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EDITORIAL

Inflammatory markers, oxidative stress, and mitochondrial dynamics: Repercussions on coronary artery disease in diabetes

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Abstract

Inflammatory markers and mediators that affect the development of cardiovascular diseases have been the focus of recent scientific work. Thus, the purpose of this editorial is to promote a critical debate about the article titled "Nε-carboxymethyl-lysine and inflammatory cytokines, markers, and mediators of coronary artery disease progression in diabetes", published in the *World Journal of Diabetes* in 2024. This work directs us to reflect on the role of advanced glycation end products, which are pro-inflammatory products arising from the metabolism of fatty acids and sugars whose main marker in tissues is Nε-carboxymethyl-lysine (NML). Recent studies have linked high levels of pro-inflammatory agents with the development of coronary artery disease (CAD), especially tumor necrosis factor alpha, interleukins, and C-reactive protein. These inflammatory agents increase the production of reactive oxygen species (ROS), of which people with diabetes are known to have an increased production. The increase in ROS promotes lipid peroxidation, which causes damage to myocytes, promoting myocardial damage. Furthermore, oxidative stress induces the binding of NML to its receptor RAGE, which in turn activates the nuclear factor-kB, and consequently, inflammatory cytokines. These inflammatory cytokines induce endothelial dysfunction, with increased expression of adhesion molecules, changes in endothelial permeability and changes in the expression of nitric oxide. In this sense, the therapeutic use of monoclonal antibodies (inflammatory reducers such as statins and sodium-glucose transport inhibitors) has demonstrated positive results in the regression of atherogenic plaques and consequently CAD. On the other hand, many studies have demonstrated a relationship between mitochondrial dynamics, diabetes, and cardiovascular diseases. This link occurs since ROS have their origin in the imbalance in glucose metabolism that occurs in the mitochondrial matrix, and this imbalance can have its origin in inadequate diet as

well as some pathologies. Photobiomodulation (PBM) has recently been considered a possible therapeutic agent for cardiovascular diseases due to its effects on mitochondrial dynamics and oxidative stress. In this sense, therapies such as PBM that act on pro-inflammatory mediators and mitochondrial modulation could benefit those with cardiovascular diseases.

Key Words: Mitochondrial dynamics; Diabetes; Oxidative stress; Coronary artery disease; Nε-carboxymethyl-lysine

Core Tip: Increased oxidative stress promoted by pro-inflammatory mediators such as Nε-carboxymethyl-lysine causes changes in mitochondrial dynamics and has been associated with insulin resistance and cardiovascular diseases. Therapies that promote the health of mitochondria by balancing the mechanisms of mitochondrial fusion and fission may be a path forward in the context of coronary artery disease.

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INTRODUCTION

The accumulation of lipids and hypertension associated with hyperglycemia for decades has been the main risk factor for reducing cholesterol and developing coronary artery disease (CAD) in patients with diabetes mellitus (DM). However, pro-inflammatory agents are now considered the major orchestrators of CAD development and atherosclerotic implications[1]. Among these agents, Nε-(carboxymethyl) lysine (NML) stands out as a stimulant of macrophage uptake *via* receptors for advanced glycation end products (AGEs). AGEs result from the reaction between reducing sugars and the amino group of proteins, leading to dysfunctional glycated proteins[2,3], which play a significant role in diabetes pathophysiology. Additionally, NML is associated with atherogenic precursors by stimulating foam cell formation[4]. Another mechanism by which these pro-inflammatory mediators cause endothelial dysfunction is through decreased nitric oxide (NO) release, increased adhesion molecules, and increased permeability[5]. One of these pro-inflammatory protagonists is Pyrin Receptor 3 (NLRP3), which induces the release of pro-inflammatory cytokines. Moreover, the thioredoxin (TXNIP)-NLRP3 complex promotes pro-caspase-1 activation and apoptosis. In pathological situations, the myocardium increases reactive oxygen species (ROS) production, leading to increased K+ efflux and mitochondrial damage. Bisht *et al*[6] suggested that NLRP3 could be an interesting target in myocardial injury treatment. Recent studies have linked high levels of pro-inflammatory agents with CAD development, particularly tumor necrosis factor-alpha, interleukins, and C-reactive protein.

OXIDATIVE STRESS, MITOCHONDRIAL DYNAMICS, AND THEIR IMPLICATIONS IN DIABETES

The hyperglycemic state increases oxidative stress, which in turn induces the dissociation of the thioredoxin complex that interacts with TXNIP[7]. Concomitantly, NO acts on certain adhesion and pro-inflammatory molecules, decreasing their release through an inhibition mechanism of nuclear factor-kappa B (NF-κB)[8]. NF-κB induces the transcription of pro-inflammatory cytokines and activates NLRP3, thereby increasing the inflammatory response[9]. In conditions where the inflammatory process is exacerbated (as in DM), there is an increase in the production of peroxynitrite anion and ROS that end up inhibiting the activities of NO[10]. In turn, increased ROS promotes the degradation of tetrahydrobiopterin, an important cofactor of NO synthesis. Therefore, there is a decrease in NO production, and endothelial dysfunction progresses, progressively affecting the muscle tone of the endothelium[10]. Some authors have argued that the therapeutic target in this clinical setting should be the pursuit of mitochondrial health[11,12], as mitochondria mediate the conversion of substrates into adenosine triphosphate (ATP), delivering energy to maintain cellular functions. Furthermore, they regulate signaling pathways in the cell and buffer intracellular calcium and apoptosis. These organelles have a significant capacity for self-regulation through cycles of fusion and fission, known as mitochondrial dynamics[12]. It is important to highlight that insulin resistance (IR) is associated with dysfunctional mitochondria, characterized by reduced bioenergetic responses to insulin stimulation and decreased mitochondrial biogenesis[13]. Changes in the transcription of mitochondrial genes, lipotoxicity, and glucotoxicity appear to be some of the mechanisms involved in IR [11]. Additionally, mitochondrial dysfunction promotes a reduction in energy expenditure, overproduction of ROS, as well as altered oxidation of fatty acids, thereby aggravating IR. The balance between mitochondrial fusion and fission is fundamental for cardiometabolic homeostasis. Mitofusins (MFN1) and (MFN2) are proteins that act in mitochondrial fusion, together with dynamin-related protein 1 (DRP1) and fission protein 1 (FIS1)[12,13]. Due to this crucial role of

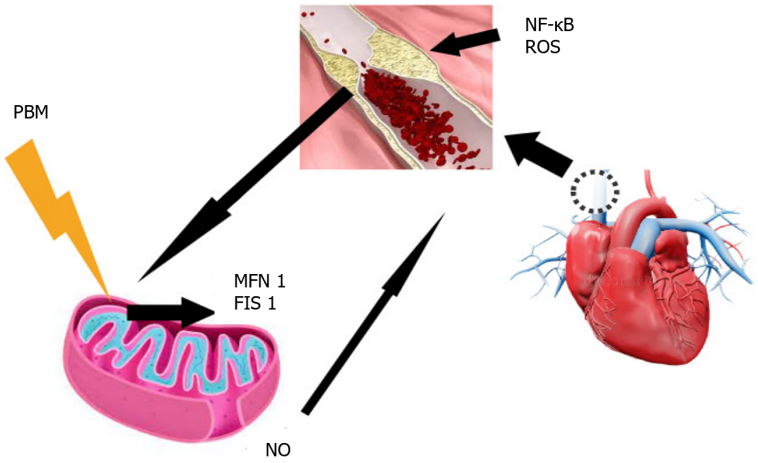

Figure 1 Activation of nuclear factor kappa B by reactive oxygen species modulates inflammatory responses. Illustrative scheme demonstrating the activation of the nuclear factor kappa B transcription factor by reactive oxygen species and its modulation in inflammatory responses in vascular smooth muscle cells, endothelial cells, and macrophages. FIS: Fission protein; MFN: Mitofusins; NO: Nitric oxide; PBM: Photobiomodulation; ROS: Reactive oxygen species; NF-κB: Nuclear factor-kappa B.

mitochondrial dynamics in metabolism, therapeutic approaches aimed at mitochondrial homeostasis could strongly impact the treatment of these pathologies. In this sense, some antihyperglycemic drugs have played a modulatory role in mitochondrial homeostasis, acting on the cardiovascular system by reducing DRP1 levels and increasing OPA1 and MFN2 protein levels in cardiomyocytes[14]. Among these drugs, we can highlight glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors (SGLT2i), which act on glycemic control and body weight[15]. Shao *et al*[16] demonstrated that SGLT2i increased the protein expression of OPA1, DRP1, and MFN1, as well as mitochondrial respiration, suggesting that SGLT2i could attenuate defects in mitochondrial function in diabetic cardiomyopathy by modulating mitochondrial dynamics[16]. According to these authors, several studies[17-19] have observed that SGLT2 inhibitors minimize the risks of non-fatal myocardial infarction and non-fatal death or stroke related to heart failure. Some theories about the possible mechanisms of cardioprotection by SGLT-2 inhibitors, including apoptosis, antioxidant effects, prevention of cardiac inflammation, mitochondrial dysfunction, and ionic homeostasis[20-22], suggest repolarization through the improvement of mitochondrial health and oxidative stress, as well as prolonged ventricular pressure suppression. Other authors, such as Lee *et al*[23], highlight a late Na^+ and Na^+/H^+ exchange current and changes in Ca^{2+} regulation.

PHOTOBIOMODULATION, INFLAMMATORY MEDIATORS, AND MITOCHONDRIAL DYNAMICS

Photobiomodulation (PBM) is a therapy based on electromagnetic irradiation using a light emitter such as a laser or light-emitting diode[24]. The effects of this electromagnetic light irradiation primarily target the mitochondrial membrane, where it acts on cytochrome c oxidase of the respiratory chain, facilitating electron transport and resulting in increased ATP production and transmembrane proton gradient[25]. Previous studies have shown that PBM initially increases ROS production, followed by an adaptive decrease in oxidative stress[26,27], and that PBM acts on mitochondrial dynamics [21], modulating the expressions of MFN2 and FIS1 in diabetic-induced rat models[27]. Furthermore, it activates the redox-sensitive transcription factor NF-κB through brief generation of ROS. This modulation of NF-κB attenuates inflammatory responses in vascular smooth muscle cells, endothelial cells, and macrophages[28], as well as the production of inflammatory cytokines tumor necrosis factor-alpha and NO[29] (Figure 1).

CONCLUSION

The interaction between inflammatory mediators, oxidative stress, and mitochondrial dynamics substantially influences the pathogenesis of cardiovascular diseases, especially in the context of DM. Pro-inflammatory agents play a fundamental role in the development of CAD and atherosclerosis, contributing to endothelial dysfunction and subsequent cardiovascular complications. Mitochondrial dysfunction, exacerbated by hyperglycemia and IR, further intensifies oxidative stress and inflammation, leading to compromised cellular metabolism and impaired energy production. Therapeutic strategies targeting mitochondrial homeostasis, such as certain antidiabetic medications like SGLT2 inhibitors, have the potential to mitigate cardiovascular risks by modulating mitochondrial dynamics and oxidative stress. Additionally, PBM emerges as a potential therapeutic approach, exerting anti-inflammatory effects and influencing mitochondrial function. In light of this, innovative therapeutic interventions can be developed to effectively manage cardiovascular diseases associated with DM.

FOOTNOTES

Author contributions: Tatmatsu-Rocha JC and Mendes-Costa LS contributed to this article; Tatmatsu-Rocha JC designed the overall concept and draft of the manuscript; Mendes-Costa LS contributed to the discussion and conception of the manuscript; Both authors contributed to writing and editing the manuscript and literature review.

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