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Pharmacological activation of Nrf2: Cardioprotective effects of statins and metformin against dyslipidemia-induced oxidative stress

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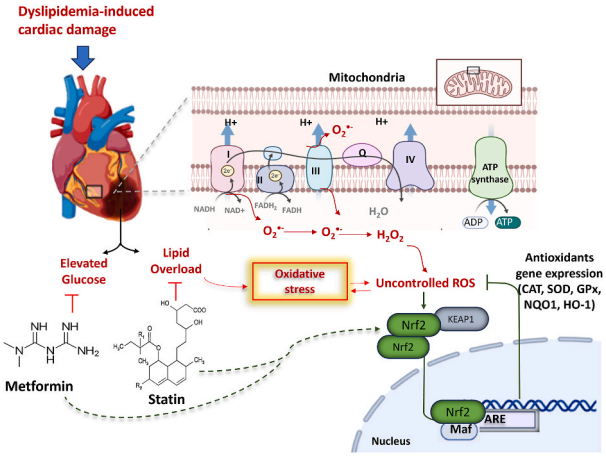
HIGHLIGHTS

- Nrf2 activation may reduce oxidative stress and help prevent cardiovascular damage in CVD and T2D patients.
- Statins and metformin modulate Nrf2, adding cardioprotective effects beyond their usual therapeutic roles.
- Dietary interventions with standard therapy may enhance Nrf2 activation and support better heart health outcomes.

GRAPHICAL ABSTRACT



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ABSTRACT

Oxidative stress plays a central role in dyslipidemia-related cardiovascular complications, driving cellular damage and disease progression. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a critical defense mechanism against oxidative stress, helping to protect cardiac function under pathological conditions. This review explores the potential of enhancing Nrf2 activation as a therapeutic strategy to mitigate oxidative damage in cardiovascular diseases associated with dyslipidemia. While statins and metformin are primarily known for their lipid- and glucose-lowering effects, emerging evidence suggests that they also influence Nrf2

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Statins
Metformin

activation. These drugs do not directly activate Nrf2 but rather modulate its activity by reducing oxidative stress and improving mitochondrial function, offering dual protection against cardiovascular dysfunction. By examining the relationship between oxidative stress, Nrf2 activation, and commonly used therapies, this review proposes a novel approach to enhance cardiovascular protection in patients with metabolic disorders, offering insights into new therapeutic avenues to improve outcomes in cardiovascular diseases associated with metabolic conditions.

1. Introduction

The myocardium predominantly relies on a sustained supply of fatty acids as its primary energy source for its primary contractile function [1]. Under normal physiological conditions, cardiomyocytes maintain a delicate balance between lipid uptake and oxidation under normal physiological conditions to prevent excessive lipid accumulation which could lead to metabolic complications and increase the risk of cardiovascular disease (CVD) [2]. Dyslipidemia, which is closely associated with type 2 diabetes (T2D) [3], is characterized by abnormal lipid levels in the blood, especially elevated concentrations of low-density lipoproteins-cholesterol (LDL-C). This pathological state plays a significant role in disrupting myocardial energy metabolism, contributing to cellular damage and the development of cardiovascular complications [4,5]. The Randle theory [6] well defines this phenomenon through the glucose-fatty acid cycle, which describes the metabolic interplay between glucose and fatty acid oxidation within the myocardium and other prominent energy-modulating tissues. Preclinical studies confirm that elevated fatty acids within the human body can inhibit glucose oxidation within a pathological state, thus contributing to dyslipidemia-related alterations in energy metabolism [7–9]. These metabolic alterations are often accompanied by structural and functional impairments in cardiomyocytes, as seen in diabetic patients without overt atherosclerotic features [10]. These observations have prompted a great interest in researching and understanding the molecular mechanisms driving cardiovascular complications under metabolic stress [11–13], particularly those linked to dyslipidemia [14].

Current therapeutic approaches for managing dyslipidemia and T2D typically focus on controlling lipid and glucose levels. However, emerging evidence suggests that targeting the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway offers a novel approach to mitigating oxidative stress and metabolic dysfunction in CVD [15,16]. This review explores the therapeutic potential of activating Nrf2, with a focus on how its activation intersects with existing pharmacological treatments such as statins and metformin (Fig. 1), these are commonly prescribed drugs that may benefit from an additional mechanism of action through Nrf2 modulation [17,18]. The Nrf2 pathway has emerged as a critical cytoprotective mechanism that plays a critical role as a key transcription factor that regulates cellular defense against oxidative stress by activating the expression of antioxidant genes and proteins [19,20]. In the myocardium, Nrf2 activation plays a critical role in maintaining redox homeostasis by promoting the expression of enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which work to neutralize reactive oxygen species (ROS) and protect myocardial cells from oxidative damage [21,22]. Consequently, the pharmacological activation of Nrf2 has emerged as a promising therapeutic strategy to combat various chronic diseases characterized by oxidative stress, including dyslipidemia-associated cardiovascular complications [23,24].

Beyond their primary lipid-lowering effects, statins have been shown

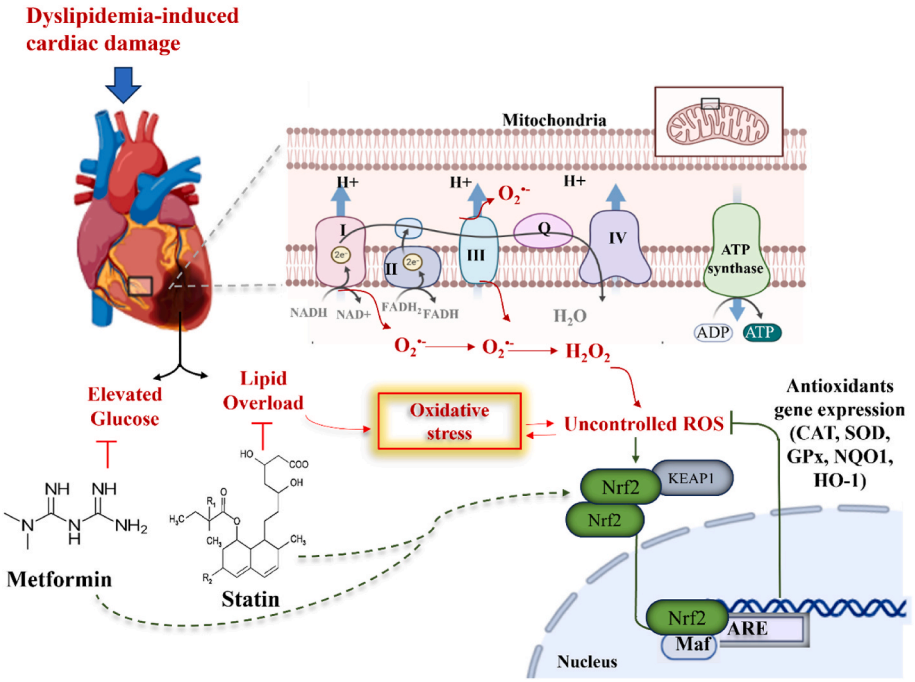

Fig. 1. This illustration shows how metformin and statins confer cardioprotective effects in the myocardium by targeting metabolic stressors associated with dyslipidemia. Metformin effectively lowers elevated glucose levels, while Statins reduce lipid overload. Both interventions converge on the modulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, a master regulator of cellular antioxidant responses. Activation of Nrf2 leads to a significant reduction in oxidative stress by upregulating key antioxidant genes such as catalase (Cat), superoxide dismutase (Sod), glutathione peroxidase (GPx), NAD(P)H quinone dehydrogenase 1 (Nqo1), and heme oxygenase-1 (Ho-1). This coordinated response enhances the myocardium's defense against oxidative damage, underscoring the therapeutic potential of statins and metformin in mitigating cardiovascular complications arising from dyslipidemia-induced oxidative stress.

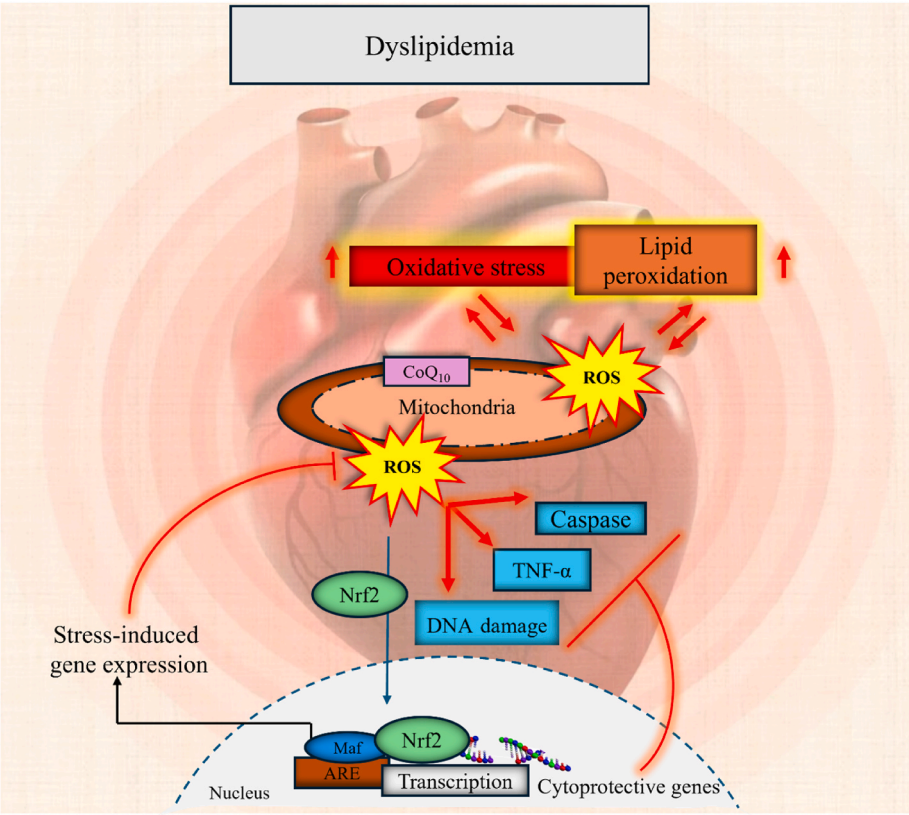

Fig. 2. Illustrates the role of oxidative stress in cardiovascular complications associated with dyslipidemia. In dyslipidemic conditions, elevated circulating lipids interact with reactive oxygen species (ROS), leading to lipid peroxidation, one of the primary contributors to oxidative stress. Additionally, impaired mitochondrial function exacerbates oxidative damage, resulting in myocardial injury and increased cardiovascular risks. The nuclear factor erythroid 2-related factor 2 (Nrf2) plays a central role in defending against oxidative stress by activating antioxidant responses. Upon activation, Nrf2 translocate to the nucleus, where it binds to the antioxidant response element (ARE), triggering the expression of protective genes that neutralize ROS. This response can be further enhanced by exogenous supplementation with coenzyme Q10 (CoQ10), which supports mitochondrial function and antioxidant defenses. In conditions like heart failure or ischemia-reperfusion injury, excessive ROS production activates Nrf2 to boost antioxidant defenses and mitigate oxidative stress-induced damage.

to exert pleiotropic effects that modulate oxidative stress, potentially through Nrf2 activation [25]. Recent studies suggest that statins may reduce ROS production and indirectly enhance the expression of antioxidant enzymes, providing additional myocardial protection [17,26]. Similarly, metformin, the first-line treatment for T2D, has been reported to influence Nrf2 pathway activation through its effects on mitochondrial function and AMP-activated protein kinase (AMPK) signaling [27]. Both statins and metformin, through their potential modulation of the Nrf2 pathway, may offer dual benefits in managing dyslipidemia and protecting against oxidative damage in the myocardium. Despite these promising findings, the precise molecular mechanisms through which statins and metformin modulate Nrf2 in the context of cardiovascular disease remain underexplored. This review aims to critically evaluate the therapeutic potential of modulating the Nrf2 pathway in the context of dyslipidemia-associated cardiovascular complications, with a particular focus on the mechanistic roles of statins and metformin in modulating Nrf2 activity. Furthermore, we address the clinical implications of Nrf2 modulation and propose strategies for integrating these findings into current treatment paradigms to improve patient outcomes.

2. The role of oxidative stress in dyslipidemia-associated cardiovascular complications

Oxidative stress refers to an imbalance between the production of ROS and the body's ability to detoxify these intermediates, leading to cellular or tissue damage [28]. The concept of oxidative stress as a significant factor in biological processes was first proposed with the free radical theory of aging by Denham Harman in the 1950s, which suggested that the accumulation of reactive oxygen species (ROS) contributes to aging and disease [29]. Under normal physiological conditions, ROS is fundamental for processes, such as the mitochondrial respiratory process [30], and even more integral for myocardial development, including cardiomyocyte maturation [31], cardiac calcium regulation [32], excitation-contraction coupling [33], and vascular tone regulation [34]. However, excessive ROS production can overwhelm antioxidant defenses, leading to cellular dysfunction, tissue injury, and contributing to the development of CVDs, especially in conditions like dyslipidemia and T2D [35]. Within a diabetic heart, excessive ROS levels contribute to myocardial structural and functional abnormalities leading to an increased risk of heart failure [30,36].

Preclinical studies have shown that elevated ROS production in dyslipidemia can directly affect the myocardium, causing damage to cardiac cells by accelerating apoptosis [37]. Apoptosis, defined as programmed cell death, is a necessary process to eliminate unwanted or damaged cells within the human body [38]. However, in dyslipidemia, mitochondria, which play a prominent role in ROS production within the myocardium [39], display an impaired oxidative process that exacerbates the pro-apoptotic mechanisms [9,40]. This vicious cycle induces the release of pro-apoptotic proteins from the mitochondria such as bcl-2–associated X protein (Bax), bcl-2 homologous antagonist killer (Bak), bcl-2–associated death protein (Bad), and bcl-2–interacting mediator of cell death (Bim), which accelerates oxidative stress-induced cellular damage [41,42]. Thus, intracellular defence mechanisms against oxidative stress have become vital to neutralize the excessive production of ROS [43]. These mechanisms, especially the intracellular antioxidants within the myocardium, protect cardiac cells from the toxic

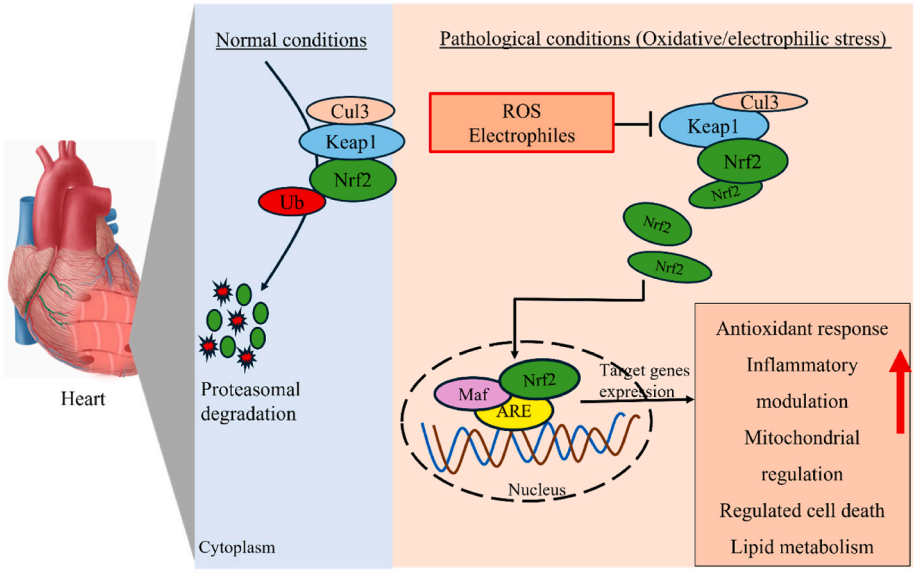

Fig. 3. Illustrates the activation of the Nrf2 pathway in the myocardium under both physiological and pathological conditions. Under normal conditions, Kelch-like ECH-associated protein 1 (Keap1) maintains Nrf2 stability by promoting its ubiquitination and proteasomal degradation. However, in pathological conditions, such as dyslipidemia, which increases reactive oxygen species (ROS) or electrophilic stress, Keap1 dissociates from Nrf2. This dissociation enables Nrf2 to accumulate in the nucleus, forming complexes with small Maf proteins. Together, Nrf2 and Maf proteins bind to antioxidant response elements (ARE) in the DNA, activating the expression of cytoprotective genes, including antioxidants that help mitigate oxidative stress and prevent cellular damage.

effects of ROS, preserving myocardial function and preventing the progression of various cardiovascular diseases associated with dyslipidemia.

In clinical conditions, markers of oxidative stress, such as malondialdehyde (MDA), are elevated in patients with heart failure, diabetic cardiomyopathy, and ischemic heart disease, highlighting the central role of ROS in driving cardiovascular pathology [44,45]. For example, patients with heart failure associated with iron deficiency present with increased MDA levels, which correlate with worsened endothelial function [45,46]. Additionally, T2D patients, who are at greater risk for myocardial infarction and heart failure, exhibit high ROS levels, leading to oxidative damage to myocardial proteins and further cardiac dysfunction [47–49]. The mechanisms through which ROS contribute to CVD are not limited to direct cellular injury [50]. ROS also activate pro-inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which further exacerbate oxidative stress, endothelial dysfunction, and fibrosis, all of which contribute to cardiovascular disease progression [51,52]. Importantly, ROS-induced DNA damage can impair gene expression, particularly genes involved in myocardial energy metabolism and antioxidant defense, worsening oxidative damage and cardiovascular complications [30,53].

Given the critical role of oxidative stress in dyslipidemia-associated cardiovascular disease, strategies aimed at enhancing intracellular antioxidant defenses, particularly through the activation of the Nrf2 pathway, have gained attention [54,55]. Nrf2 is a key transcription factor that regulates the expression of antioxidant enzymes such as SOD, glutathione peroxidase GPx, and catalase CAT, which neutralize ROS and protect against oxidative damage [21,22]. Activation of Nrf2 has been shown to improve myocardial function, reduce oxidative stress, and mitigate the progression of cardiovascular diseases in preclinical models of dyslipidemia and diabetes [56,57]. Therefore, activating Nrf2 represents a promising therapeutic strategy for managing oxidative stress and improving outcomes in patients with dyslipidemia-associated cardiovascular complications. Strengthening intracellular antioxidants, particularly through Nrf2 activation, is crucial to combating oxidative stress-related cellular damage (Fig. 2), offering a potential path to develop therapeutic strategies targeting oxidative stress to prevent or alleviate dyslipidemia-associated cardiovascular diseases.

3. The role of NRF2 in cellular defense mechanisms

Nrf2 is a transcription factor that belongs to a family of conserved amino acids with Nrf2-ECH homology 2 (Neh2) being the major regulatory domain [58,59]. Nrf2 is constitutively expressed in almost all prominent tissues, showing higher expression levels in the brain, kidney, muscle, lung, heart, and liver where it helps maintain cellular homeostasis and protect against oxidative damage [60,61]. Nrf2 plays a crucial role in regulating the expression of antioxidant proteins and enzymes, which are vital for defending cells against oxidative stress [20]. It directly influences the transcription of about 1 % of the human genome which counts over 240 genes involved in various cellular functions like bioenergetics, metabolism of carbohydrates, lipids, iron, and upregulation of other transcription factors [62,63]. Within a physiological state (Fig. 3), Nrf2 is kept inactive with a short lifespan, however, its stability increases when exposed to inducers, such as oxidative stress or other pathological conditions [64]. The stability of Nrf2 is tightly regulated by kelch-like ECH-associated protein 1 (Keap1), which facilitates the ubiquitination and proteasomal degradation of Nrf2 under normal conditions [65]. In response to stress, particularly oxidative stress, Keap1 dissociates from Nrf2, allowing Nrf2 to accumulate in the nucleus [66]. Interestingly, in addition to this dissociation, newly synthesized Nrf2, which is not necessarily released from Keap1 can also translocate to the nucleus [67]. Both the dissociation from Keap1 and the de novo translation of Nrf2 are critical for activating Nrf2-mediated cytoprotective responses. Once in the nucleus, Nrf2 interacts with small Maf proteins, forming a complex that binds to the antioxidant response elements (ARE), triggering the expression of genes that protect against ROS-induced damage [65,68].

Ultimately, Nrf2 regulates the expression of various downstream genes, including intracellular redox-balancing proteins such as glutamate cysteine ligase (GCL), GPx, and heme oxygenase-1 (HO-1), as well as phase II detoxifying enzymes like glutathione S-transferase (GST) and NAD(P)H quinone oxidoreductase-1 (NQO1) transporters such as multidrug resistance-associated protein 2 (MRP2) [69–71]. In the myocardium, Nrf2 is crucial for maintaining redox homeostasis and

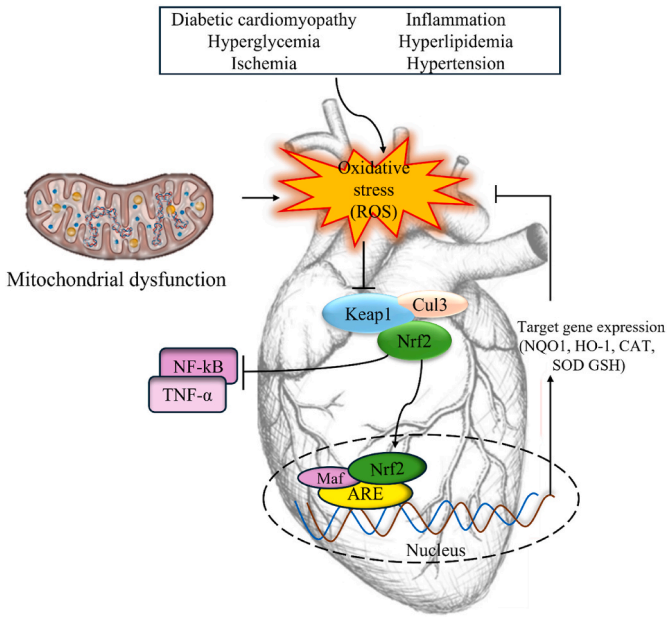

Fig. 4. Illustrates the role of the Nrf2 pathway in protecting the myocardium from oxidative stress-induced damage under pathological conditions, such as dyslipidemia. In these conditions, mitochondrial dysfunction and excessive reactive oxygen species (ROS) exacerbate oxidative stress. Activation of Nrf2 within the myocardium triggers a cascade of events, including the binding of Nrf2 to antioxidant response elements (ARE) in the DNA, which stimulates the transcription of cytoprotective genes. This pathway upregulates the expression of several antioxidant genes, including heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH), all of which help reduce lipid peroxidation and prevent myocardial apoptosis. Additionally, Nrf2 activation inhibits NF-κB signaling, suppressing the expression of pro-inflammatory cytokines and promoting the secretion of anti-inflammatory cytokines, thus further protecting the heart from inflammation and oxidative damage.

protecting against oxidative stress-induced damage, as observed in experiments where its deficiency accelerates myocardial pathological mechanisms associated with myocardial infarction [57]. In fact, knocking out Nrf2 in wild-type mice accelerates heart failure progression [72]. Clinical evidence also suggests that age-related changes may impact the Nrf2 pathway regulation, potentially leading to increased oxidative stress in older adults [73,74], making them more susceptible to cardiovascular diseases. In aging mice, impaired transcriptional activity of Nrf2 correlates with oxidative stress-related damage in the myocardium [75]. Thus, precise control of Nrf2 activity is essential for maintaining cellular homeostasis, as both excessive and insufficient Nrf2 activity can have detrimental effects on the myocardium and exacerbate disease processes [76].

4. Nrf2 activation is necessary to effectively counteract oxidative stress-induced cardiac damage

Nrf2 has emerged as a promising target for managing CVDs [55,77]. Preclinical models of diabetes, for instance, have shown a significant reduction in Nrf2 expression within the myocardium, correlating with an elevation of oxidative stress-related cellular damage [72,78] (Fig. 4). Under conditions of dyslipidemia, Nrf2 plays a critical role in neutralizing reactive oxygen species (ROS) to prevent further cellular damage [79,80]. Reduced Nrf2 gene expression levels are consistent with myocardial ultrastructural modifications in T2D (*db/db)* mice, supporting the concept that impaired Nrf2 activation exacerbates myocardial damage in metabolic diseases [81]. The downregulation of Nrf2 is accompanied by decreased expression of key Nrf2-related genes, such as GCL, GPx, and HO-1 as well as GST and MRP2 in the heart of a diabetic mouse [81]. Beyond combating oxidative stress, Nrf2 activation has shown promise in enhancing the heart's anti-inflammatory response [82]. Because of the proximity between oxidative stress and inflammation, Nrf2 activation has been shown to affect the pro-inflammatory pathway, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) within the myocardium [83]. Interestingly, elevated plasma levels of tumor necrosis factor-alpha (TNFα), a key cytokine regulated by NF-κB, have been associated with an increased risk of T2D linked to dyslipidemia [84]. In the context of T2D, the suppression of Nrf2 within the myocardium results in a reduction in antioxidant and cytoprotective gene expression, further contributing to myocardial dysfunction [85]. Furthermore, in conditions of dyslipidemia, diminished Nrf2 activity leads to a decrease in the expression of antioxidants, such as SOD, CAT, GPx, and GSH, which allows oxidative damage to accumulate within the myocardium [86,87].

Beyond the intracellular responses, Nrf2 activation also enhances mitochondrial function by modulating key pathways involved in mitochondrial biogenesis and respiration, including those regulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Pgc1α) and mitochondrial transcription factor A (Tfam), both of which are essential for mitochondrial DNA stability and function [88,89]. For instance, supplementation with CoQ_{10}, an important component of mitochondrial respiration, has been shown to promote Nrf2 and HO-1 expression in the heart of rats subjected to exercise training [90], this was associated with decreased NF-κB levels, highlighting the potential of Nrf2 activation to counteract oxidative stress and inflammation. Furthermore, overexpressing Nrf2 has been shown to inhibit ROS production, strengthen intracellular antioxidant defence, and alleviate fibrosis thereby improving cardiac function within models of dyslipidemia [91–93].

Pharmacological activation and genetic overexpression of Nrf2 have been shown to increase the expression of antioxidant enzymes like HO-1 and NQO1, within the myocardium in experimental models of dyslipidemia and T2D [85,94,95]. These findings further support the cardioprotective potential of Nrf2 activation in alleviating oxidative stress and metabolic disruptions in the heart [96]. As a result, there has been growing interest in exploring therapeutic compounds like sulforaphane, n-acetyl cysteine, aspalathin, and more for their potential to activate Nrf2 response and alleviate dyslipidemia-associated cardiovascular complications [55,85,96–98].

5. Statins activate Nrf2 to protect against dyslipidemia-associated cardiovascular complications

Statins were first introduced around the 1980s [99], these are a class of drugs that reduce cholesterol levels by inhibiting 3-hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase in the mevalonate pathway [100,101]. Statins are widely prescribed for managing dyslipidemia, particularly in patients with T2D [102,103], with common statins including atorvastatin, simvastatin, rosuvastatin, and pravastatin [104,105]. To achieve each patient's needs statidaily andmally prescribed at different doses, atorvastatin doses range from 10 to 80 mg daily [106]; simvastatin from 10 to 40 mg daily, and is well-established for its efficacy [106,107]. Rosuvastatin, known for its high potency, is usually prescribed in doses of 5–40 mg daily [108], while pravastatin, considered to have a lower risk of muscle-related side effects, is typically used at doses of 10–40 mg daily [109]. Statins are absorbed from the gastrointestinal tract and undergo first-pass metabolism in the liver, with peak plasma concentrations generally reached within 1–4 h after ingestion [110]. Due to their ability to lower LDL-C levels and improve cardiovascular outcomes, statins have become a cornerstone in managing dyslipidemia and reducing CVD risk [111,112].

Beyond cholesterol-lowering effects, statins also exert pleiotropic effects that benefit cardiovascular health, including reducing myocardial fibrosis and ameliorating pathological cardiac states [113]. Prominent markers of oxidative stress, such as oxidized lipid peroxidation

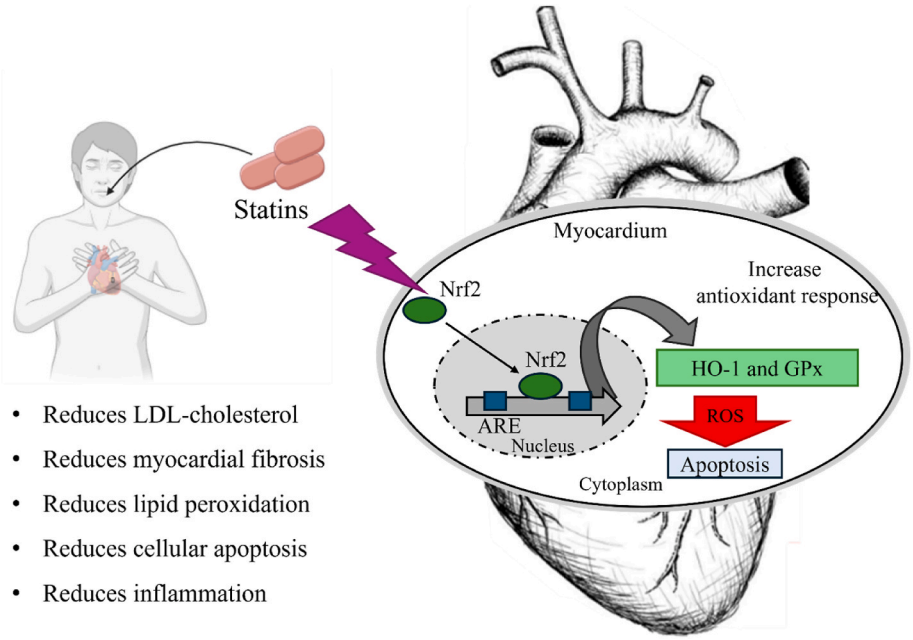

Fig. 5. Illustrates the role of statins in reducing oxidative stress and cellular damage in the myocardium, particularly under conditions like dyslipidemia or type 2 diabetes (T2D). In addition to their cholesterol-lowering effects, statins exert pleiotropic benefits by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. This activation stimulates the transcription of antioxidant genes such as NAD(P)H: quinone oxidoreductase 1 (NQO1) and glutathione peroxidase (GPx), which help reduce reactive oxygen species (ROS) production. By lowering ROS levels, statins effectively decrease lipid peroxidation, inflammation, and cellular apoptosis in the heart, thereby protecting against myocardial damage and fibrosis.

products, are primary targets for statins in preclinical models of T2D, where they have been shown to protect against cellular apoptosis and improve cardiac ultrastructure [114–116]. In one study, atorvastatin administered at 10 mg/kg once daily for 16 weeks in T2D (db/db) mice resulted in reduced myocardial fibrosis and lower MDA levels, thereby mitigating the harmful effects of oxidative stress [117]. Evidence suggests that statins modulate the Nrf2 pathway, leading to increased expression of antioxidant genes such as HO-1 and GPx, which are crucial for mitigating oxidative stress-induced damage [118] (Fig. 5). Certainly, preclinical models have demonstrated that statins can suppress oxidative stress and inflammation, reducing myocardial cellular damage in various disease states [17,119]. Although limited evidence exists regarding the modulation of the Nrf2 pathway in the myocardium in response to statin treatment in humans [120,121]. Several studies have shown that statins reduce oxidative stress markers and promote antioxidant responses, ultimately lowering the risk of CVDs [121–123]. These findings affirm the potential role of statins in modulating the Nrf2 pathway as a part of their pleiotropic effects, thereby contributing to their cardioprotective role in dyslipidemia and T2D. However, further studies, particularly well-designed clinical trials, are needed to confirm the activation of Nrf2 in the myocardium and evaluate its therapeutic potential in dyslipidemia-associated CVDs.

6. Metformin activates Nrf2 to protect against dyslipidemia-associated cardiovascular complications

Metformin, a drug belonging to the biguanide class, was first discovered in the 1920s and has been widely used since the 1950s [124]. It is primarily prescribed as a first-line treatment for T2D due to its effectiveness in lowering blood glucose levels [125,126]. The pleiotropic effects of metformin extend beyond glucose regulation, including reducing hepatic glucose production, enhancing insulin sensitivity, and improving peripheral glucose uptake and utilization in patients with T2D [127]. Typically, the initial dose for adults ranges from 500 mg to 850 mg once daily, which can be adjusted based on efficacy and tolerability, with a common maintenance dose of 2000 mg per day divided into two or three doses [128]. Metformin has a favourable absorption profile with bioavailability between 50 and 60 % and is absorbed mainly from the small intestine [129]. Its peak plasma concentrations are usually reached within 2–3 h of oral administration, and it is not metabolized by the liver, being excreted unchanged in the urine [129].

Metformin has been shown to improve cardiac function by attenuating oxidative stress to salvage myocardial damage in various preclinical models [130]. For example, the administration of metformin, at 200 mg/kg for 12 weeks, blocked the pathological consequences of inducible nitric oxide synthase in the heart tissue of rats with diabetic cardiomyopathy, effectively controlling energy metabolism and alleviating oxidative stress-related complications [130–132]. In patients with dyslipidemia, metformin administration over approximately 12 months has been shown to improve insulin sensitivity and LDL-C levels, ultimately reducing cardiovascular risk [133]. However, other studies argue that metformin administration can improve total cholesterol and triglyceride levels but does not affect LDL-C in some patients with dyslipidemia [134]. Despite this, metformin has been shown to improve myocardial oxygen consumption while reducing prominent markers of heart failure in patients with diabetes [135–137]. In fact, in patients suffering from both heart failure and T2D, metformin demonstrated cardioprotection by improving left and right ventricular function independent of glycemic control [136].

Emerging evidence supports the idea that metformin can modulate the Nrf2 pathway, including its downstream target genes, to protect against oxidative stress-related cellular damage. Although the therapeutic potential of Nrf2 pathway modulation through metformin has been more widely recognized in cancer research [138,139], its relevance in cardiovascular toxicity is also increasing [140]. Metformin administration at a dose of 300 mg/kg for up to 24 weeks has been shown to enhance the expression of genes and proteins associated with the Nrf2/Keap1 signaling pathway to reverse cardiac remodeling in obese mice [18]. Similarly, 200 mg/kg of metformin for 2 weeks activated Nrf2 and its associated antioxidant genes like HO-1, GSH, and catalase CAT to protect against ischemia-reperfusion injury in rats [27]. Beyond oxidative stress, metformin strengthens intracellular responses and

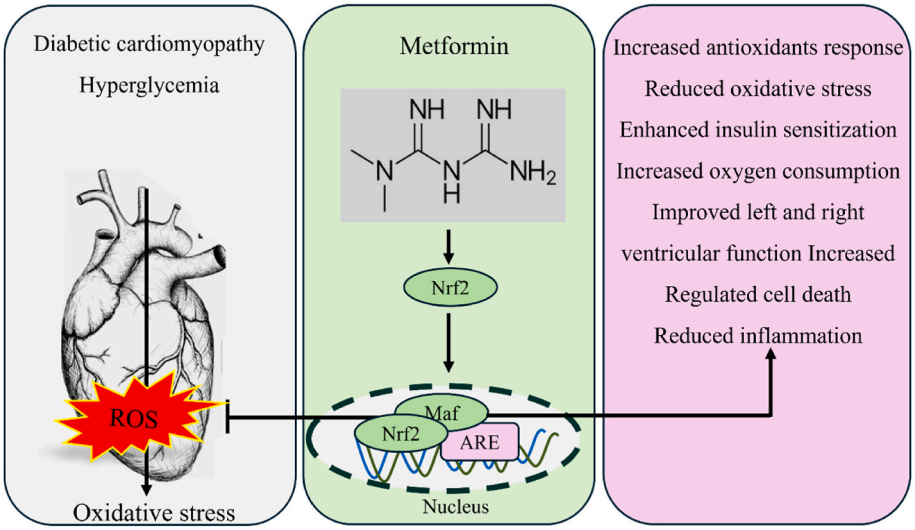

Fig. 6. Highlights the role of metformin, a widely used biguanide for managing type 2 diabetes, in protecting against cardiovascular complications associated with dyslipidemia. Metformin activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which enhances the antioxidant response, improves oxygen utilization, and regulates cell death pathways. These effects help mitigate oxidative stress, reduce myocardial damage, and improve cardiac function. Interestingly, combining metformin with statins, such as atorvastatin, has shown synergistic effects in protecting against hyperglycemia-induced fibrosis and inflammation in mice, suggesting added benefits in managing cardiovascular complications in dyslipidemia. Clinically, metformin also improves insulin sensitivity, which is associated with reductions in low-density lipoprotein cholesterol (LDL-C), highlighting its dual role in both glycemic control and lipid profile management. These combined effects may reduce cardiovascular risk in patients with diabetes.

boosts antioxidant defenses via Nrf2 activation, while inhibiting pro-inflammatory factors independent of glucose control [141], (Fig. 6). Interestingly, combination therapy of metformin and atorvastatin has been found to protect against hyperglycemia-induced fibrosis, while suppressing nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3), a key pro-inflammatory mediator, in mice with T2D [142]. This suggests a synergistic benefit of combining metformin and statins to manage cardiovascular complications in diabetic conditions. However, further research is essential to better understand how Nrf2 activation through this combination therapy can alleviate oxidative stress-related complications in CVDs.

7. Concluding remarks

Oxidative stress is the key pathological feature implicated in the development of dyslipidemia-associated cardiovascular complications [143]. The human body has evolved a critical cytoprotective system, activated through Nrf2, which plays a vital role in neutralizing oxidative stress and protecting against related cardiovascular damage [144,145]. As such, interventions aimed at activating Nrf2 have emerged as a promising therapeutic strategy to address a range of chronic diseases, including those linked to oxidative stress, such as cardiovascular issues and dyslipidemia [144]. The evidence presented in this review suggests that commonly used treatments for dyslipidemia and T2D like statins and metformin, may protect the myocardium from oxidative stress-induced damage through the modulation of the Nrf2 pathway and promoting the expression of related antioxidants. These drugs, through their pleiotropic effects, offer the potential to mitigate cardiovascular risk factors associated with dyslipidemia and T2D. Given the crucial role of Nrf2 in maintaining redox homeostasis, further research is necessary to explore whether alternative therapies, such as dietary interventions alone or new pharmacological agents, can complement conventional treatments by enhancing Nrf2 activation and strengthening the intracellular antioxidant defense system. In conclusion, this review reveals the potential of Nrf2 as a viable therapeutic target for preventing cardiovascular diseases, particularly in individuals at risk of both CVD and T2D. Continued exploration of Nrf2-activating strategies, could provide valuable insights into improving cardiovascular outcomes in high-risk populations.

Authors' contributions

Conceptualization and original draft, Sinenhlanhla X.H. Mthembu; writing, reviewing and editing, Sithandiwe E. Mazibuko-Mbeje, Khanyisani Ziqubu, Sonia Silvestri, Patrick Orlando, Bongani B. Nkambule, Christo J.F. Muller, Luca Tiano, and Phiwayinkosi V. Dludla; funding acquisition, Sithandiwe E. Mazibuko-Mbeje and Phiwayinkosi V. Dludla. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The manuscript reviews literature from published studies and does not require a data availability statement.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ARE: antioxidant response elements; CAT: catalase; CVD: cardiovascular disease; CoQ_{10}: coenzyme Q_{10}; GSH; glutathione; GPx: glutathione peroxidase; HMG CoA reductase: 3-hydroxy-methylglutaryl coenzyme A reductase; HO-1: heme oxygenase-1; NQO1: NAD(P)H: quinone oxidoreductase 1; Keap1: Kelch-like ECH-associated protein 1; LDL-C: low-density lipoprotein cholesterol; MDA: malondialdehyde; mTOR: mammalian target of rapamycin; MRP2: multidrug resistance-associated protein 2; NF-κB: nuclear factor-κB; ROS: reactive oxygen species; Nrf2*:* nuclear factor erythroid 2-related factor 2; Pgc1α: peroxisome proliferator-activated receptor, gamma coactivator 1-alpha; SOD: superoxide dismutase; Tfam: mitochondrial transcription factor A; T2D: type 2 diabetes.

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