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Mitochondrial and inflammatory mechanisms linking SGLT2 inhibition to cardiac aging: a narrative review of mitohormesis, NLRP3 suppression, and cellular senescence

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Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce cardiovascular mortality and heart failure hospitalization independently of glycemic status, an effect that has prompted interest in mechanisms beyond glucose lowering. This narrative review examines the hypothesis that part of this benefit reflects favorable modulation of pathways implicated in cardiac aging, namely mitochondrial dysfunction, chronic low-grade inflammation, and cellular senescence. Clinical and preclinical data indicate that SGLT2 inhibition induces a mild catabolic state—marked by glucosuria, reduced insulin, and increased β-hydroxybutyrate (β-OHB)—that is associated with improved myocardial substrate utilization, enhanced mitochondrial calcium handling, and reduced oxidative stress in animal and ex vivo models. β-OHB itself has signaling properties consistent with a mitohormetic response, including histone deacetylase inhibition and suppression of nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome assembly, although direct evidence linking these pathways to cardiac mitohormesis in vivo remains limited. Preclinical work further suggests that SGLT2 inhibitors may promote immune-mediated clearance of senescent cells, a mechanism so far demonstrated mainly in progeroid and diabetic rodent models. We argue that these convergent mitochondrial, anti-inflammatory, and senolytic mechanisms provide a plausible—though still largely preclinical and mechanistic rather than clinically proven—basis for the cardioprotective effects of SGLT2 inhibitors observed in randomized trials, rather than evidence that these agents reverse cardiac aging in humans. A recent placebo-controlled trial of a related SGLT2 inhibitor reported increased leukocyte telomere length and cytotoxic T-cell activity after 26 weeks in patients with type 2 diabetes, providing the first direct human evidence for an aging-biomarker effect, yet a Mendelian randomization study using genetic proxies for SGLT2 inhibition found no effect on any of four epigenetic clocks, underscoring that the evidence for a true anti-aging effect remains mixed. Prospective studies incorporating mitochondrial and senescence biomarkers in non-diabetic aging cohorts are needed to test this hypothesis directly.

Introduction

Cardiovascular disease (CVD) is the most common cause of mortality worldwide, and chronological age is its most powerful unmodifiable risk factor. The aged heart is characterized by stereotypic pattern of structural and functional remodeling— Specifically, aging of the heart involves a well-characterized sequence of events starting with the accumulation of molecular damage and leading to adaptive hypertrophy of the left ventricle. The next step in the process is pathological interstitial fibrosis and collagen accumulation. Such remodeling is characterized by a significantly increased stiffness in the diastole phase and combined with progressive metabolic inflexibility of the myocardium represents the optimal substrate for the development of heart failure with preserved ejection fraction (HFpEF). Underlying this structural remodeling is a complex of interrelated cellular mechanisms such as mitochondrial dysfunction, sterile low-grade inflammation ("inflammaging"), oxidative stress, proteostatic imbalance, and cellular senescence.[1] These mechanisms are characterized by the presence of corresponding biomarkers which have systemic metabolic correlate in the form of

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alterations of amino acids serum profile which occurs age- and sex-specifically. The latter correlates with age-related reduction in metabolic flexibility of the tissue.[2] The pivotal role in this cellular aging is played by the mitochondrion. The effectiveness of SGLT2 inhibitors targeting precisely this pathophysiological domain of cardiorenal disease was conclusively shown in the landmark EMPEROR-Preserved and DELIVER trials. Specifically, empagliflozin and dapagliflozin were associated with unprecedented reductions in cardiovascular death and heart failure hospitalizations in patients with HFpEF. It has been shown in the DAPA-HF and EMPEROR-Reduced trials that SGLT2 inhibitors possess substantial cardiorenal protective effects including significant reduction of cardiovascular mortality and hospitalizations in patients with heart failure regardless of their diabetes status and glycemic control. Thus, the contemporary guidelines emphasize the disease-modifying cardiorenal role of SGLT2 inhibitors.[3-5]

SGLT2 inhibitors were initially developed as a class of antidiabetic drugs. However, randomized outcome trials (EMPA-REG OUTCOME, DECLARE-TIMI 58, DAPA-HF, and EMPEROR program) have revealed that their cardiorenal benefits are not restricted to but are often even greater in patients without diabetes.[6]

Indeed, in DAPA-HF, dapagliflozin reduced the risk of worsening of Heart Failure (HF) or CVD death by 26% (Hazard range [HR] 0.74, 95% confidence interval [CI] 0.65–0.85, $P < 0.001$) regardless of the presence of diabetes, highlighting the need to identify the target beyond glycemic control.[7]

Similarly, EMPEROR-Reduced has shown a reduction of 25% in cardiovascular death and HF hospitalization with empagliflozin (HR 0.75, 95% CI 0.65–0.86) along with a slowdown of eGFR decline, proving the presence of a cardiorenal protective effect of SGLT2 inhibition.[8] These and other human studies are reviewed below and led to a recommendation to consider SGLT2 inhibitors as disease-modifying cardiorenal agents instead of just glycemic ones.[9] This recommendation is supported by consistent benefit in frail older patients who demonstrate reduction of mortality and HF rehospitalization despite different risk profile compared to young trial population; in a 2025 meta-analysis of 9 studies, it was confirmed that this benefit exists in patients aged 75 years and above, where efficacy of virtually all classes of drugs is known to wane.[10,11] Central to understanding this direct cardiac action is the concept of 'mitohormesis.' The dissociation between the effectiveness of SGLT2 inhibition in terms of glucose lowering and cardiorenal protection has led researchers to focus on its direct cardiac action on mitochondrial function, redox state, and innate immune signaling. Framework based on the idea of the presence of a specific adaptive pathway, called "mitohormesis," has been developed to unite these observations.[12,13] Mitohormesis can be considered as a biological response to mild and transient metabolic or energy stress, leading to the production of low-level reactive oxygen species (ROS). The key point of this phenomenon is that this tightly controlled production of reactive oxygen does not damage cells but serves as an important signal initiating the processes of antioxidant defense enhancement, mitochondrial biogenesis, and stimulation of stress resistance, increasing cell survival and longevity.[14]

This review evaluates the available and limitations of the evidence of a role of SGLT2 inhibitors in engagement of mitohormesis, anti-inflammatory, and senolytic pathways, which are important for the biology of cardiac aging, rather than being merely glucose-lowering or natriuretic agents.

This review comprehensively evaluates the current data and the gaps in the evidence concerning the possible role of SGLT2 inhibitors in the regulation of mitohormesis, anti-inflammatory, and senolytic pathways which are integral parts of cardiac aging biology and proposes the hypothesis of the involvement of pharmacological modulation of those domains in the cardioprotection provided by SGLT2 inhibitors. A summary of the landmark clinical trials and other key human studies is provided in Table 1.

a. Cellular and molecular hallmarks of cardiac aging: mitochondrial decline and the NLRP3-driven inflammatory cycle

On the organ level, cardiac aging follows a reproducible pattern of structural and functional remodeling. Lakatta, followed by Strait and Lakatta, identified left ventricular hypertrophy, arterial stiffness, endothelial dysfunction, and concurrent diastolic-systolic dysfunction as key aspects of the aging cardiovascular system, which make the onset of heart failure, especially HFpEF, easier. [23,24] Histologically, the aged heart undergoes the development of interstitial fibrosis and collagen deposition and hypertrophy of cardiomyocytes, making the ventricle stiff and impairing its ability to fill. [25,26] On a functional level, maximum heart rate, heart rate variability, and the ability to maintain adequate contractility under stress decrease with age; moreover, this process is exacerbated by coexisting diseases such as hypertension, obesity, and diabetes, but can be detected even in otherwise healthy elderly people, which suggests that these changes are inherent to cardiac aging. [25,26]

Below this phenotype, the mitochondrion serves as a key central node of cardiac aging. As mitochondria produce over 90% of the ATP used in myocardium to sustain contraction, the gradual malfunction of mitochondria due to the accumulation of mitochondrial DNA (mtDNA) damage, decreased biogenesis, and quality control impairment directly leads to energetic problems in the heart.[27] The increased inefficiency of the electron transport chain not only results in the lower ATP generation but also in the higher leakage of electrons and production of reactive oxygen species (ROS), which cause damage to proteins, lipids, and nucleic acids and thus further damage mitochondria, creating a vicious cycle of mitochondrial dysfunction (Fig. 1). [28,29]

Similarly, the balance between fission and fusion, regulated by dynamin-related protein 1 (Drp1) (division) versus mitofusin 1 and 2 (Mfn1/2) and optic atrophy 1 (OPA1) (fusion), becomes skewed towards fission, leading

Table 1. Clinical evidence for SGLT2 inhibitors in cardiovascular and age-related conditions

Citation (author, year)	Study acronym	Study type	Sample size	Population	Intervention	Comparator	Primary outcome	Effect direction	Magnitude (HR [95% CI])	Short note
McMurray et al, 2019[7]	DAPA-HF	RCT	4,744	HFrEF patients (with/without T2DM)	Dapagliflozin 10 mg	Placebo	Worsening Heart Failure (HF) or Cardiovascular (CV) death	↓	0.74 (0.65-0.85)	Benefit independent of diabetes
Packer et al, 2020[8]	EMPEROR-Reduced	RCT	3,730	HFrEF patients (with/without T2DM)	Empagliflozin 10 mg	Placebo	CV death or HHF	↓	0.75 (0.65-0.86)	Slowed eGFR decline
Wiviott et al, 2019[15]	DECLARE-TIMI 58	RCT	17,160	T2DM patients (ASCVD or risk factors)	Dapagliflozin 10 mg	Placebo	MACE; CV death or HHF	↓ (HHF)	0.83 (0.73-0.95)	HHF benefit in broad population
Fitchett et al, 2019[16]	EMPA-REG OUTCOME	RCT (sub-analysis)	7,020	T2DM patients with ASCVD	Empagliflozin 10/25 mg	Placebo	CV death, all-cause mortality, HHF	↓	Consistent	Benefit across risk spectrum
Cannon et al, 2020[17]	VERTIS CV	RCT	8,246	T2DM patients with ASCVD	Ertugliflozin 5/15 mg	Placebo	MACE	Non-inferior	0.97 (0.85-1.11)	Confirmed CV safety
Solini et al, 2017[18]	N/A	Pilot study	16	T2DM patients	Dapagliflozin 10 mg (2 days)	Hydrochlorothiazide	Endothelial function (FMD)	↑	$P < 0.05$	Acute vascular benefits
Mone et al, 2022[19]	N/A	Cohort	150	Frail, older T2DM/HTN patients	Empagliflozin 10 mg	Standard care	Cognitive/ physical function	↑	$P < 0.05$	Benefit in frail elderly
Hacil et al, 2025[10]	N/A	Observational	496	Geriatric acute HF patients (mean age 90)	SGLT2 Inhibitors (empa/dapa)	Standard care	All-cause mortality or HHF	↓	0.60 (0.44-0.82)	Real-world evidence in frail elderly
Sperry et al, 2025[20]	N/A	Cohort	374	Patients undergoing FDG-PET	SGLT2 Inhibitors use	No SGLT2 Inhibitors use	Myocardial FDG uptake	↓	$P < 0.001$	Direct evidence of cardiac glucose suppression
Jeon et al, 2024[21]	N/A	Review	N/A	Older T2DM patients	SGLT2 Inhibitors	N/A	Risk-benefit profile	Favorable	N/A	Supports use in older adults
Minami et al, 2025 [11]		Meta-analysis (9 studies)	N/A	Adults ≥ 65 y with CVD	SGLT2 Inhibitors	standard care	HHF, urgent HF visit, or CV death	↓	0.75 (0.67–0.83)	Benefit retained in age ≥ 75 y: 0.71 (0.57–0.88)
Zhang et al, 2025 [22]		RCT	142	T2DM	Henagliflozin 10 mg	placebo	Leukocyte telomere length (26 wk)	↑	$P < 0.05$	First human RCT on aging biomarkers; T2DM population, surrogate endpoint

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; FMD, flow-mediated dilation; HCTZ, hydrochlorothiazide; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; HTN, hypertension; MACE, major adverse cardiovascular events; N/A, not applicable; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; FDG-PET, fluorodeoxyglucose (FDG)-positron emission tomography.

to the formation of smaller, dysfunctional mitochondria, which become more likely to induce apoptosis.[14] The causality of this theory is supported by animal studies: mice genetically modified to develop mtDNA damage faster reproduce left ventricular hypertrophy, diastolic dysfunction, and fibrosis typical for cardiac aging, thus demonstrating that the damage to mitochondria is sufficient to initiate this process rather than just accompanying it. Supports the hypothesis that even in mice the initial damage to mitochondria might be enough to start the process, making the damage not merely a bystander effect.[30]

The chronic low-level inflammation, or inflammaging, works together with the deterioration of mitochondria to harm the myocardium. The capacity of chronic

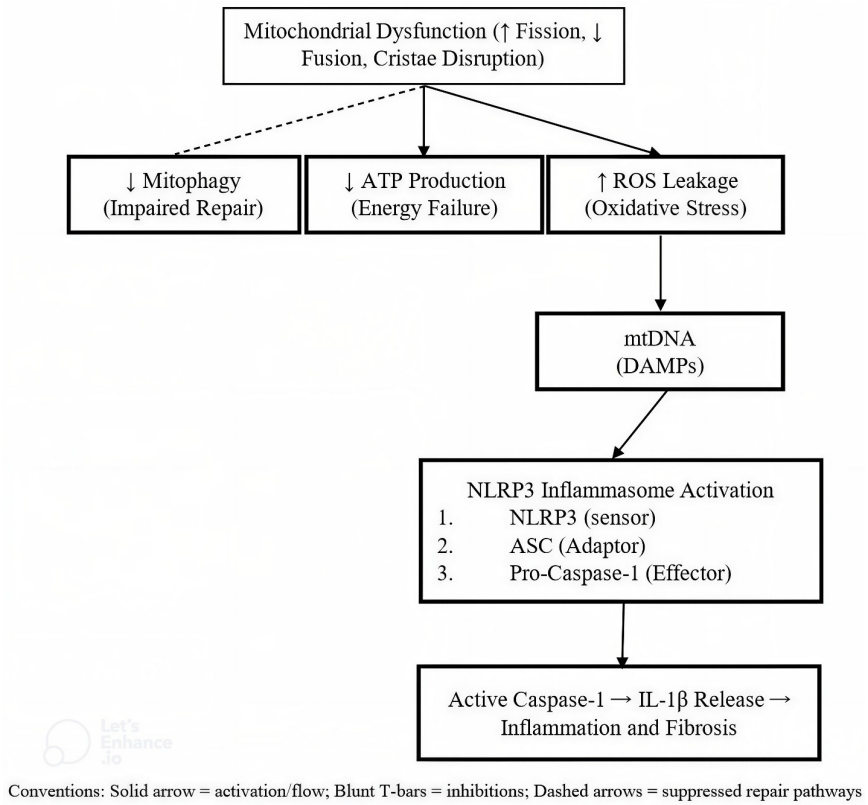

Fig. 1. The mitochondria-NLRP3 cycle of the aging myocardium. Abbreviations: ATP, adenosine triphosphate; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; DAMPs, Damage-associated molecular patterns; NLRP3, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; ASC, Apoptosis-associated speck-like protein containing a CARD; IL-1β, Interleukin-1beta.

inflammation to cause myocardial damage can be well demonstrated in the paradigm of sterile "inflammaging." In the context of myocardial aging, the accumulation of metabolic waste and mitochondrial damage leads to the activation of NLRP3 inflammasome in a low-grade chronic manner. As a result, there is a pathological release of pro-inflammatory cytokines, mainly IL-1β and IL-6. The sterile inflammation drives progressive endothelial dysfunction, extracellular matrix remodeling, and formation of interstitial fibrosis constituting the substrate of HFpEF.[31]

The main molecular hub of inflammaging is the NLRP3 inflammasome, a cytoplasmic complex of a sensor NLRP3, adaptor Apoptosis-associated speck-like protein containing a CARD (ASC), and caspase-1 effector. NLRP3 activation needs two steps: a priming signal, usually caused by Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation ligands, such as TNF-α or interleukin-1β (IL-1β), that upregulates NLRP3 and pro-IL-1β; and an activating one, that can be an extracellular Adenosine triphosphate (ATP), crystalline substance, or ROS produced by dysfunctional mitochondria, and triggers the assembly of inflammasome and activation of caspase-1. Active caspase-1 then cleaves pro-IL-1β and pro-IL-18 into the active forms and initiates the cell death program of pyroptosis, a pro-inflammatory lytic cell death program. In the case of aging myocardium, the ROS and mtDNA released by dysfunctional mitochondria act as activating signals for NLRP3; elevated levels of NLRP3, ASC, and active caspase-1 have been detected in animal experiments with models of accelerated aging, and the deletion of NLRP3 in these models prevents age-related cardiac fibrosis and preserves the contractility of the heart, supporting the assumption about the causality of this pathway for cardiac aging. Similarly, the inflammation driven by NLRP3 is also present in the aged endothelium: excessive ROS generated by dysfunctional mitochondria in it cause uncoupling of Endothelial nitric oxide synthase (eNOS), thus switching the product of eNOS activity from nitric oxide to superoxide. The resulting oxidative stress damages vasodilator functions of the aged endothelium and activates NLRP3 even more, thus creating a self-propelling cycle of inflammation, which is enhanced by high glucose level, obesity-related inflammation, and hypertension typical for metabolic syndrome (Fig. 1).[32] Pharmacologic evidence of the tractability of this cycle has been obtained in animals: aged mice, whose NLRP3 was inhibited with an SGLT2 inhibitor, had their endothelial dysfunction and arterial stiffness ameliorated by decreasing oxidative stress.[33] the topic will be discussed in detail in the following section. This NLRP3-driven remodeling cycle has also been found to be involved in pathologies other than metabolic disorders, including postoperative atrial fibrillation after cardiac surgery, making it a generally applicable rather than diabetes-specific mechanism.[34] In conclusion, the mitochondria-NLRP3 cycle described in this section is based on a reasonable amount of evidences: mitochondrial dysfunction and NLRP3 biology are each studied separately, but the specific role of the combination

of the two of them in human cardiac aging has not been confirmed yet; the inference is drawn mostly from animal and cross-sectional human data.

Fig. 1 illustrates the "vicious cycle" in which mitochondrial dysfunction drives NLRP3 inflammasome activation, contributing to inflammation and fibrosis in the aging heart.

b. SGLT2 inhibitors: from glucosuria to systemic metabolic reprogramming

SGLT2 inhibitors originate from phlorizin, a nonspecific glucosuric drug discovered over a century ago in the bark of apple tree; specific compounds such as empagliflozin, dapagliflozin, and canagliflozin have been synthesized to achieve selective blockage of SGLT2 in the kidneys.

Physiologically, SGLT2 in the proximal tubules reabsorbs approximately 90% of the filtered glucose, with sodium-glucose cotransporter-1 (SGLT1) taking care of most of the rest; in diabetes, the upregulation of SGLT2 increases this reabsorption and reinforces hyperglycemia. Pharmacologic inhibition of SGLT2 breaks this vicious cycle and causes the glucosuria and the corresponding reduction of plasma glucose levels regardless of insulin.[35]

Apart from lowering glucose, SGLT2 inhibition causes the reprogramming of fuel choice for the body. In the study by Ferrannini et al, empagliflozin increased endogenous glucose production, decreased peripheral glucose utilization and stimulated lipolysis and ketogenesis in both type 2 diabetic and healthy subjects; this effect was achieved via the hormonal shift towards lowered insulin and raised glucagon.[36] The induced glucosuria is interpreted by the body as nutrient deficiency, leading to the stimulation of gluconeogenesis and lipolysis and elevation of β-OHB; in case of chronic administration, fasting β-OHB level in patients with diabetes almost doubles.[36,37] As ketone bodies are oxidized in the myocardium more efficiently comparing to oxygen, this effect has been proposed to work as a "super-fuel" for the heart; However, the hypothesis remains theoretical in the case of humans. Although a reduction in heart failure hospitalization rate seen in such trials as DECLARE-TIMI 58 may be consistent with the improvement of myocardial energetics, the reduction in clinical outcomes is highly multi-factorial involving hemodynamic unloading, natriuresis, and reduced vascular stiffness and thus cannot be the sole support of super-fuel mechanism.[15] It should be noted that there is an important ceiling for the mechanism described above: despite being responsible for 80-90% of glucose reabsorption, SGLT2 inhibitors can only excrete 30-50% of the filtered load; it has been explained by the upregulation of SGLT1, compensating for the blockage of SGLT2. This could partly explain the superior glucosuria achieved by SGLT1/SGLT2 inhibitors in comparison to selective SGLT2 inhibitors; however, the latter seems to be able to provide the necessary glucosuria to stimulate the metabolic shift.[38]

Besides, SGLT2 inhibitors reduce the levels of serum uric acid, mitigate the glomerular hyperfiltration, reduce arterial stiffness and visceral adiposity and adipose tissue inflammation in both diabetic and non-diabetic subjects; some of these effects have been shown to be caused by the changes in circulating adipokines beyond the canonical cytokines. In EMPA-REG OUTCOME study, these renal and metabolic benefits accompanied the reduction of cardiovascular deaths and heart failure hospitalizations, proving the cardiometabolic modulating nature of this class of drugs.[16] Unlike insulin, the mechanism of action of which includes insulin secretion, the SGLT2 inhibitors do not carry any risks of hypoglycemia and acute kidney injury, which might be valuable in the case of cardiac aging, where prevention of metabolic stress is beneficial.[39]

The metabolic reprogramming described in this section is, on the whole, the best-studied part of the proposed mechanism; it is supported not only by animal and cellular data, but also by human randomized studies, and the direction and approximately the magnitude of the glucosuria-to-ketogenesis shift is fairly consistent among those studies. The next steps are to establish how much of the systemic shift and the direct cardiac effect are responsible for clinical benefit.

c. SGLT2 inhibitors and mitochondrial resilience in the aging heart

There is compelling evidence to suggest that there are direct effects of SGLT2 inhibition on the mitochondria of the heart, separate and above any system-wide metabolic effects as described in sections ‘a’ and ‘b’. This phenomenon is supported by human data, as observed in a matched cohort study utilizing 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET) scans showing significantly decreased glucose uptake by the heart muscle in those taking SGLT2 inhibitors.[20] Santos-Gallego et al, using a heart failure model of non-diabetic pigs, showed that empagliflozin causes reprogramming of myocardial energy substrate metabolism from anaerobic glycolysis to ketones, free fatty acids, and branched-chain amino acids, which resulted in increased myocardial ATP levels and improved cardiac efficiency regardless of glycemia.[40]

In diabetic mice (db/db strain), empagliflozin prevented development of heart failure and boosted cardiac ATP production by 31% relative to untreated animals; paradoxically, the boost was associated with a 61% increase in the contribution of glucose oxidation even in spite of the observed increase in the overall utilization of ketones as an energy source.[37] Notably, all mentioned effects are not diabetes-dependent: in non-diabetic rats with myocardial infarction, empagliflozin treatment significantly improved left ventricular ejection fraction and prevented pathological remodeling through mechanisms associated with decreased myocardial oxidative stress, less mitochondrial DNA damage, enhanced mitochondrial biogenesis, and increased ATP production.[41] Direct evidence for the cardiomyocytes comes from the model of non-diabetic pressure overload in mice (transverse aortic constriction), where empagliflozin improved mitochondrial oxidative phosphorylation and biogenesis without any impact on systemic glucose levels.[42]

The first described impact of SGLT2 inhibitors on mitochondria is linked to calcium handling. In isolated rat cardiomyocytes, acute treatment with empagliflozin (1 μM) increased mitochondrial calcium ion (Ca^{2+}) uptake induced by electrical stimulation, which resulted in stronger coupling of Ca^{2+} signaling and ATP synthesis. This effect is especially valuable in the aging myocardium because dysfunctions in Ca^{2+} cycle play an important role in contractile abnormalities.[43] A 2026 study using isolated cardiac mitochondria – reductionist model that does not take into account the effect of whole-cell signaling, SGLT2 transporter (which is not expressed in cardiomyocytes) or systemic metabolic adaptations – offers direct evidence that dapagliflozin can affect the mitochondrial functioning independently of other components of the cell. Exposure of isolated mitochondria to dapagliflozin increases the rate of respiration and induces the membrane hyperpolarization; this effect is strongest in the presence of Ca^{2+} ions, somewhat weaker in the presence of K^+ and absent under Na^+ conditions.[44]

Furthermore, SGLT2 inhibitors reduce oxidative damage by activating AMP-activated protein kinase (AMPK), which acts as a major energy sensor in cells. In mouse cardiomyocytes, empagliflozin (0.5 μM) reduced ROS generation after hypoxia-reoxygenation in an AMPK-dependent way; downstream, AMPK mediates mitochondrial biogenesis and antioxidant protection via PGC-1α and Nrf2. This pathway has been identified as the key component of protective effects of this class of drugs on kidney, liver, and cardiovascular system numerous times.[45]

In right atrial biopsies taken during cardiac surgery, canagliflozin decreased basal and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-produced superoxide levels and inhibited the redox-sensitive pro-inflammatory and pro-apoptotic transcriptional program, while empagliflozin showed no significant effect on oxidative stress metrics in the same tissue; the reason behind the observed difference was supposed to be the off-target SGLT1 inhibition by canagliflozin in clinically relevant concentrations, as this inhibitor but not empagliflozin or dapagliflozin inhibited SGLT1 at such concentrations.[46] In a second series of experiments performed on isolated mouse hearts, empagliflozin and canagliflozin led to acute coronary vasodilation, whereas dapagliflozin did not produce any effect; once again, the explanation proposed by the authors of the study was the higher efficacy of the compounds in question,[47] though the nature of this effect requires independent validation.

The immediate result of the described changes is the measurable increase in the bioenergetic state of the cells. In diabetic mice (db/db strain), empagliflozin prevented development of heart failure and boosted cardiac ATP production by 31% relative to untreated animals; paradoxically, the boost was associated with a 61% increase in the contribution of glucose oxidation even in spite of the observed increase in the overall utilization of ketones as an energy source, with β-OHB providing additional ATP, even in the face of a diminished ability of the heart muscle to utilize ketones in the diabetic state. This example warns us not to simplify the matter of SGLT2-inhibition-induced cardiac benefits by reducing it to mere ketone substrate switching; rather, there seems to be a convergence of multiple bioenergetic adaptations leading to improved energy balance of myocardial cells.

The list of positive myocardial changes induced by empagliflozin in diabetic animals includes the normalization of levels of mitofusin-2 and optic atrophy 1 (OPA1); both of these proteins are generally reduced in both aging and diabetic hearts; mitofusin-2 mediates the fusion of outer membranes and attachment to the endoplasmic reticulum, OPA1 – the fusion of inner membranes and organization of cristae; thus, their re-expression leads to better integration of the mitochondrial networks. Additionally, SGLT2 inhibitors apparently improve the process of autophagic degradation of dysfunctional mitochondria (mitophagy), which generally deteriorates with age and, failing, allows the accumulation of damaged mitochondria that cause oxidative stress and inflammation; the restoration of mitophagy is expected to help replace damaged mitochondria with healthier ones, though this effect remains unquantified in the case of cardiac aging.

This specificity is important in this context: it corroborates and explains the mechanism behind the calcium-channeling effect of SGLT2 inhibitors described in the previous section, while highlighting the fact that at least part of the observed effects on the mitochondria does not require the whole-cell machinery and, even more importantly, an intact organism – a crucial boundary when extrapolating the results of the reductionist experiments to a therapeutic context. The principal preclinical and mechanistic studies backing the present section are summarized in Table 2.

d. SGLT2 inhibitors and mitohormesis: a hypothesized pathway to cardiac longevity

The phenomenon of mitohormesis can serve as an explanatory paradigm for the above findings: the mild stress exerted on the mitochondria – classically, caloric restriction, exercise or intermittent fasting – triggers a transitory spike in the levels of reactive oxygen species or metabolic stress, followed by strengthening of the cellular defenses that improves the functionality of mitochondria and, in model organisms, prolongs life.[14] It has been suggested that SGLT2 inhibitors produce the same kind of effect by limiting cardiac glucose supply and forcing ketone-body utilization as a metabolic strategy – the effect that has yet to be proved to be directly associated with enhanced mitochondrial functioning and improved cardiac efficiency. This mechanism is compatible with, though not demonstrated to be a consequence of, the evidence that empagliflozin alters the cardiac Na^+ and Ca^{2+} balance via inhibition of cardiac Na^+/H^+ exchanger (NHE-1) independently of renal function.[43] β-OHB has been shown to promote mitohormesis in various disease models, including traumatic brain injury and neurodegenerative conditions; the increase in the antioxidant enzyme

Table 2. Preclinical and mechanistic evidence for the anti-aging effects of SGLT2 inhibitors

Citation (author, year)	Study type	Model	Intervention	Comparator	Key pathway investigated	Primary outcome	Effect direction	Magnitude (%change/ fold)	Short note
Ferrannini et al, 2016[36]	In vivo	Humans (T2DM & non-diabetic)	Empagliflozin	Placebo	Systemic metabolism	Ketogenesis (β-OHB)	↑	~2-fold	Shift to fatty substrate use
Verma et al, 2018[37]	In vivo	Diabetic db/db mice	Empagliflozin	Vehicle	Myocardial energetics	Cardiac ATP production	↑	+31%	Increased glucose/fatty acid oxidation
Santos-Gallego et al, 2019[40]	In vivo	Nondiabetic HF pigs	Empagliflozin	Placebo	Myocardial metabolism	Myocardial ATP content	↑	N/A	Shift from glucose to ketones/FFA/ BCAA
Yurista et al, 2019[41]	In vivo	Nondiabetic MI rats	Empagliflozin	Vehicle	Mitochondrial function	↓ mtDNA damage	↓	N/A	Increased cardiac ATP production
Baartscheer et al, 2017[43]	Ex vivo	Rat/rabbit cardiomyocytes	Empagliflozin	Vehicle	Ion homeostasis (NHE-1)	Cytoplasmic Na+	↓	N/A	Direct cardiac effect
Shimazu et al, 2013[48]	In vivo/ vitro	Mice, cultured cells	β-OHB	Vehicle	Epigenetics (HDAC)	Histone acetylation	↑	N/A	β-OHB suppresses oxidative stress
Soares et al, 2022[33]	In vivo	Aged mice	Empagliflozin	Vehicle	Vascular aging	Endothelial function (FMD)	↑	N/A	Reduced arterial stiffness
Katsuumi et al, 2024[49]	In vivo	Progeroid mice	Canagliflozin	Vehicle	Cellular senescence	Lifespan extension	↑	+9-14%	Immune-mediated senolysis via PD-L1
Li et al, 2024[42]	In vivo	Nondiabetic HF mice (TAC)	Empagliflozin	Vehicle	Mitochondrial function	Mitochondrial OXPHOS	↑	N/A	Direct cardiac effect
Wen et al, 2025[50]	In vivo/ vitro	Diabetic mice, AC16 cells	Empagliflozin	Vehicle	Cellular senescence	Cardiomyocyte senescence	↓	N/A	Via FOXO1/ ANGPTL4 axis
Kim et al, 2020[51]	Ex vivo	Human PBMCs from T2DM patients	Empagliflozin (in vivo)	Placebo (in vivo)	NLRP3 inflammasome	IL-1β secretion	↓	N/A	Correlated with increased serum BHB
de Souza et al, 2026[44]	Ex vivo	Isolated rat cardiac mitochondria	Dapagliflozin	direct exposure	Bioenergetics / Ca^{2+} handling	Respiration; membrane potential	↑	N/A	Effect Ca^{2+}-dependent; absent with Na^{+}

Abbreviations: ATP, adenosine triphosphate; β-OHB, β-hydroxybutyrate; BCAA, branched-chain amino acids; FDG, fluorodeoxyglucose; FFA, free fatty acids; FMD, flow-mediated dilation; HDAC, histone deacetylase; HF, heart failure; MI, myocardial infarction; mtDNA, mitochondrial DNA; N/A, not applicable; NHE-1, Na^{+}/H^{+} exchanger 1; OXPHOS, oxidative phosphorylation; PBMC, peripheral blood mononuclear cell; TAC, transverse aortic constriction; T2DM, type 2 diabetes mellitus.

expression and reduction of the ROS production in these models aligns well with the characteristics of the mitohormetic reaction.[48,52,53] In view of the consistent increase in the β-OHB level triggered by SGLT2 inhibitors, one can reasonably assume, though cannot prove at the moment, that the same adaptation occurs in the aging myocardium. To corroborate this assumption, it is known that β-OHB functions as an efficient additional cardiac fuel, enhancing cardiac output and ejection fraction without raising myocardial oxygen consumption.[54] this effect, as the theory of "thrifty substrate" suggests,[55] explains the cardio-protective properties of SGLT2 inhibitors observed in the EMPA-REG OUTCOME study. Preclinical evidence in this respect is provided by the positive effect of empagliflozin on the cardiac function in various rat heart failure models[56] and the evidence that empagliflozin inhibits myocardial oxidative stress and fibrosis in diabetic mice via inhibition of Transforming growth factor-β (TGF-β1)/Smad pathway and activation of Nrf2/ARE defense pathways–[57] the effects consistent with, though not specific for, mitohormesis. Along with functioning as a fuel source, β-OHB also acts as a signaling metabolite independently of the ATP production. β-OHB inhibits class I histone deacetylases (HDACs), increasing acetylation of histones and transcription factors such as FOXO3a, thus increasing the expression of genes responsible for antioxidative and DNA repair mechanisms; this mechanism was described first in the context of oxidative stress resistance and, potentially, applies to the prevention of cellular senescence and inflammation as well.[48] There is also a loose analogy in the context of systemic processes: in aging mice, feeding with the ketogenic diet decreased mortality and improved cognitive performance at midlife; the fact that this effect has been described in the context of the dietary rather than pharmacologic ketosis, this observation is nonetheless consistent with the hypothesis that prolonged exposure

to the elevated level of ketone bodies triggers longevity-associated mechanisms.[58] Independently of this epigenetic effect, β-OHB also inhibits NLRP3 inflammasome activation via the inhibition of ASC oligomerization – another mechanism, distinct from being a metabolic fuel, that will be discussed in section 'e'.

All this information allows us to assemble an integrative model according to which the low-intensity ROS signal generated by the metabolic shift caused by glucosuria activates the redox-sensitive transcription factors (Nrf2 and Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) in particular), enhancing mitochondrial biogenesis and oxidative resistance and, potentially, translating, if verified in clinical setting, into reduced fibrosis and delayed functional decline of the heart muscle. However, this model relies on disparate experimental data – human metabolic studies, rodent heart-failure models and isolated-cell epigenetic research – and cannot be considered an experimentally verified pathway.

e. Suppression of the NLRP3 inflammasome by SGLT2 inhibitors

Although the activation of mitochondrial hormesis providing a protective buffer against intracellular damage, the possibility to modulate the aged myocardium by SGLT2 inhibitors also implies the pharmacological suppression of the already established inflammatory networks, primarily the NLRP3 inflammasome. In addition to the above-described effects on bioenergetics, SGLT2 inhibitors reduce the levels of IL-6, TNF-α and IL-1β; this effect has been increasingly explained by NLRP3 inhibition rather than just improvement of glycemia.

Clinical evidence in this context was provided by Kim et al, who applied empagliflozin therapy for 30 days to patients with type 2 diabetes and high cardiovascular risk and observed a statistically significant decrease in IL-1β production by peripheral blood mononuclear cells (PBMCs); the functional readout of the reduced activity of the NLRP3 inflammasome in this case corresponds to the metabolic explanation, as the increased β-OHB and decreased insulin level (also associated with NLRP3 inhibition in vitro) were observed in the course of the treatment.[51]

Additional human evidence for rapid and wide-scale anti-inflammatory effect was provided by two studies of relatively short duration: in frail, old patients with hypertension and diabetes, empagliflozin treatment resulted in the improvement of the endothelial function and reduction of the oxidative stress markers – changes potentially, but not directly linked to NLRP3 modulation.[19] In a pilot study with n = 16, the effects of dapagliflozin on the same endpoints were observed in just two days – much faster than any potential changes in the glycemia.[18] These studies are hampered by the small size of the sample population and the use of surrogate rather than hard clinical endpoints. Preclinical evidence in the form of experiments on diabetic mouse models links these findings with the direct measurement of cardiac inflammasome components: dapagliflozin inhibited myocardial NLRP3/ASC assembly, decreased markers of oxidative stress and enhanced mitochondrial function, thus slowing the progression of diabetic cardiomyopathy – the mechanistic link between metabolic effects and NLRP3 inhibition.[59] As diabetic cardiomyopathy shares basic pathological features with the age-related cardiac dysfunction (inflammation, oxidative stress and fibrosis), these findings are relevant to the model of non-diabetic cardiac aging.

The mechanism by which SGLT2 inhibitors inhibit NLRP3 is multifactorial and interrelated: it includes the reduced ROS production by mitochondria (the main trigger of NLRP3); the inhibition of the NF-κB-dependent priming of NLRP3; the enhancement of autophagy/mitophagy responsible for removal of damaged mitochondria and inflammasome components prior to their activation; and the ASC oligomerization blocking effect of the increased β-OHB described in Section 'd'.[60] These mechanisms interrupt the cycle described in Section 'a' and Fig. 1.

Overall, the anti-inflammatory effects of SGLT2 inhibition are among the more robustly supported mechanisms in this review, with concordant signals across human immune cells, human endothelial function studies, and animal myocardium; the principal remaining uncertainty is one of tissue specificity—whether what has been measured in blood and endothelium faithfully represents what occurs inside the aging myocardium itself—rather than one of whether the effect exists at all.

f. Cellular senescence and the immuno-senolytic hypothesis

Apart from the mitigation of active inflammatory signaling, the genuine tissue rejuvenation in the aging myocardium requires the clearance of irreversibly damaged cells, providing the senolytic potential due to metabolic reprogramming. More recent and different lines of evidence suggest that SGLT2 inhibitors not only prevent cellular damage but also may promote the removal of the cells that are already damaged and have entered a state of senescence. In progeroid mice, canagliflozin treatment led to the reduction of senescent cells in visceral adipose tissue and increase of lifespan by 9-14%. This finding goes beyond the damage-limitation paradigm and introduces a mechanism of tissue rejuvenation.[49] Unlike classical senolytics that directly induce apoptosis in senescent cells via BCL-2 pathway interference, SGLT2 inhibitors appear to function as metabolic seno-modulators. By downregulating immune checkpoint molecules such as PD-L1, they effectively lower the threshold for endogenous immune surveillance, facilitating T-cell mediated clearance rather than direct cellular cytotoxicity.[49,61]

The same mechanism was studied in specific conditions of cardiomyocytes. In diabetic mice and AC16 cardiomyocyte cultures, empagliflozin inhibited the expression of markers of cardiomyocyte senescence through the axis of Forkhead box protein O1 and Angiopoietin-like 4 (FOXO1/ANGPTL4) signaling in the model of diabetic

cardiomyopathy.[50] However, it is unclear if this immuno-senolytic effect works similarly well and at all in aging myocardium without underlying diseases, and this is, perhaps, the main evidential gap in transferring the effect from a disease-related rejuvenation model to anti-aging therapy in humans.

A 2025 randomized, multicenter, double-blind, placebo-controlled study of 142 patients with type 2 diabetes answered this question to some extent (at least, not limited to the heart). Henagliflozin administration for 26 weeks (10 mg/day) significantly increased the telomere length of white blood cells – the primary endpoint of the study – compared to placebo group (90.5% vs 65.6%), along with increased levels of insulin-like growth factor 1 (IGF)-binding protein-3, β-OHB, granzyme B, and perforin expression in cytotoxic T lymphocytes – markers supporting the immuno-senolytic mechanism described above.[22]

This study is, as far as we know, the first randomized study on humans evaluating SGLT2 inhibitors on the panel of aging biomarkers and not a cardiovascular endpoint. The simultaneous increase in β-OHB and Cytotoxic T lymphocytes (CTL) markers in particular support the likelihood of the aforementioned pathway of AMPK activation and Programmed Cell Death Ligand 1 (PD-L1) inhibition leading to immune clearance of senescent cells. However, it is crucial to recognize that while leukocyte telomere lengthening represents a systemic replicative marker of immune cells, it does not biologically confirm localized myocardial senolysis or structural cardiac rejuvenation. Still, several important gaps remain in this evidence. The study included individuals with diabetes (instead of the non-diabetic aging population, which would be more relevant for anti-aging claims), employed henagliflozin (an agent much less studied than empagliflozin or dapagliflozin), evaluated a systemic leukocyte marker (not a cardiac-specific one), and lasted only 26 weeks. The clinical relevance of telomere length is debatable and requires confirmation with longer follow-up.[22]

g. Discussion: Integration, limitations, and future directions

Taken together, the evidence presented here is consistent with the following model: SGLT2 inhibitors act on three interrelated axes of cardiac aging – mitochondrial metabolism, NLRP3 inflammaging, and cellular senescence, through the common upstream factor – metabolic stress induced by glucosuria and activation of AMPK/Silent mating type information regulation 2 homolog 1 (SIRT1)/PGC-1α/Nrf2 signaling (Fig. 2). Limiting chronic inflammation and oxidative stress, two major aspects of inflammaging, SGLT2 inhibitors may help maintain myocardial structure and function.[45] It is important to emphasize explicitly that this model is an integrated hypothesis based on human, animal, and cell evidence of different quality, not an experimental demonstration of the pathway in one aging cardiac model.

Several important caveats accompany the model described above. First, A critical limitation of the current model is the overgeneralization of the data on pathology to physiological aging. Most of the mechanistic data on the mitochondria adaptation, NLRP3 suppression, and senolytic activity was derived from the mouse models of diabetes or myocardial injury (myocardial infarction or transverse aortic constriction). Though there are overlaps between diabetic cardiomyopathy and aging (e.g., oxidative stress and fibrosis), these diseases have different etiologies. Therefore, the assumption of the seamless transition of the described disease-related pathways into the senescent, non-diabetic human myocardium has not been proven yet. Future mechanistic claims should clearly distinguish between the responses to the acute insults from the gradual deterioration specific for physiological aging. Second, the mechanisms described above are not the only ones responsible for cardiorenal benefits of SGLT2 inhibitors – hemodynamic unloading through osmotic diuresis and natriuresis, decrease of epicardial and visceral fat, and erythropoietin-mediated increase in hematocrit and tissue oxygen delivery were also suggested and do not contradict the mitochondrial-centered mechanism described in this review. Third, several of the molecular effects summarized above – mitochondrial dynamics, mitophagy, and relative contribution of glucose and ketone oxidation to the ATP gain described in the Verma et al. study – are based on a single preclinical study each and require replication.[37]

Aside from these, it is worth considering why apparently similar studies in this field often come up with conflicting results and not just treat discrepancy as a noise. Drug-specific differences described above,[46,47] can be an example. Exposure of isolated mitochondria or hearts to the acute, single dose of SGLT2 inhibitors may cause pharmacological effects, such as direct ion channel or redox effects at the supratherapeutic local concentrations, which do not necessarily occur in chronic low-dose oral administration over months and years. Second, species-specific differences, which are crucial in this field because of dominating rodent experiments, also can explain discrepancies: mouse and rat models, which dominate in this literature, differ from human myocardium in their basal metabolic rate, substrate preference, and NHE-1 density, so the magnitude and sometimes even direction of the effect in rodents cannot be automatically transferred to humans. Third, sex is almost never taken into account as a variable in this literature, while the Mendelian randomization study below showed a sex-specific effect of SGLT2 inhibition on longevity; in addition, most preclinical cardiac studies in this field used male animals only. Fourth, the preclinical literature on SGLT2 inhibitors and cardiac mitochondria is almost entirely positive, raising the possibility of publication bias towards statistically significant, nicely mechanistic results.

One clear contradiction is worthy of discussion since it bears directly on the ability of the described mechanisms to reduce biological aging. The 2025 Mendelian randomization study used genetic variations in the SGLT2 gene (SLC5A2) as lifelong surrogate markers of pharmacological SGLT2 inhibition and found a beneficial causal effect of the latter on fathers' attained age (a proxy for lifespan, notably male-

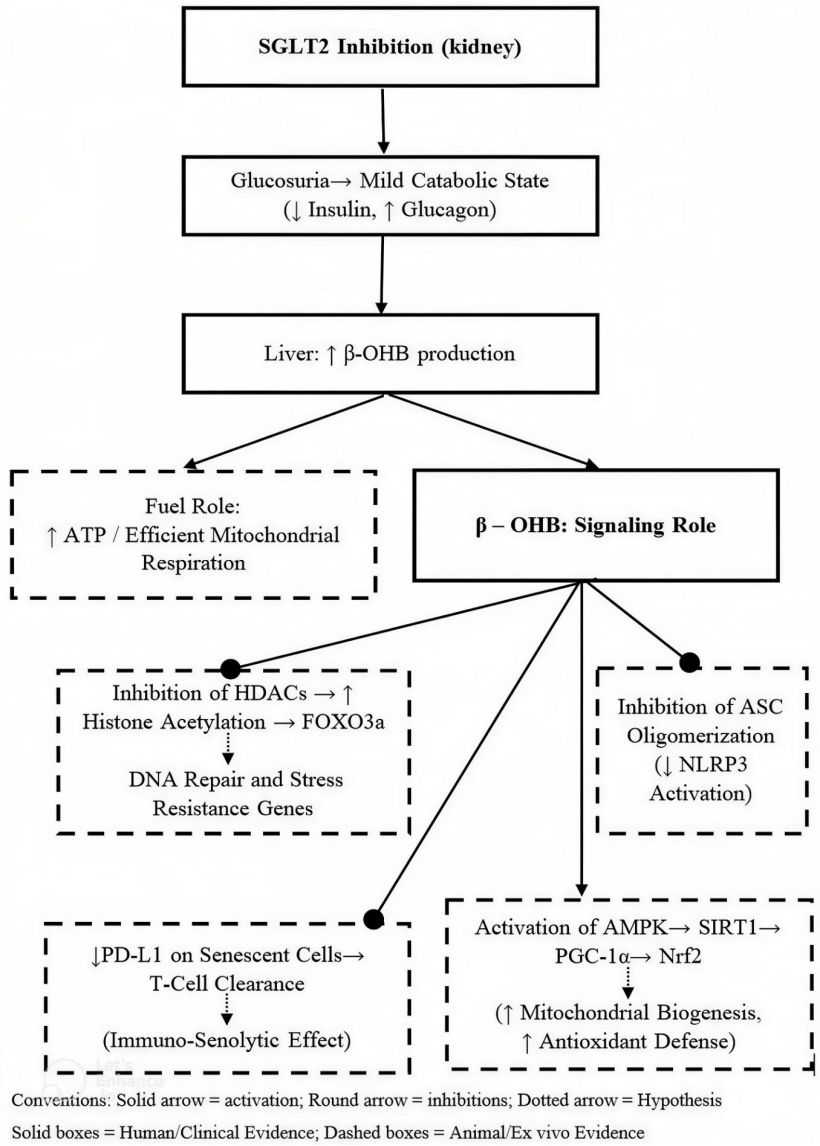

Fig. 2. Proposed mitohormetic and anti-inflammatory cascade engaged by SGLT2 inhibition in the myocardium.

specific, without significant effect on mothers' attained age) and on cognitive function and intelligence, mediated by certain brain imaging-derived phenotypes.[62]

On the other hand, the same genetic approach failed to detect any effect of SGLT2 inhibition on any of the four validated epigenetic clocks (HannumAge, Horvath intrinsic age, PhenoAge, or GrimAge) – arguably the most direct proxies for biological aging available. [62] To resolve the discrepancy, it is important to distinguish two types of aging biomarkers. The leukocyte telomere length (LTL) primarily measures replicative aging and the history of cell divisions. On the other hand, the epigenetic clocks measure the biological or phenotypic aging caused by the widespread changes in DNA methylation accumulated throughout the life due to metabolic, environmental, and oxidative exposure. Since these biomarkers track different biological aspects of aging, they usually show low correlation. It means that pharmacological intervention like SGLT2 inhibition may theoretically slow the process of replicative aging (as measured by LTL) without substantially changing the system-wide DNA methylation pattern.[63,64]

These results represent a clear contradiction and not a simple caveat since they suggest that whatever the effect SGLT2 inhibitors have on longevity and cognition, it does not work via the same epigenetic aging process described in the henagliflozin trial above or simply that telomere length and epigenetic age are different aspects of biological aging not fully overlapping. Or that the genetic proxy of SGLT2 inhibition throughout an entire lifetime cannot be equated with months-long pharmacological SGLT2 inhibition-initiated mid-life. We consider the evidence insufficient to reconcile this contradiction and discuss it as an open question.

The significant discrepancy between replicative biomarkers (LTL) and DNA methylation clocks can be explained by different biological targets of SGLT2 inhibitors. Epigenetic clocks measure the cumulative changes in DNA methylation pattern in the lifetime of the individual caused by the environment, while LTL tracks the history of cell division. It is quite possible that SGLT2

inhibitors-induced metabolic reprogramming preserves the replicative potential of the immune cells and allows to clear the damaged tissue through immunosenescence without changing the established methylation pattern. [62]

Finally, any anti-aging rationale for SGLT2 inhibitors must be weighed against the risk profile of these drugs. The regulatory authorities issue warnings on rare but serious adverse events associated with SGLT2 inhibitors, including Fournier's gangrene, as well as increased fracture risk in particular with canagliflozin; a lower-limb amputation signal first detected in the CANVAS program has been monitored across the entire SGLT2 inhibitor class, though in VERTIS CV, ertugliflozin demonstrated only a numerically higher but statistically insignificant amputation risk compared to placebo (54–57 vs. 45 events per 1,000 patient-years). [17]

The absolute risk of these complications seems low, and careful patient selection remains appropriate (avoiding use in patients with prior history of foot ulcers, peripheral arterial disease, or amputations). However, compared to heart failure and mortality benefits suggested in randomized trials, the benefit-risk ratio is favorable for most patients; yet, this calculation has been performed in cardiorenal indications and has not been independently validated for potential anti-aging indication.

Closing these gaps would require a shift in priorities from mechanistic and disease models to longitudinal non-diabetic aging cohorts. Several possible approaches include hyperpolarized magnetic resonance spectroscopy to monitor the change in myocardial substrate preferences non-invasively; assessment of senescence burden by circulating biomarkers or, where possible, endomyocardial biopsy to check if the immuno-senolytic mechanism discussed in Section 7 is applicable to humans; study of the mammalian target of rapamycin (mTOR) pathway in the context of SGLT2 inhibitors to explore synergistic anti-aging interventions[65]; and replication of the henagliflozin telomere findings in non-diabetic patients with a broader panel of validated epigenetic clocks in view of the current discordance between genetic and trial-based evidence on the effects of SGLT2 inhibitors on epigenetic aging.[22,62]

Several emerging methodologies could be helpful in answering some specific gaps outlined above faster than incremental research. Single-cell and single-nuclei RNA sequencing of myocardial tissue could clarify whether the NLRP3 suppression and senescence clearance signals, as proposed in Sections 6-7, are uniformly distributed among cardiomyocytes, fibroblasts, and resident immune cells, or are specific to one of the populations – something that bulk-tissue assays, all of the mentioned animal experiments being examples, cannot show. Spatial transcriptomics could localize these signals in relation to fibrotic areas and clarify whether NLRP3 suppression comes before or after fibrosis. Multi-omics analysis (combination of metabolomics and proteomics) is a logical extension of the metabolomic study of the henagliflozin trial[22] and could help to clarify if the changes in thiamine pathway observed in the trial were a side effect of the ketogenic shift or were mechanistically related to it. Digital biomarkers and wearable-derived measures of autonomic function of the heart would be a non-invasive, repeatable measure of the aging phenotype described in Section 2, in addition to molecular biomarkers discussed elsewhere, although their relationship to the particular mechanisms described in this review is yet to be established and would require validation. Combination therapies – SGLT2 inhibition with glucagon-like peptide-1 (GLP-1) receptor agonists, with mTOR modulators, or even more speculatively, with senolytic agents – could be interesting, as each of these drugs targets partially distinct nodes of the aging hallmark network (metabolic, nutrient sensing, and senescence clearance, respectively); it is not known whether such combinations produce additive, synergistic, or redundant effects on the mechanisms reviewed in this review and would require dedicated mechanistic studies, not extrapolation from the single-agent data summarized in Tables 1-2. Such studies would be required before the SGLT2 inhibitors could be considered, at least tentatively, as potential candidates for cardiac anti-aging therapy rather than very effective, but mechanistically still poorly understood cardiorenal treatments. Fig. 3 presents an integrated visual representation of the suggested mechanisms along with corresponding evidence level (from ex vivo experiments up to human clinical studies).

Conclusion

The SGLT2 inhibitors have already disrupted the therapeutic paradigm for heart failure and chronic kidney disease, regardless of any effects on glucose homeostasis. These mechanisms elucidated above – mitohormesis, suppression of the NLRP3 inflammasome activation and the removal of senescent cells by the immune system – provide a physiologically sound rationale for the benefit realized in part from this therapy. Nonetheless, none of these mechanisms has ever been proven to delay or reverse cardiac aging in humans without diabetes. While the preclinical research is solid and relevant for understanding these effects, there is little human evidence necessary to claim that these effects are anti-aging. The only reasonable way forward here is to say that SGLT2 inhibitors affect several important cellular aspects of cardiac aging and thus provide a strong rational basis for clinical trials proposed above.

Authors' Contribution

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Competing Interests

The authors have no conflicts of interest to declare.

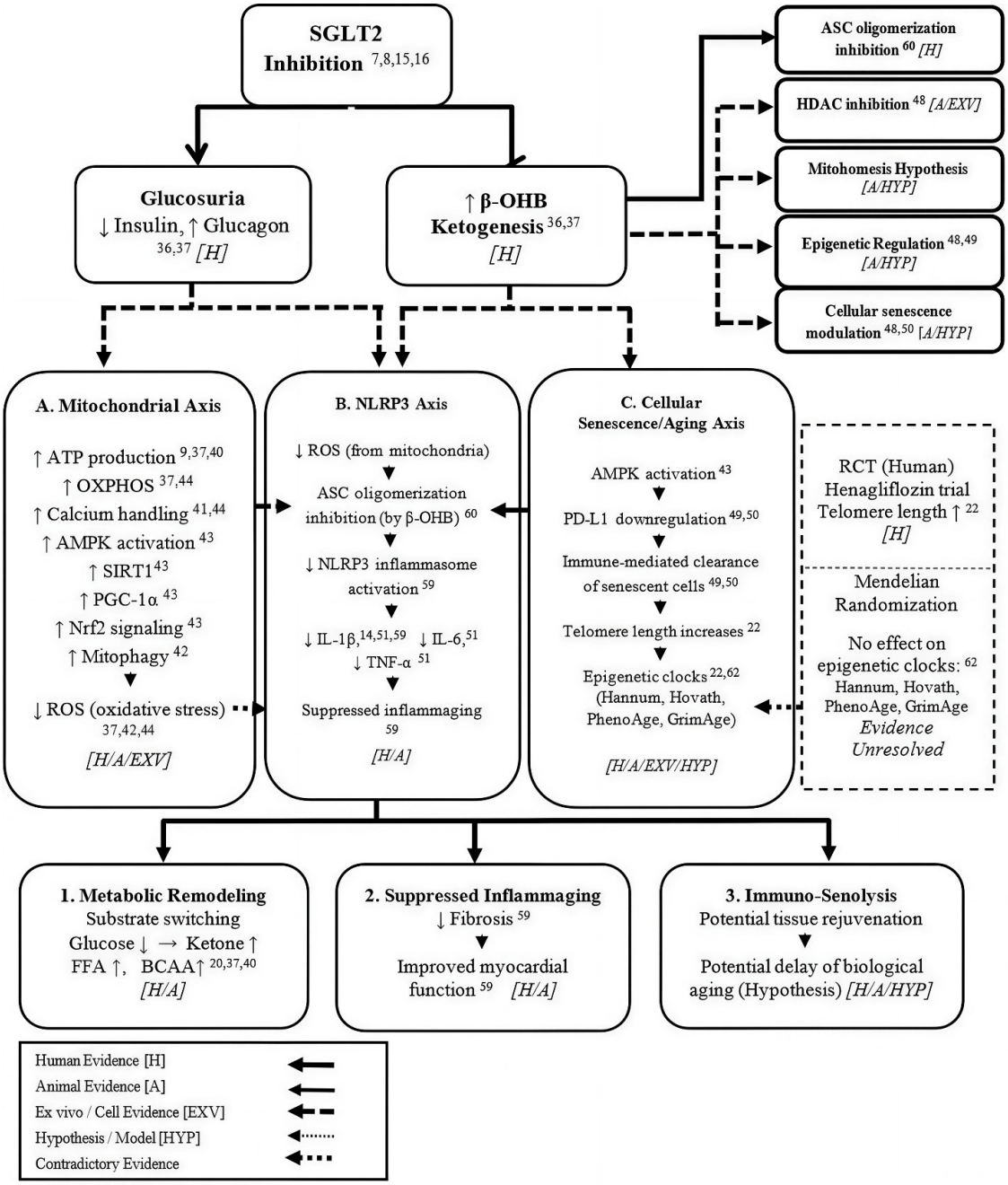

Fig. 3. Integrated Evidence Map of SGLT2 Inhibition on Cardiac Aging Pathways. The mechanisms and pathways depicted in this integrative model are derived from studies examining metabolic remodeling, inflammaging suppression, immuno-senolysis, and mitochondrial bioenergetics.[7-9,14-16,20,22, 36, 37,40-44,48-51,59,60,62]

Data Availability Statement

No new data were generated or analyzed in support of this research.

Declaration of AI-Assisted Tools in the Writing Procedure

Our research team utilized AI-assisted tools (ChatGPT, OpenAI) solely for language enhancement and readability improvement during the manuscript preparation process. We explicitly confirm that all scientific content, including research methodology, data collection, analyses, interpretations, and conclusions are entirely original and were independently developed by our research team. The AI tools were exclusively employed to refine linguistic elements and improve clarity of presentation, without any contribution to the intellectual or scientific substance of the work.

Ethical Approval

Not applicable.

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