https://doi.org/10.31925/farmacia.2021.4.2 **REVIEW**

OXIDATIVE STRESS AND CYTOKINES' INVOLVEMENT IN THE OCCURENCE AND PROGRESSION OF DIABETIC COMPLICATIONS IN THE COVID-19 PANDEMIC CONTEXT

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Abstract

Diabetes mellitus is a metabolic disease presenting growing prevalence worldwide. Oxidative stress is involved in the development of micro- and macrovascular complications in diabetic patients. Several pro-oxidative pathways contribute to the production of reactive oxygen species which can damage different biomolecules and a variety of inflammatory cytokines are also involved in the aggravation of diabetic manifestations. COVID-19 infection enhances oxygen free radical production and intensifies the inflammation, thus has a negative impact on the evolution of diabetes mellitus and its complications. The complications of diabetes including the macrovascular and microvascular conditions as well as the psychological illnesses have a major influence on the patients' quality of life.

Rezumat

Diabetul zaharat este o boală metabolică prezentând o prevalență crescândă la nivel mondial. Stresul oxidativ este implicat în dezvoltarea complicațiilor de tip micro- și macrovascular la pacienții diabetici. Diverse procese pro-oxidative contribuie la producerea de specii reactive ale oxigenului care pot afecta diferite biomolecule și o varietate de citokine inflamatorii sunt implicate în agravarea manifestărilor diabetice. Infecția cu COVID-19 promovează producerea de radicali liberi ai oxigenului și intensifică inflamația, având astfel un impact negativ asupra evoluției diabetului zaharat și a complicațiilor sale, fiind implicat în decesul multor pacienți cu boli cronice. Complicațiile diabetului, atât cele macrovasculare și microvasculare, cât și afecțiunile psihologice au o influență majoră asupra calității vieții pacientului.

Keywords: oxidative stress, cytokines, diabetes mellitus, COVID-19

Introduction

Diabetes mellitus (DM) is a complex, heterogeneous, chronic disease characterized by the presence of hyperglycaemia due to a deficiency of insulin secretion and/or decreased glucose consumption in the periphery with simultaneous impact on glucose, lipid and protein metabolism. Chronic hyperglycaemia causes vascular damage and leads to the occurrence of macrovascular (atherosclerotic, coronary, cerebrovascular and peripheral artery disease) and microvascular complications (diabetic retinopathy, neuropathy, and nephropathy). In 2017, The International Diabetes Federation reported that 415 million adults (1 in 11) had diabetes mellitus in 2015, the number of cases being predicted to rise to 642 million by 2040 [52].

For a better control of diabetes, it is recommended to assess the risk factors: obesity, smoking, lipid parameters, blood pressure, renal function. Many organ damage and comorbidities such as coronary heart disease, heart failure, cerebrovascular disease and kidney impairment have a greater prevalence in type 2 DM [49].

Diabetes mellitus, as a metabolic disorder, can lead to oxidative stress through production of reactive molecules. These are reactive oxygen species (ROS) and reactive nitrogen species (RNS), which initiate oxidative damage of biomolecules (proteins, lipids, nucleic acids), thus enhancing the development of several diseases. The penetration of reactive molecules

through biological tissues can be different, but their presence is significant as they are formed in different cell structures such as cell membranes, cytoplasm, and in different cell organelles, including lysosomes, peroxisomes, mitochondria, nucleus and endoplasmic reticulum [18].

Diabetes mellitus and SARS-CoV-2 infection

Since the late 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world prompting World Health Organization to declare COVID-19 a global pandemic. Until the time of the writing of this review almost 192 million cases and more than 4.1 million deaths have been reported [79]. Despite previous reports of greater risk of diabetic patients for severe acute respiratory syndromes [8], this pattern has not been reported for COVID-19, although it was found that the prevalence of diabetes mellitus is significantly higher in patients with severe COVID-19 [21]. Diabetes mellitus and its complications and comorbidities (such as hypertension and heart disease) had a major influence on mortality and admission to hospital of the patients infected with SARS-CoV-2 [6] and this trend has been observed globally in many retrospective studies [9, 16, 26, 28, 55, 66]. In one study higher blood glucose levels were observed in diabetic patients who did not survive COVID-19 during hospitalization than in those who recovered from this infection [67]. It was hypothesized that SARS-CoV-2 itself, like other viruses, may be responsible for oxidative stress (OS) [37, 50] which might further increase the existing imbalance already found in poorly controlled diabetes mellitus, opening the possibility for effective anti-oxidant treatment.

Oxidative stress and cytokines in diabetes and its complications

Nowadays, the mechanisms that generate oxidative stress in diabetic patients, and the role of the reactive oxygen species involved in the infection with SARS-CoV-2 represent an open subject for all specialists in this field.

Free radicals are molecules that contain an unpaired electron in an atomic orbital which makes them highly reactive and unstable. There are several types of reactive species, but the most important in this case are reactive oxygen species. The main source of ROS is the mitochondria while other sources are circumstantial and cumulative: inflammation, phagocytosis, ischemia/reperfusion, exercise, xanthine oxidase catalysed reactions, peroxisomes, arachidonate path-ways [43, 68, 82]. Antioxidants are molecules capable of donating an electron to a free radical in order to neutralize it and prevent further cellular damage. Antioxidants are either produced during metabolic processes (glutathione) or are found in diet (vitamin C). Oftentimes there is an imbalance between ROS and available antioxidants, resulting in damage of biomolecules such as nucleic acids, proteins, lipids. The term used to describe this imbalance is called oxidative stress [44, 68, 84].

Most ROS are produced in the cell by the mitochondrial electron transport chain (mETC) not only as by-products of the normal metabolism, but they are also considered essential molecules in physiological processes of the cell [13, 59, 63]. Most of the super-oxide is generated at Complex I and Complex III, but is also mediated by monoamine oxidase and electron transfer flavoprotein oxidoreductase. These processes are amplified by hypoxia and substrate availability [20, 84]. There are many non-mitochondrial sources of ROS of which nicotinamide adenine nucleotide phosphate oxidase (NOS) and endothelial NOS (eNOS) are the most important in the course of diabetes mellitus and its vascular complications [70, 84].

The OS signalling pathway involves the redox (reduction/oxidation) mechanism through which ROS induce reversible and irreversible modifications of amino acids. Oxidation of cysteine during the redox process results in changes of the structure and function of the protein. Some of the modifications are reversible by reducing compounds [58].

Oxidative stress itself may impair insulin sensitivity and cause beta-cell dysfunction and eventually diabetes mellitus through several mechanisms involving inflammation, mitochondrial dysfunction, damaging of signalling pathways and apoptosis [38, 81, 82]. There are several molecular mechanisms of glucose-induced damage in the development of all chronic diabetic complications: increased activity of glucose oxidation pathway (glycolysis), increased production of advanced glycation end-products (AGE), diacyl-glycerol formation and protein kinase C (PKC) activation, hyperactivity of the hexosamine pathway, increased flux through polyol pathway. In the hyperglycaemic state, there is an excess of superoxide anion radical produced mainly by mitochondria that induces oxidative stress which inflicts damage to nuclear DNA. The DNA repair mechanisms inhibit glyceraldehyde-3-phosphate (GAP) dehydrogenase, resulting in high levels of GAP and other glycolytic intermediates. Within the cell, these molecules stimulate the pro-oxidative pathways [31, 73].

The intertwining of oxidative stress pathways with inflammatory pathways leads to pathophysiological outcomes at multiple levels. Dysfunction of the nuclear (erythroid-1) related factor pathway in diabetic cells reduces the production of antioxidant cytoprotective enzymes, such as superoxide dismutase and glutathione-s-transferase [64]. As superoxide generation under hyperglycaemic conditions inflicts DNA damage and finally necrosis, the resulting cellular debris promotes a local inflammatory response. Inflammation may also be initiated or augmented by the activation of

the transcription factor NF-κB pathway due to OS. Oxidant species have a direct influence on the phosphorylation of inhibitory kappa B protein and subsequent release of free NF-κB heterodimer capable of crossing the nuclear membrane. Binding of NF-κB to genome promotes the production of inflammatory cytokines like tumour necrosis factor α (TNF-α), interleukin-6, and cyclooxygenase-2 [64, 75, 76].

The activation of hexosamine pathway in the hyperglycaemic state leads to a cascade of reactions involving production of glucose-6-phosphate (G-6-P) from both glucose and glucosamine, which further represents the substrate for the generation of hexosamine products like proteoglycans, glycolipids and glycoproteins. On the other hand, glucosamine produced on this pathway contributes to the levels of H2O2 to additionally increase oxidation. The toxic effects of ROS are mediated in this case by inhibition of glyceraldehydes-3-phosphate dehydrogenase activity. This inhibition not only promotes an influx of hexosamine products, but also augments AGE pathway activity through the effect of methylglyoxal [80].

Microvascular disease refers to damage of the capillaries and arterioles at the level of the basement membrane that can lead to diabetic nephropathy, retinopathy, and cardiomegaly. The macrovascular disease represents atherosclerosis of the large vessels related to diabetes mellitus and involves myocardial infarction, stroke and foot gangrene. Oxidative stress, infections, and mechanical injuries contribute to endothelial dysfunction, an early trigger of atherosclerosis [47].

Several of the most frequently reported elements reported in SARS-CoV-2 infection are disseminated intravascular coagulopathy and hypoxia despite preserved pulmonary function [35], narrowing the cause at the mitochondrial level [4, 46, 72].

Individuals diagnosed with diabetes mellitus have a higher risk of subsequently developing macrovascular complications including myocardial infarction, stroke and peripheral artery disease. In myocardial injury secondary to ischemia and reperfusion, reactive species of oxygen play an integral role in diabetes mellitus. Following a myocardial infarction, OS led to an accumulation of calcium in mitochondria, up-regulating the formation of mitochondrial permeability transition pores with a direct effect on the membrane potential. These events have been linked with reperfusion injury [7, 30, 74]. The hydroxyl radical is produced both in the ischemia and reperfusion phases. Re-oxygenation of the cells combined with the previous accumulation of ROS during ischemia initiates a chain reaction in which more ROS are generated, the mitochondrial membrane potential is altered affecting the energy stores and pro-apoptotic signals are initiated [5, 41]. Transforming growth factor beta-1 (TGF-β1) production and signalling in OS conditions induce the expression of BLC2-associated X protein which releases cytochrome-C, also resulting in apoptosis [62]. On the other hand, excessive TGF-β1 signalling increases mitochondrial production of ROS, contributing to the overall OS and apoptosis.

Respiratory viral infections are known to induce OS by activation of NF-κB pathway and deregulation of the nuclear transcription factor NF-E2-related factor 2 [36].

Some recent studies [15, 25, 54] reported the so called "cytokine storm" as the most dangerous and life-threatening event in COVID-19, while other authors consider this event just the manifestation of endothelial dysfunction and systemic inflammation [69]. Regardless of a lack of consensus, it is well documented that the inflammatory mediators such as interleukin-6 and C-reactive protein found elevated in COVID-19 patients [14] contribute to the cyclic generation of OS in patients with diabetes mellitus [51].

In a septic medium rich in reactive oxygen species several alterations of erythrocyte membranes take place, ultimately generating heme and free iron which further induces damage to cells, apoptosis and blood coagulation [10]. It has been hypothesized that in patients with COVID-19 neutrophilia leads to OS that exacerbates the immune responses, in a process called reverse trans-endothelial migration of rigid, deregulated neutrophils which results in a more severe disease [39].

The combination of ROS and cytokines generate severe OS and organ failure in patients infected with SARS-CoV-2 [10, 34]. It was found that in hospitalized diabetic patients with COVID-19 elevated serum glucose levels promoted cytokine profiles [86], but the use of glucose lowering agents such as metformin, which has the ability to inhibit proinflammatory cytokines [27], led to a more favourable prognosis. Consequently, both data from the medical literature as well as medical practice emphasize that an accumulation of ROS from both a poorly controlled diabetes mellitus and concomitant SARS-CoV-2 infection might generate a significant OS which could be an important factor in the prognosis and mortality of these category of patients [33].

Type 2 diabetes is a complex metabolic disease characterized not only by chronic hyperglycaemia, but also by an inflammatory state given the fact that obesity is frequently encountered in this condition [42]. Taken this into consideration various inflammatory biomarkers like CRP, MCP-1, TNF- alpha, IL-1 beta may be determined before and after starting the diabetic therapy in order to have an optimal management of the disease. There has been observed a positive association between circulating IL 10 levels and pro-inflammatory mediators such as CRP and IL 6 [57, 78].

Antidiabetic medications with a potential anti-oxidant role

Some blood glucose-lowering drugs are involved in the OS. Thus, metformin is the primary antidiabetic

treatment used in type 2 diabetes mellitus for its benefits on weight loss, improvement of HbA1C levels and lipid profile with minimal risk of hypoglycaemia. Metformin therapy reduces ROS formation and consequently mitigates the damaging effects of OS. Administration of this biguanide has the potential of reducing the advanced oxidation protein products, AGE and pentosidine production while improving the activity of NOS through augmented blood flow [1, 12]. Because of its structure, metformin may be able to interact with hydroxyl free radicals and α-dicarbonyls. By reducing NADPH and oxidative reactions in mitochondria, metformin is limiting the production of ROS intracellularly. Another protective role is to reduce the concentration of insulin, thus diminishing the hyperinsulinism associated stress [19, 53]. In patients with poor glycaemic control and diabetic complications, with documented high OS levels, metformin could prevent further development of complications [17, 60, 83].

Liraglutide is a glucagon like peptide-1 receptor agonist that improves glucose-dependent insulin secretion capacity and beta-cell function [77]. Beta-cells are sensitive to OS because of the diminished availability of local antioxidants. The incretin protects them by combating the oxidative species. Although the mechanisms by which liraglutide reduces OS is not fully understood, it is suggested that they involve cyclic AMP/protein kinase-A signalling pathway, phosphoinositide 3-kinase, and MAPK [11, 71, 85]. In experimental studies, vildagliptin reduced both oxidative stress and endoplasmic reticulum stress, thus preventing beta-cell apoptosis [2]. It directly increased beta-cell mass by promoting their differentiation and proliferation [22]. In clinical studies, vildagliptin was able to control acute glucose fluctuations, leading to a reduction of OS markers such as nitrotyrosine [61].

Diabetes and mental health

According to the literature individuals with diabetes mellitus have higher anxiety, depressive symptoms, panic attacks and impaired functioning especially when another stressor is added [45]. Clinical features such as sweating, anxiety, tachycardia and confusion are similar in both hypoglycaemic episodes and anxiety induced by a stressful life event. As up to 45% of the cases of mental health issues and diabetes-related psychological distress in individuals with diabetes goes undetected, the management of their mental and physical health amidst of COVID-19 pandemic outbreak is even more needed [23, 24, 40, 56].

It is well established that depression and type 2 diabetes are comorbid conditions with a bidirectional relationship [32]. There is a close association between type 2 diabetes and psychiatric diseases such as depression, anxiety disorders and alcohol dependence [29, 65].

The association between diabetes and mental health disorders could be exacerbated in a stressful environment and psychological distress could increase depressive symptoms and cause adverse diabetes outcomes. The emergence of a potentially fatal pandemic represents a new reason for uncertainty and anxiety in the group of diabetic patients [3, 48].

Conclusions

The assessment and follow-up of the circulating inflammatory biomarkers have a great importance in the management and also in the progression of diabetes mellitus.

Therefore, an attentive management is needed in type 2 diabetes which may include the measurement of inflammatory cytokines. This can improve the tracking of disease's evolution as well as medication effectiveness in order to delay the occurrence or progression of this condition. COVID-19 infection has a negative impact on the evolution of diabetes and its complications. There is a wide range of complications of diabetes including not only the macrovascular and microvascular conditions but also the psychological illnesses with a highly negative impact of the quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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