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Commentary

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Commentary: The Effects of Inflammation, Aging, and Oxidative Stress on the Pathogenesis of Type II Diabetes

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Abstract

Type II Diabetes Mellitus (T2DM) is a high-risk metabolic condition associated with high mortality due to hyperglycemia. Many studies have focused on how inflammation, aging, or oxidative stress influences the pathogenesis of T2DM. The functional anomalies of the pancreatic beta cells attribute to insulin resistance which is the primary cause of T2DM manifestations and complications. This is evidenced in polymorphism in the TNF-α gene which inhibits insulin production, metabolism, and utilization during T2DM development. The dysregulation of insulin signaling involves multiple pathways. Various factors such as epigenetics, oxygen radicals, and glucolipotoxicity are implicated in the pathogenesis. Low-grade inflammation mediated by pro-inflammatory cytokines and chemokines such as interleukin-1 attack peripheral tissues and mediates the activation of critical pathways involved in T2DM pathogenesis via transcriptional factors. The core factor resulting in inflammation is hyperglycemia. The result is the release of inflammatory mediators which then affect neurons in the nervous system and alter microvascular and enzymatic pathways to elicit severe complications such as neuropathy. Oxidative stress and inflammation share an intertwined relationship in the pathogenesis of T2DM. High levels of reactive oxygen species increase the level of DNA damage markers and expose pancreatic beta-cell lines to dysregulation through reduced expression of the insulin gene. The link between the interaction of oxidative stress and inflation in the human body increases the level of interleukin-6 which triggers superoxide radicles and oxidative stressors increase which have been shown to affect free fatty acids metabolism inversely Finally, the aspect of cellular senescence in adipocytes and pancreatic beta cells explain why age is a critical factor in T2DM pathogenesis. Overall, the three factors discussed have a crucial role in T2DM disease states, progressions, and complications.

Keywords

T2DM, Inflammation, Oxidative Stress, Ageing, Pathogenesis, Pancreatic Beta Cells, Insulin Signalling, Insulin Resistance

Commentary

Introduction

The multifactorial, evolving, and complex nature of type II diabetes mellitus (T2DM) makes it a significant risk factor for mortality due to hyperglycemia [1,2]. The review [3] presents an in-depth discussion on how inflammation, aging, and oxidative stress exacerbate the pathophysiology of T2DM and its direct and indirect complications on the vascular tree. The commentary offers a more profound insight into how the three factors interact with T2DM and complement the knowledge presented in the review.

The Pathogenesis of T2DM

The review article presents pancreatic beta cells dysfunction as the mainstay of T2DM pathophysiology as a result of peripheral resistance and insensitivity to insulin and dysregulation of hepatic glucose production. Various characteristics of T2DM pathogenesis can support the rate at which the associated complications occur. As [4–6] discussed the activation of multiple pathways mediated by transcriptional factors with the augmentation of varying levels of pro-inflammatory cytokines results in the manifestation of the primary characteristic in T2DM: insulin resistance. Also, [4,7] outlines that epigenetic factors, reactive oxygen species (ROS) generation, and glucolipotoxicity are the multi-stimuli factors that play a critical role in T2DM pathogenesis. All the above would explain why [3] discussed the events that result in defects in the homeostatic processes of glucose metabolism.

Inflammation and T2DM

Many pro-inflammatory cytokines play a critical role in the development and progression of T2DM and its complications through low-grade inflammation (recently defined as “metaflammation”) [8,9]. The tumour necrosis factor-alpha (TNF- α) stands out as the most crucial pro-inflammatory mediator with critical involvement in insulin resistance and T2DM pathogenesis [4]. Considering that the peripheral tissues and adipocytes are the primary producers of TNF- α (and other cytokines such as interleukin-1 and 6) [10–12] would explain why [3] discuss obesity when linking inflammation to T2DM. Also, the pro-inflammatory mediator has a significant role in the induction of tissue-specific inflammation because it incorporates the ROS generated as well as activate pathways mediated by transcriptional factors involved in T2DM pathogenesis [13,14]. The review highlighted that inflammatory responses could either augment or establish a causal relationship to T2DM which implies that high levels of inflammatory mediators can induce insulin resistance in peripheral and adipose tissues by impairing pathways of insulin signaling.

High glucose concentration results in the release of inflammatory mediators. The hyperglycemia-induced production of pro-inflammatory cytokines affects neurons in the autonomic, central, and peripheral nervous systems. These effects result in enzymatic, metabolic, and microvascular alterations, which would explain why T2DM patients present with diabetic neuropathy as the primary complication of the disease [2,9,15,16]. Overall, the pancreatic cells, adipose tissues, and muscle cells are crucial sites of pro-inflammatory cytokines production in the presence of obesity. The cells act as paracrine and autocrine pathways that enhance resistance to insulin by disrupting its signaling in peripheral tissues.

Increased level of cytokines has been shown to pose a risk in T2DM development and progression. Research has found that TNF- α -863C>A, IL-6-174C>G is associated with the cause of diabetes mellitus by approximate two-fold [18]. This due to the ability of the genes to promote polymorphism in the TNF-α gene, which is a predictor in the conversion of IGT to T2DM as well as gene-gene interaction in C-174C genotype of the IL-6 gene. In a different case, the IL6 in adipose and hepatic tissues presents pro-inflammatory adipokine thus cause insulin resistance. Through increased insulin resistance, the adipokine impairs its receptors and IRSI phosphorylation, thus increasing the prevalence of T2DM development. Increased resistance to insulin utilization during glucose metabolism results in the continuous accumulation of fatty acids in the body, thus increasing the prevalence of obesity (**Table-1**).

Oxidative Stress and T2DM

Inflammation and oxidative stress have an

Table-1: Some pro-inflammatory cytokines single nucleotide polymorphism (SNPs) that are closely related to T2DM pathogenesis [17]

Condition	SNP
T2DM	TNF- α -863C>A, IL-6-174C>G
Insulin resistance	TNF- α -308G>A, IL-5-174C>G
Obesity	TNF- α -308G>A, IL6R 394T>G

inextricable relationship in the physiological and disease states and this would explain why the reviewers provide a more comprehensive discussion on ROS and inflammation as well as ROS and oxidative stress. Both aspects have a complex interaction in which there is mutual amplification, which can be termed as a "vicious cycle" or a positive feedback mechanism [4,19,20]. Although [3] fails to provide an explicit link between oxidative stress and T2DM, [19,21,22] discuss that a hyperglycaemic state can result in elevation of DNA damage markers, and products of protein and lipid peroxidation, all of which lower enzymatic activity of antioxidants. Also, exposure of pancreatic beta-cell lines to oxidative stress inhibits insulin gene expression through reduced mRNA expression, which yields chronic insulin resistance, induced by chronic hyperglycemia [16,23,24]. One critical point to consider when establishing a link between oxidative stress and T2DM pathogenesis is that prolonged exposure of cells to hyperglycaemic results in non-enzymatic protein glycation which yields products that culminate ROS production [21,25]. As such, chronic hyperglycemia induces ROS production which damages proteins, lipids, and DNA, promoting macro-and microvascular complications of T2DM [20,26-28]. As [3] attempt to link oxidative stress and ROS, it is apparent that the former reduces the production of glutathione (GSH) which consequently exacerbate the latter.

The pathophysiology of T2DM indicates that oxidative stress plays a critical role in insulin resistance pathogenesis. This is characterized by impaired insulin secretion and inhibited glucose utilization which results in impaired hepatic glucose metabolism alongside pro-inflammation cytokines inflammation activation. Chronic progression of T2DM is, therefore believed to be linked to the interaction of oxidative stress and inflation in the human body. The increase in the level of interleukin-6 directly increases superoxide radicles and oxidative stressors which have been shown to affect free fatty acids metabolism

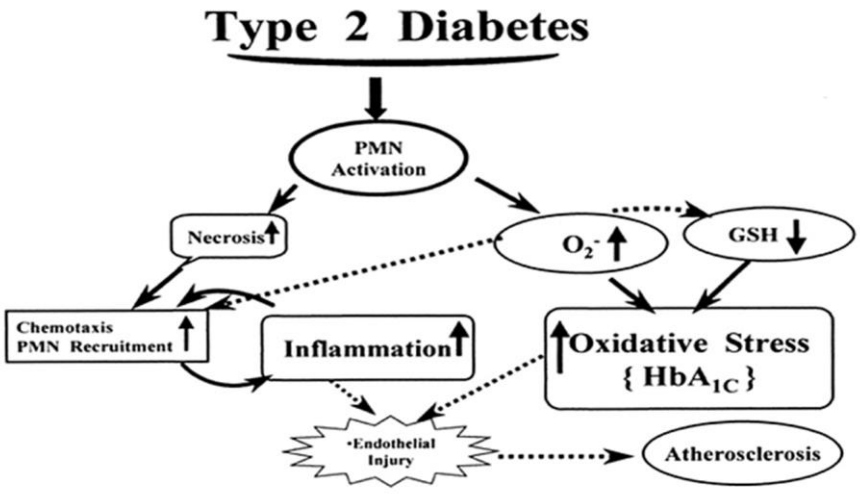

Fig-1: Relationship between T2DM, Inflammation, and Oxidative Stress [19]

inversely. Oxidative stress results in mitochondria uncoupling which triggers an oxidative reaction, thus eliciting the inflammatory process [19] (**Fig-1**).

Aging and T2DM

There is a close association between aging and insulin resistance as a result of reduced beta-cell proliferation and increased sensitivity to apoptosis [3,28,29] which implies that older adult populations are more susceptible to insulin insensitivity. The apparent reason for the above is because cellular senescence emerges as an important mechanism in the progression of T2DM among geriatric patients and has further implications for conditions such as cardiovascular and kidney disease [30]. Obesity is a crucial determinant to cellular senescence, particularly the pancreatic beta cells and adipocytes, and the consequent effects to T2DM disease processes [14,31]. Here, aging predisposes a person to adipose tissue dysfunction and results in systemic effects such as inflammation, ectopic lipid deposition, and peripheral insulin resistance, which play a critical role in the pathogenesis of T2DM [32]. Also, beta-cell failure due to aging has been linked to T2DM pathophysiology due to monogenic dysfunction of mitochondria where apoptotic pathways converge [33]. The reviewers presented a general overview of the phenomena discussed, linked it the explanation to oxidative stress using sarcopenia as the primary concept. All the above demonstrate that age is an inevitable risk factor to T2DM.

Conclusion

The reviewers provided a comprehensive overview of how aging, inflammation, and oxidative stress affect the pathogenesis of T2DM. The utilization of insulin in the control of the human body glycaemic index is controlled by TNF- α genes which activate pro-inflammation cytokines inflammation, superoxide radicles and oxidative stressors increase. The prevailing view in the discussion presented in this commentary is that all three factors have a critical role in inhibiting insulin production pathways and the resulting resistance to insulin. Moreover, there is an intertwined relationship between the three factors in exacerbating T2DM progression among individuals and can guide the development of targeted therapies.

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