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Review

Oxidative stress biomarkers in type 2 diabetes mellitus for assessment of cardiovascular disease risk

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ABSTRACT

Aims: Type-2 Diabetes Mellitus (T2DM) is one of the most prevalent and progressive metabolic conditions affecting approximately 8.5% of the global population. Individuals with T2DM have a significantly increased risk of developing chronic conditions such as cardiovascular disease (CVD) and its associated complications, therefore, it is of great importance to establish strategies for combatting T2DM and its associated chronic conditions. Current literature has identified several biomarkers that are known to play a key role in the pathogenesis of CVD. Many of these biomarkers affecting CVD are influenced by an increase in oxidative stress as seen in T2DM. The purpose of this review is to analyse and correlate the oxidative stress-related biomarkers that have been identified in the literature to provide an updated summary of their significance in CVD risk factors.

Data synthesis: This review has analysed current research on T2DM, CVD, and oxidative stress. Four key cardiovascular risk factors: thrombosis, inflammation, vascular homeostasis and cellular proliferation were searched to identify potential biomarkers for this review. These biomarkers stem from seven major cellular pathways; NF-κB, Keap1-Nrf2, protein kinase-C, macrophage activation, arachidonic acid mobilisation, endothelial dysfunction and advanced glycation end products.

Conclusions: The pathways and biomarkers were analysed to show their role as contributing factors to CVD development and a summary is made regarding the assessment of cardiovascular risk in T2DM individuals.

Contents

1. Introduction

Obesity and a sedentary lifestyle as part of urbanisation along with ageing are considered as one of the primary causes for a

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constant rise in type-2 diabetes mellitus (T2DM) [1]. In 2014, it was estimated that the world prevalence of diabetes was 8.5% of the global population. It has been predicted that by 2030 the incidence of diabetes will rise significantly, with an estimated 69% increase in developing countries especially, making diabetes the 7th leading cause of mortality [2]. A vast range of chronic conditions are known to be associated with T2DM and cardiovascular diseases (CVD) being one of the primary causes of mortality within individuals [3].

Type-2 diabetes mellitus is characterised by chronically elevated blood glucose levels; this may be caused by increased insulin resistance and glucose intolerance. Chronic hyperglycaemia in T2DM can lead to increased oxidative stress and over time, it can generate a vicious cycle of reactive oxygen species (ROS) generation, thus, leading to alterations in vascular endothelium [4]. Elevated oxidative stress in T2DM individuals has been shown to be one of the major risk factors for an increased risk of CVD [5]. Increased free radical production has been shown to alter and induce several risk factors for CVD such as lipid peroxidation, endothelial dysfunction, inflammation and platelet activation [6]. Hence identifying the mechanisms and possible treatments to reduce the incidence of CVD has become a field of great significance. Chronic hyperglycaemia due to factors such as impaired glucose tolerance and insulin resistance can often lead to a range of chronic diseases in later life of individuals with T2DM [4].

As per a previous report, CVD can account for up to 65% of the mortality in individuals with T2DM. It is believed that the changes in an individual's thrombotic and inflammatory state through oxidative stress can be one of the causes for an increased mortality rates in T2DM [7]. These changes can individually or synergistically play a significant role in elevating the risk of intravascular pathologies like thrombosis and atherosclerosis [4]. Increased thrombogenicity, vascular cell proliferation, inflammation and reduced vascular homeostasis, may not only accelerate the progression of CVD but further contribute to the production of ROS in a positive feedback loop [8].

2. Oxidative stress and diabetes

The current understanding of T2DM associated oxidative stress and its influence on vascular disease revolve around four key aspects and they are: thrombogenicity, vascular homeostasis, inflammation and cellular proliferation, as shown in Fig. 1. Oxidative stress is an imbalance between the oxygen/nitrogen free radical production and the endogenous physiological antioxidant mechanisms [8]. Based on the literature, it is clear that the pathogenesis of CVD is multifactorial and therefore it is crucial to identify the specific ROS molecules and their associated pathways of production, in order to develop an effective and targeted therapy [9]. Glutathione, glutathione peroxidase (GPx), superoxide dismutase (SOD), and heme-oxygenase are some of the crucial antioxidant enzymes that negate the deleterious effects of excess free radicals [6]. In T2DM high blood glucose and free fatty acids (FFA) are responsible for an increase in ROS production due to metabolic stress resulting in changes within the electron transport chain (ETC) [10]. Literature shows that excessive mitochondrial ROS formation namely superoxide ($O2^{-}$) and hydrogen peroxide (H2O2), is primarily due to the abnormalities seen in the mitochondrial respiratory chain when present in hyperglycaemic environments [11]. It is believed that this takes place in complex I of the ETC, through the activation of the receptor for advanced glycation end-products (RAGE) and a reduction in oxidative phosphorylation enzymes [12]. Previous research has shown that polyol pathway flux exacerbates intercellular oxidative stress and ROS interaction within the cell due to an increase in intracellular glucose and the hyperglycaemic environment found in T2DM [13]. The changes from the polyol pathway flux include increased enzyme activity of aldose reductase resulting in excessive fructose, inactive alcohols and $NADP^{+}$. This changed metabolic environment often leads to a decrease in cellular NADPH and thus a reduction in NADPH dependent antioxidants like glutathione, thus possibly aggravating the intercellular oxidative stress [14]. The compromise of physiological antioxidant defences may be a cause of increased oxidative stress in T2DM individuals [15]. It is believed that hyperglycaemia, glucose toxicity and excessive production of FFA's are the three main sources of diabetes related $NADP^{+}$ development. Furthermore, previous studies have shown hyperglycaemia directly contributes to atherosclerotic tissue damage through changes in the gene expression of endothelial cells caused by the increased hexamine pathway activity [16]. The increased production of FFA's alters metabolic pathways (insulin receptor substrate-1/PI3-Kinase/akt), increasing platelet aggregation and the production of oxidative free radicals exacerbating oxidative stress, ROS production and increasing the risk of CVD [17].

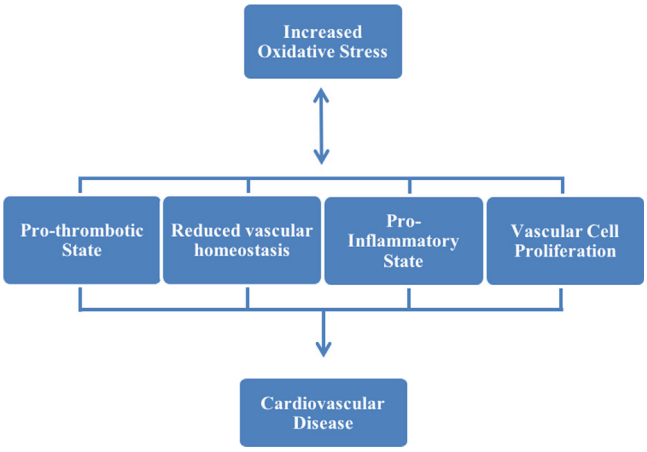

Fig. 1. Oxidative stress changing thrombotic state, vascular homeostasis, inflammation and cellular proliferation in T2DM.

3. Major pathways leading to cardiovascular disease

Many studies have identified that the altered metabolic state associated with T2DM is one of the major issues causing an increase in oxidative stress and the subsequent changes in vascular homeostasis [8]. Evidence from the literature has exemplified that antioxidants play a promising role in the field of preventative therapies [18]. Chronic hyperglycaemia and insulin resistance in T2DM has been associated with a specific change in platelet physiology leading to an increase in platelet activation and aggregation [13]. Increase in platelet activation can occur through multiple stimulating factors, where oxidative stress has been identified as one of the key contributors to positively influence these activation pathways [8]. Numerous studies have already shown the ability of free radicals ($O2^{-}$, H2O2, NADPH Oxidase, NOX) to increase cellular adhesion molecules such as P-selectin, PCAM, E-selectin, and VCAM-1 on platelet and endothelial cell surfaces. P-Selectin is a cellular adhesion molecule released from activated platelet and endothelial cells; it is known to play a key role in leukocyte recruitment and the formation of large thrombus [19,20]. Similarly E-Selectin, an endothelial-leukocyte adhesion molecule, is overexpressed under elevated oxidative stress and inflammatory states. Other thrombogenic factors associated with an increase in oxidative stress include arachidonic acid mobilisation, thromboxane A2 and prostaglandin (PG) production [21]. On an endothelial level, oxidative stress has been shown to directly increase vessel wall damage and disruption to the endothelium

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