]. Consequently, under these conditions, the TCA cycle is repurposed to prioritize cell division [18, 91], which may initially be misinterpreted as "mitochondrial dysfunction". During the cell cycle, mitochondria exhibit reduced pyruvate consumption (the end-product of cytoplasmic glycolysis) and instead predominantly utilizes glutamine as a substrate [91]. Glutamine is transported into the mitochondria as glutamate and subsequently converted to α-ketoglutarate, a key intermediate of the TCA cycle [92–94]. Thus, in this context, it is primarily glutamine, rather than pyruvate, that sustains the TCA cycle (Fig. 1) [25].

Excess pyruvate is secreted from the cell as lactate, facilitating the conversion of NADH back to NAD^+ [3, 91, 92] and preventing the accumulation of NADH, which would otherwise inhibit glycolysis. The secreted lactate is reconverted to glucose in the liver via the Cori cycle, thereby

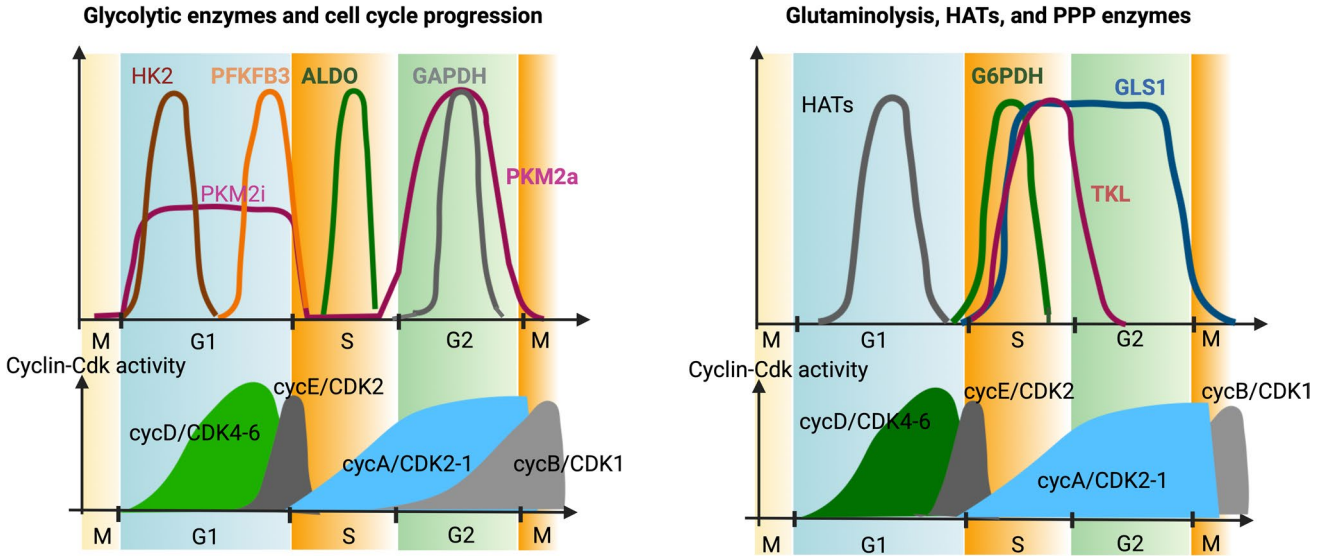


Fig. 2 The relationship between cell cycle phases and specific metabolic requirements in each phase (collectively termed the "Warburg effect"). *Abbreviations:* ALDO, aldolase; CDKs, cyclin-dependent kinases; c-Myc, MYC proto-oncogene, bHLH transcription factor; Cyc, cyclin; G6PDH, glucose-6-phosphate dehydrogenase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLS1, glutaminase 1; HATs, histone acetyltransferases; HK2, hexokinase 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; PKM2, pyruvate kinase M2; PKM2a, PKM2 active form; PKM2i, PKM2 inactive form; PPP, pentose phosphate pathway; TKL, transketolase 1. *Note.* This figure is adapted with permission from Elsevier, originally published in Trends in Biochemical Sciences ("Interconnection between Metabolism and Cell Cycle in Cancer" by Icard P, Fournel L, Wu Z, Alifano M, Lincet H, 2019) [40]. The original figure can be accessed at https://www.sciencedirect.com/science/article/pii/S096800041830273 1#fig0015 (License Number: 5683030821911, accessed on 06 December 2023). Recreated using BioRender.com. This Figure illustrates the dynamic interaction between the progression of the cell cycle and its metabolic requirements. The cell cycle's progression is governed by checkpoints and the sequential activation of cyclin-dependent kinases (CDKs). CDKs, when associated with cyclins (proteins that regulate cell division), become activated. These activated cyclin-CDK complexes phosphorylate target proteins, leading to their activation or deactivation. Specifically, cyclin D/CDK4-6 regulates the G1 phase, cyclin E/CDK2 oversees the S phase, cyclin A/CDK2-1 controls the G2 phase, and cyclin B/CDK1 manages the M phase (see lower panels). Essential enzymes/proteins for glycolysis, glutaminolysis, epigenetic modification (including histone acetyltransferases, HATs), and the pentose phosphate pathway (PPP) are among those activated (refer to top panels).

shifting the metabolic burden to the liver. Although NADH can yield 2.73 ATP molecules (a departure from the once-assumed 3 ATP) during the initial step of mitochondrial oxidative phosphorylation (OXPHOS) [28], recycling NAD^+ is crucial for maintaining glycolysis. Altogether, this ensures the continuous generation of pyruvate, sustaining the ATP production and molecular building blocks necessary for rapid cell division [92].

Lactate, far from being a mere metabolic byproduct, serves as a versatile energy source for multiple organs and acts as a signaling molecule [95]. For instance, organs and tissues known as "lactate users", such as the myocardium, efficiently use lactate for energy production [95]. However, lactate has also been identified as an oncometabolite, with emerging evidence suggesting its involvement in tumor growth and progression by altering the expression of cancer-related genes and actively shaping the tumor microenvironment [21, 96].

The reduced OXPHOS activity observed in dividing cells also decreases NADH consumption, helping to prevent its accumulation, which could otherwise inhibit glycolysis. Moreover, this reduction in OXPHOS activity has another advantage: it lowers oxidative stress by minimizing the number of electrons that escape during electron transfer and generate oxygen radicals [9, 40], such as superoxide [15]. This feature is particularly critical because dividing cells are highly sensitive to oxidative stress [97]. For instance, unwound DNA during replication becomes less protected and more vulnerable to oxidative damage.

Dividing cells also activate the pentose phosphate pathway, leading to increased production of NADPH, a key cofactor in several cellular anabolic processes [9]. NADPH plays a pivotal role in the reduction and recycling of glutathione, an essential intracellular antioxidant [15, 98]. Additionally, NADPH is required for lipid synthesis [9], which is crucial for the formation of cellular membranes [9]. The pentose phosphate pathway also generates pentoses, necessary for the synthesis of DNA and RNA [98].

In summary, the metabolic reprogramming observed during cell division is a key component of the Warburg effect (Fig. 1). Unlike mature cells, which typically generate up to 33.45 ATP molecules per glucose molecule through OXPHOS (a revision of the previously estimated 36 ATP) [28], cells undergoing the Warburg effect yield

only 2 ATP molecules per glucose molecule via glycolysis [11]. This metabolic shift might initially be perceived as mitochondrial dysfunction; however, it reflects a deliberate strategy, wherein the primary goal is to support the biosynthetic needs of cell division rather than to produce energy for specialized cellular functions [3, 5–7, 11, 21, 36, 37]. Notably, glycolysis, despite its lower ATP yield, proceeds approximately 100 times faster than OXPHOS [11]. As a result, the increased glycolytic flux compensates for the reduced ATP production, meeting the energy demands of rapidly dividing cells.

4 Hyperplasia/hypertrophy in diabetic kidneys and heart

When an organ faces increased functional demands due to physiological stress (e.g., elevated blood pressure forcing the left ventricle to pump more vigorously) or disease conditions (e.g., diabetes impairing kidney tissue), it responds by either producing more cells (hyperplasia) or enlarging existing ones (hypertrophy) [31, 99–102]. In adults, the cells of several organs have limited or impaired capacity for division and thus adapt by optimizing their function and undergoing hypertrophy. A classic example is the skeletal muscle of individuals engaging in resistance training, wherein myocytes do not significantly proliferate but instead enlarge, increasing in size and enhancing contractile strength [100]. This physiological hypertrophy is a normal, adaptive response to increased workload. In contrast, diseases such as T2D induce pathological hypertrophy, which is a primary contributor to renal and heart failure [31, 103].

The kidneys and heart are particularly susceptible to the diabetic milieu [104, 105]. In the kidneys, mesangial and tubular cells, as well as podocytes and peritubular capillaries, are especially vulnerable to damage from metabolic stress and excessive growth [106, 107]. These cells, when exposed to increased glucose and growth factors, experience abnormal growth stimuli [108–111]. Animal studies have shown that the ability of kidney cells to divide in T2D is confined to the early stages of this condition [63, 108, 112]. On the other hand, human heart cells lose the ability to divide shortly after birth, limiting their regenerative capacity when damaged [31]. Consequently, in response to increased physiological stress, adult heart cells do not adapt by increasing in number, but through hypertrophy, enlarging in size to maintain function and efficiency [31]. Renal mesangial cells play a crucial role in maintaining the filtration function of the kidneys, and mesangial expansion is considered one of the earliest structural lesions in diabetic kidney disease [113]. Research by Wolf demonstrated early on that renal mesangial cells exposed to a diabetic environment become arrested in the G1 phase after one or two divisions, leading to a shift from hyperplastic to hypertrophic growth, which is typical in early T2D [108]. Therefore, under diabetic conditions, the attempt of renal mesangial cells to divide results in cell cycle arrest and a metabolic state resembling the Warburg effect [42, 63, 108, 112].

This unique metabolic state is characterized by anabolic metabolism aimed at cell division while coexisting with the need to sustain organ-specific functions that require substantial energy and oxygen (i.e., catabolic metabolism). It is this paradox that underlies the pathological hypertrophy observed in the kidneys and heart of individuals with T2D, ultimately leading to renal and cardiac failure. The Warburg-like effect is also evident in the cells of other critical organs affected by late diabetic complications, such as retinal cells [114] and peripheral and central neurons [115]. These cells share a common denominator of very high metabolic activity, which makes them particularly susceptible to the adverse effects of the diabetic milieu.

5 Senescent cells

Senescent cells are characterized by a long-lasting cell cycle arrest [116], and are increasingly recognized as key factors linking age-related degenerative diseases to the Warburg effect [117, 118]. Cellular senescence refers to the cessation of the cell cycle, which normal cells can experience upon exposure to various stimuli [118–120]. The cell cycle arrest may occur at “checkpoints”, notably at the transitions of G1/S or G2/M [120–122]. Arrests derive from tumor suppressor mechanisms that prevent cells from replicating and passing on a potentially damaged genome [123]. While short-lived senescent cells have beneficial effects, such as during development and wound healing, their prolonged survival can become detrimental [124–128]. Their condition has been compared to a car in which the driver simultaneously accelerates and brakes: cell growth is stimulated while the cell cycle is blocked [129, 130]. Lasting senescent cells, often referred to as “zombie cells” [131], arise from multiple mechanisms, including chronic inflammation, DNA damage, telomere dysfunction, oncogenic shifts, epigenetic alterations, and organelle damage [121, 132]. Despite their reduced ability to divide, these cells exhibit high anabolic activity associated with the Warburg effect [117, 128]. Importantly, they continuously release proinflammatory signals, which can, paradoxically, be accompanied by anti-inflammatory ones. Alongside pro- and anti-inflammatory cytokines, these signals encompass chemokines, immune modulators, proteases, and various other factors, collectively known as the “senescence-associated secretory phenotype” (SASP) [133, 134].

Senescent cells are heterogeneous and can be found in several age-related pathological conditions such as cardiovascular disease, pulmonary fibrosis, kidney disease, osteoarthritis, osteoporosis, sarcopenia, and Alzheimer's disease [135–137]. These cells have experienced DNA damage, which may remain unrepaired. Hyperglycemia is a major driver of senescence [128]. Other causes include exposure to DNA-damaging agents, radiation or cytotoxic substances (including chemotherapy drugs), telomere erosion (also known as replicative senescence), cytokines, mitogenic stimuli, and activated oncogenes, as well as downregulated tumor suppressor genes such as TP53, the gene encoding p53 [119, 123, 130, 138–140]. When the p53 system detects DNA damage, it halts the cell cycle and initiates repair mechanisms. When this fails, p53 instructs the cell to undergo apoptosis, thereby preventing it from becoming a cancer cell [140, 141]. Senescent cells should ideally have been eliminated; however, they share with cancer cells the ability to evade elimination through robust survival mechanisms [120, 122, 123, 141]. As a result, they can accumulate, leading to various adverse effects [123]. For example, senescent cells may exhibit downregulated autophagy [142, 143], which impairs the removal of damaged proteins (e.g., as seen in Alzheimer's disease with beta-amyloid aggregate accumulation [144]). Additionally, senescent cells can drive tumorigenesis by altering their surrounding microenvironment through the secretion of various bioactive molecules as part of the aforementioned SASP [138, 145]. Furthermore, the SASP may induce senescence in neighboring healthy cells [146], potentially contributing to the dysfunction of distant organs [125, 134]. Injecting such cells into young mice leads to persistent physical dysfunction, as if witnessing accelerated aging [147].

Currently, numerous efforts are underway to eliminate senescent cells or enhance their intended functionality, as a potential strategy to overcome age-related disease and achieve healthy aging. One approach involves the use of senolytics, which are small molecules designed to induce apoptosis in senescent cells [147–149]. Promoting the clearance of senescent cells through immune activation is another avenue of investigation [149]. These two options for the removal of senescent cells are likely the most straightforward, offering the advantage of permanent removal of the SASP source while eliminating senescent cells that may be preneoplastic. Another strategy employs senomorphics (or senostatics), which target signaling cascades to inhibit the SASP without eliminating senescent cells, as exemplified by Janus Kinase inhibitors [150, 151]. However, this approach has several drawbacks, including the need for continuous administration and the risk of inadvertently impacting healthy cells and altering various types of cellular communication and physiological inflammation processes [148, 150, 152].

A notable characteristic of senescent cells is their low cytosolic NAD^+/NADH ratio, a feature they share with dividing cells, which plays a major role in the regulation of both cell cycle arrest and SASP [153, 154]. This ratio can be potentially increased by supplementing with nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR), both of which can be converted to NAD^+ intracellularly [155]. Animal and human studies have shown that NMN and NR supplementation can indeed increase NAD^+, potentially improving senescent cell function, decreasing inflammatory markers, and providing cardiometabolic and neurological benefits [155–164]. However, randomized controlled trials remain limited, often characterized by small sample sizes, short durations, and inconsistent findings. The observed improvements in physical and metabolic outcomes have generally been modest or negligible, further constraining definitive conclusions [152, 155, 164–168]. In addition, significant concerns have been raised regarding the potential adverse effects of NAD-enhancing compounds. These include the risk of promoting cancer progression by fueling metabolic pathways exploited by cancer cells, exacerbating the SASP without reducing the overall burden of senescent cells, and amplifying inflammatory signaling in certain contexts. Excessive NAD^+ levels may also overstimulate NAD^+-dependent enzymes, such as poly(ADP-ribose) polymerases and sirtuins, potentially resulting in metabolic imbalances or cellular stress. The unintended effects on non-senescent cells or tissues further underscore the need for cautious and targeted applications of these compounds [167, 169].

While these interventions open promising avenues for research, they fall beyond the scope of this review, which instead focuses on exploring the potential of ketones to enhance the function of senescent cells and other cells exhibiting the Warburg effect, as detailed in the following sections.

5.1 Senescent cells in diabetes

Diabetic kidney disease leads to accelerated aging in various cell types. In the diabetic environment, cells are exposed to abnormal growth stimuli, leading them to adopt a paradoxical senescent phenotype [170]. Senescent cells likely contribute to complications in the kidney, heart, retina, and nervous system in diabetes, primarily due to increased exposure to glucose and growth factors [128, 171]. This growth stimulus is influenced not only by hyperglycemia but also by oxidative stress, chronic inflammation, lipid metabolism disturbances, and lipotoxicity [170].

As cells attempt to divide, they undergo metabolic reprogramming that results in a state akin to being "frozen in Warburg" metabolism. As previously mentioned, this reprogramming prioritizes cell division over the functionality of fully differentiated cells, compromising the energy supply necessary for their intended functions. In diabetes, this issue is exacerbated as cells must not only continue to fulfill their regular functions but also cope with increased stress. This "perfect storm" scenario can lead to a state described as a "glucose and fatty acid energy gap", causing cells to enlarge (hypertrophy), become dysfunctional, and eventually undergo apoptosis [63, 108, 109].

5.2 Ketones as potential "therapy" for senescent cells

By mimicking fasting, the SGLT2 inhibitor dapagliflozin increases plasma ketone levels in obese diabetic mice, thereby attenuating renal oxidative stress, cellular senescence, and the progression of diabetic kidney disease [172]. Accelerated senescence in proximal renal tubule cells, observed within four weeks after diabetes induction in mice, can be prevented by lowering glucose levels with insulin or inhibiting SGLT2 [128]. Similarly, injecting β-hydroxybutyrate into mice has been shown to decrease markers of aging in vascular smooth muscle and endothelial cells [173]. Moreover, when podocytes were subjected to a diabetic environment in vitro, treatment with β-hydroxybutyrate notably reduced the signs of cellular senescence and damage [174].

While these interventions leverage the benefits of ketosis, calorie restriction, which does not necessarily induce ketosis, has also shown effectiveness in aging-related contexts. Calorie restriction has been demonstrated to lower aging markers in the colon of both mice and humans [175], as well as in mouse inguinal and retroperitoneal white adipose tissue depots [176]. It also prevented the development of senescence in the kidneys of aged mice [177, 178], in contrast to a high-calorie diet, which promoted senescence [179]. Regular exercise—which may or may not increase circulating ketone levels depending on duration, intensity, and peri-exercise nutritional status [180]—has also been linked to reduced senescence markers in some studies. For instance, Demaria et al. observed significantly elevated levels of senescence markers in the colon mucosa of middle-aged and older individuals with overweight compared to younger, sedentary participants. However, these markers were significantly lower in similarly aged individuals who regularly engaged in endurance running [181]. Likewise, a 12-week exercise regimen combining strength and endurance training led to a decrease in senescence markers (including p16, p21, cyclic GMP-AMP synthase, and tumor necrosis factor α) in peripheral blood $CD3^+$ T cells of older adults, alongside a decrease in the circulating levels of various senescence-related proteins (including the inflammatory enzyme myeloperoxidase and serpin E1, a thrombotic, fibrinolytic, and inflammatory factor) [182]. Beyond its potential effect on cellular senescence, regular exercise improves glycemic control, body composition, insulin resistance, blood pressure, and the blood lipid profile of patients with T2D [183]. Furthermore, consistent physical activity is associated with a decreased risk of T2D-associated complications, including cardiovascular disease incidence and mortality [184]. These findings highlight the broader cardiometabolic benefits of exercise, extending far beyond its potential increase in circulating ketone levels [185, 186]. In addition, exercise stimulates mitochondrial biogenesis and activates autophagy—two fundamental processes essential for maintaining metabolic flexibility and cellular homeostasis, which are often disrupted in chronic diseases characterized by Warburg-like metabolic dysfunction [187–189]. These adaptations improve mitochondrial quality control, enhance oxidative capacity, and reduce the accumulation of damaged organelles. Together, they may complement other metabolic strategies that target similar dysfunctions in senescent or diseased tissues [187–189].

Notably, while exercise generally induces physiological myocardial hypertrophy, in heart failure, similar to the diabetic kidney, the malfunctioning heart undergoes pathological hypertrophy [31]. The key distinction between physiological and pathological myocardial hypertrophy lies in the nature of the stimuli the heart receives. Intense exercise induces a "normal" growth response, whereas conditions such as T2D, obesity, arterial hypertension, aortic stenosis, myocardial infarction, glycogen storage diseases, and genetic cardiomyopathy can trigger pathological hypertrophy of the myocardium [31], disturbing its metabolic balance. Indeed, in failing heart cells, both fatty acids (an important energy substrate for the myocardium under normal conditions) and glucose are poorly utilized [31, 190]. This reduced metabolic efficiency observed in heart failure is part of the broader metabolic dysregulation occurring in various chronic diseases and in senescent cells, where cellular energy pathways resemble the Warburg effect [39, 41, 42, 128, 191]. Such metabolic inefficiencies highlight the therapeutic potential of targeting metabolic pathways to restore or improve cellular energy production in those conditions.

6 Ketone-based interventions

Ketones present a promising strategy to address the "energy gap" in senescent cells and other cells exhibiting a metabolic state resembling the Warburg effect. They can easily

enter the mitochondria, where they are readily converted into acetyl-CoA [30], compensating for the impaired energy generation from glucose and free fatty acids. By narrowing the "energy gap", ketones may improve cellular energy metabolism and potentially reduce the risk of heart and kidney failure [74, 78, 80, 190, 192–194]. In fact, a recent PET imaging study using ^{11}C-acetoacetate demonstrated that D-beta-hydroxybutyrate administration enhances oxidative metabolism and ketone uptake in both the heart and kidneys [195]. These findings provide evidence of how ketones support energy production and substrate efficiency, potentially reducing the risk of heart and kidney failure.

In addition, there is evidence that ketones may inhibit the NLRP3 inflammasome [30], modulate the SASP [196] and, as previously noted, influence senescence in various cell types. However, the evidence supporting these effects comes primarily from preclinical studies [197], and the findings are not universally consistent. For instance, while some studies suggest that ketones can mitigate or prevent senescence, a recent study in mice has indicated that a ketogenic diet can induce p53-dependent senescence across multiple organs, including the kidney and heart [198], highlighting the complex and context-dependent nature of these effects.

Ketones are naturally produced during prolonged fasting or in response to a ketogenic diet [75, 199]. However, prolonged fasting is not a sustainable intervention, and ketogenic diets may result in chronic low-grade (compensated) metabolic acidosis [200, 201], which has various potential adverse effects [201, 202]. In fact, evidence from animal and human studies suggests that long-term adherence to such diets may increase the risk of osteopenia and nephrolithiasis [200, 203–206]. While it is beyond the scope of this discussion to delve into these risks, they emphasize the need to explore alternatives to prolonged fasting or ketogenic diets.

Promising alternatives (detailed in Table 1) include supplementation with exogenous ketones, available as ketone esters or salts [190], and medium-chain triglycerides (MCTs) [190].

MCTs, particularly caprylic acid (C8), have been shown to significantly increase ketone body synthesis [190, 214], albeit to a lower extent than ketogenic diets [190]. However, unlike a ketogenic diet, using MCTs or exogenous ketones does not require restricting carbohydrates to below 5–10% of total daily energy intake. This reduces the likelihood of low-grade metabolic acidosis and minimizes the risk of vitamin and mineral deficiencies, as there is no need to limit the intake of fruits and vegetables, which are both net-base yielding [200–202] and micronutrient-rich [215–217]. Furthermore, maintaining a less restrictive diet is generally more manageable over the long term. Another potential option for harnessing the benefits of ketones could be

Table 1 Strategies for elevating plasma ketone levels

Interventions [190]	Ketone Concentrations Attained [190]	Effect Duration [190]	Main Benefits [46–48, 190, 207, 208]	Main Limitations [190, 200, 203–207, 209–213]
Ketogenic diets	1.2–4.2 mM	24 h	- Decreases body weight[a] - Increases HDL-cholesterol[a] - Reduces triglycerides[a] - Decreases HbA_{1c}[a]	- May increase LDL-cholesterol[b] - May increase the risk of nephrolithiasis and osteopenia - Poor adherence
Intermittent fasting	1–4 mM	12 h	- Decreases body weight[a] -Reduces LDL-cholesterol[a] - Increases HDL-cholesterol*[a] - Decreases triglycerides[a] - Reduces fasting glucose and insulin[a]	- May decrease fat-free mass - Poor adherence
MCTs	0.8 mM	3 h	- Safe - No need for a restrictive diet	- Gastrointestinal discomfort
Ketone esters	0.5–1 mM	3 h	- No need for a restrictive diet	- Oral palatability issues
Ketone salts	0.9 mM	Very short	- No need for a restrictive diet	- Oral palatability issues - Limited duration
SGLT2 inhibitors	0.8–1 mM	24 h	- Decreases body weight - Improves blood glucose homeostasis - Reduces the risk of major adverse cardiovascular events[c] - Improves cardiorenal outcomes[d]	- Higher cost - Carries an increased, albeit small, risk of several side effects

This table is adapted from a figure originally published by Lopaschuk and Dyck [190], and has been further expanded to incorporate additional information from their work as well as from other relevant sources (see references cited within the table). *HbA_{1c}*, glycated hemoglobin; *HDL*, High-density lipoprotein; *LDL*, Low-density lipoprotein; *MCTs*, Medium-chain triglycerides; *SGLT2*, Sodium/glucose cotransporter 2. [a]Especially in adults with overweight, obesity and/or metabolic syndrome. [b]The effect depends on the specific nutritional composition of the diet and intrinsic factors that influence individual responses. [c]In patients with T2D; [d]In patients with kidney disease

intermittent fasting [218], especially when combined with exercise [219]. This approach might extend to adopting an "intermittent lifestyle", which includes short-term environmental stresses such as hunger, cold, and heat [220].

Other therapeutic strategies that mimic ketogenesis are also being explored to address metabolic dysfunctions associated with the Warburg effect. As previously mentioned, SGLT2 inhibitors, for instance, have the ability to induce ketogenesis [43, 69, 190] (Fig. 3).

7 The "frozen Warburg effect" in various endocrine and metabolic diseases

The Warburg effect may be a unifying factor in several diseases, wherein this metabolic pattern becomes "frozen" or persistently adopted by cells, not as a transient response to hypoxic conditions, but as a stable metabolic feature. As previously discussed, this adaptation comes at the cost of metabolic efficiency. Therefore, in conditions characterized by the "frozen Warburg effect", cells experience an energy deficit due to this inefficient metabolism, impacting their function and contributing to disease progression, which suggests a broader application for ketone-based therapies. One notable historic example is the long-standing use of ketogenic diets as therapy for drug-resistant epilepsy, now supported by numerous studies [221]. Further evidence substantiating this dietary intervention in epilepsy is provided by positron emission tomography scans, which reveal lobular glucose hypometabolism in children affected by this condition [222]. More recently, ketones have been explored as a therapeutic approach in neurodegenerative disorders, particularly Alzheimer's and Parkinson's disease [72, 223–225]. Ketogenic interventions in patients with mild cognitive impairment have shown improvements in global cognition, memory and language abilities [72, 224, 226–228]. The Warburg effect plays a significant role in neurodegenerative diseases [191, 229], which seem to share a combination of aberrant cell cycle activation/arrest [230, 231] and impaired autophagy [232]. Downregulated autophagy is thought to protect vulnerable chromosomes from autophagic destruction during the G2/M phase [33, 233]. Consequently, factors

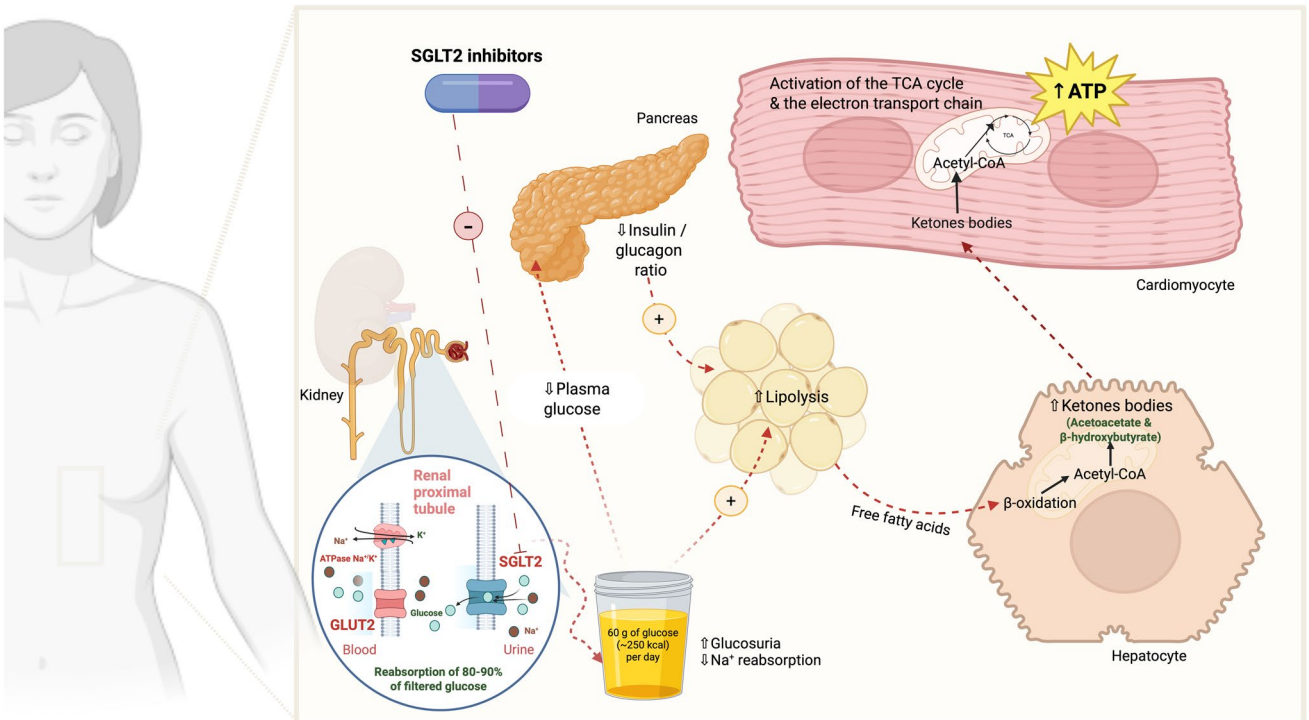


Fig. 3 Effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors on cardiac ATP production, independent of their glucose-lowering effect. *Abbreviations:* ATPase, adenosine triphosphatase; GLUT, glucose transporter; SGLT, sodium/glucose cotransporter; TCA, tricarboxylic acid cycle. *Note.* This figure was conceptually inspired by figures and ideas presented in Kaneto et al. [43] and created using BioRender.com. SGLT2 inhibitors induce a decrease in the insulin-to-glucagon ratio, thereby promoting enhanced fatty acid oxidation in the liver. This leads to an increased synthesis and release of ketone bodies (acetoacetate and β-hydroxybutyrate), mirroring a "fasting" state. Ketone bodies are readily absorbed by various organs, including the heart, where they directly enter the mitochondria. Within the mitochondria, they are processed in the tricarboxylic acid cycle, contributing to a significant supply of NADH and FADH2, which are subsequently used in oxidative phosphorylation to generate ATP. The uptake of ketone bodies by organs correlates with their plasma concentration; higher levels result in greater organ uptake. Thus, ketone bodies can provide an essential energy source for organs experiencing energy deficits due to various factors.

previously considered primary causes of these diseases, such as the formation of protein aggregates, may instead arise as secondary consequences of reduced autophagy [232, 234], which is associated with cell cycle arrest [235, 236]. Similarly, the accumulation of transition metals, such as aluminium, which was historically regarded as a primary cause of neurodegenerative diseases [237–240], may also reflect a secondary phenomenon, as protein aggregates can serve as sites for the sequestration of these metals [239, 240], further emphasizing the secondary nature of their role in the progression of disease.

Alzheimer's disease has been termed the "diabetic brain" or "type 3 diabetes"—not to be confused with type 3 C diabetes, a distinct form of diabetes caused by pancreatic disorders—underscoring its metabolic similarities to T2D [241, 242]. In this regard it is imperative to acknowledge the pioneering work of Prof. Siegfried Hoyer, which offered groundbreaking insights into the cerebral metabolic disturbances characterizing Alzheimer's disease, particularly emphasizing the early and significant disruptions in glucose metabolism [243]. Hoyer proposed that these metabolic anomalies could lead to neuronal stress and ultimately contribute to the pathophysiology of Alzheimer's disease. His hypotheses have been instrumental in guiding subsequent research toward understanding the metabolic shifts in Alzheimer's [243], including the potential implications of the Warburg effect in neurodegeneration. Accordingly, there is evidence that in Alzheimer's disease, particularly in the affected brain regions, neurons become entrapped in the cell cycle, leading to the above mentioned energy deficit [244–246]. These cells, having incurred damage, typically require a second "hit" to undergo apoptosis. The so-called "two-hit" hypothesis helps to explain the typically slow progression of the disease [247]. Intriguingly, the two-step concept parallels the "Knudsen hypothesis" in cancer research, which is also based on a two-hit model, proposed as early as 1971 to describe the origin of cancer cells [248]. The similarity reinforces a parallelism in the pathological mechanisms underlying both Alzheimer's disease and cancer [247]. An initial hit determines which cellular function is affected. In both cases, the ensuing damage remains unrepaired, thereby hindering apoptosis and forcing the cell to survive at all costs, either transforming into a cancer cell (through gain of function of oncogenes, or loss of function of tumor suppressor genes) or a senescent cell (due to damage to other genes). While there are overlaps, such as heightened inflammation, altered cellular energetics, and genome instability, there are also distinctions between the biological hallmarks of cancer and Alzheimer's disease [247]. For instance, mechanisms like cell death and evading growth suppressors are inversely regulated in these conditions [247].

Ketones have also shown potential benefits in oncology [249–260], the field where the Warburg effect was initially discovered. Alongside and in combination with conventional chemotherapy and radiotherapy, ketogenic diets [249–254, 261], calorie restriction [262], exercise [263, 264], fasting [265], fasting-mimicking diets [265, 266], and SGLT2 inhibitors [267, 268] are being investigated. The benefits of ketones extend beyond their role as energy substrates, as both ketone-based interventions and SGLT2 inhibitors exhibit several other favorable effects [52, 69, 74, 75, 199, 207, 252, 269–272]. For instance, a ketogenic diet may create an unfavorable metabolic environment for cancer cells by lowering the levels of glucose, insulin, and insulin-like growth factor 1 [252, 273], thereby decreasing the activation of key anabolic signaling pathways, including the mTOR pathway [273], which is crucial for cell growth, proliferation, and survival [274]. Nevertheless, its impact on cancer cell proliferation appears to vary depending on the tumor type [250, 275]. Currently, the most significant benefit of a ketogenic diet in oncology seems to be its ability to enhance the efficacy of traditional anti-tumor therapies [250, 254, 276–279].

Ketones may also be useful in other disorders where cells suffer from a glucose energy deficit due to the "frozen Warburg effect" [6, 34, 41, 199]. This includes conditions involving the immune system [38, 280–285], such as infections [284, 286]. Viruses rely on the host cell's machinery for their own replication, as they lack the means to perform vital functions independently. To facilitate the production of new viral particles, they reprogram the host cell's metabolism to mimic the Warburg effect [35, 287, 288]. Epstein-Barr, human cytomegalovirus, and herpes simplex virus-1 are just a few examples among many [35, 289, 290]. Intracellular bacteria like *Mycobacterium tuberculosis* (tuberculosis) [35], *Coxiella burnetii* (Q-fever) [35], and the spirochete *Borrelia burgdorferi* (Lyme disease) [291] employ a similar strategy [35, 291]. Long COVID [292, 293] (referring to chronic post-COVID-19 symptoms) and chronic fatigue syndrome [294, 295] have also been associated with ongoing or reactivated (i.e. secondary) viral infections. It has long been noted that individuals with chronic fatigue syndrome also exhibit metabolic changes akin to the Warburg effect [296, 297]. Also, Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appear to induce the Warburg effect [288, 298], suggesting its involvement in infections caused by a variety of intracellularly growing microorganisms.

8 Conclusions and future perspectives

The "frozen Warburg effect" refers to a persistent metabolic state in which cells continue to rely predominantly on glycolysis for ATP production despite sufficient oxygen

availability, while markedly reducing their mitochondrial OXPHOS activity. While initially described in cancer cells, where aerobic glycolysis supports rapid proliferation, similar metabolic features have been observed in non-proliferative and damaged cells across chronic diseases and aging. This metabolic reprogramming is thought to reduce mitochondrial reactive oxygen species production by limiting electron transport chain activity and to redirect intermediates of glycolysis and the TCA cycle toward biosynthetic and stress-response pathways. However, this adaptation comes at the cost of energy efficiency, as glycolysis yields substantially less ATP per glucose molecule compared to OXPHOS. In tissues affected by chronic disease and senescence, this metabolic inefficiency may compromise cellular function and contribute to disease progression.

This review introduces a conceptual framework that extends the Warburg model beyond oncology to encompass common features of metabolic inflexibility across chronic diseases and cellular aging. Unlike prior reviews that have focused on individual organs or conditions, we synthesize evidence from diverse biological contexts (especially involving the kidney, heart, brain, and immune cells) to identify a conserved shift in cellular bioenergetics. Rather than being dysfunctional, mitochondria in these settings appear to adopt an alternative metabolic role, with reduced oxidative phosphorylation but preserved involvement in biosynthetic and signaling pathways through anaplerotic and cataplerotic fluxes. This reprogramming is associated with chronic exposure to nutrient excess, inflammation, oxidative stress, and changes in NAD^+ availability, and it culminates in a Warburg-like phenotype that is stably maintained in affected cells.

From a translational perspective, recognizing this shared metabolic signature may facilitate the development of novel diagnostic and therapeutic strategies. For example, circulating metabolites such as lactate, pyruvate, ketone bodies, or succinate, as well as transcriptomic or proteomic markers of glycolytic predominance and mitochondrial restraint, could serve as early indicators of bioenergetic imbalance and therapeutic response.

Therapeutically, several interventions discussed in this review, such as ketone-based therapies, SGLT2 inhibitors, structured exercise, and fasting-mimicking regimens, have demonstrated the potential to restore aspects of metabolic flexibility, including improved mitochondrial efficiency, increased ketone utilization, enhanced fatty acid oxidation, and activation of autophagy. While some of these strategies are already supported by robust clinical data (e.g., SGLT2 inhibitors in type 2 diabetes and heart failure), others—including exogenous ketones, MCTs, and drugs such as senolytics, senomorphics, and NAD^+ precursors—require further substantiation via long-term clinical trials. Their integration into combinatorial approaches that address both upstream stressors and downstream metabolic rigidity may prove critical for reversing disease progression.

Importantly, future trials should incorporate mechanistic endpoints, such as mitochondrial respiration, senescence burden, and metabolic flexibility, alongside traditional clinical outcomes. Tailoring interventions to sex-specific and tissue-specific contexts will also be essential, given the heterogeneity in metabolic responses across organs and individuals.

In summary, this review reframes chronic metabolic diseases and cellular senescence as conditions marked by a conserved, maladaptive shift in cellular metabolism. It offers an integrative perspective that aligns molecular mechanisms with translational opportunities and supports the development of therapeutically targetable bioenergetic phenotypes shared across traditionally compartmentalized disease categories.

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Declarations

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