Review Article
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What are we missing in treating diabetes? inflammatory nature of diabetes as a new medical hypothesis

Abstract

In this study, the researcher reviewed the literature regarding the inflammatory nature underlying initiation and progression of diabetes. Although several studies have addressed the existence of inflammatory nature of diabetes either type 1 diabetes or type 2 diabetes, clinical implications of such therapeutic strategies are not involved in guideline of diabetic therapeutic strategies. Due to the importance of diabetes as a health problem that impacts the world, this review is an attempt to raise crucial questions regarding considering in clinical practice the involvement of anti-inflammatory medications seriously and to conduct more clinical and basic studies to confirm the same issues.

Keywords: diabetes, inflammation, clinical investigation, anti-inflammatory drugs

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Introduction

Despite the availability of multiple medications that successfully lower blood glucose levels, diabetes mellitus (type 1 and type 2) and its associated consequences continue to pose a major load on world medical resources. The avoidance of different complications, which remain the leading cause of diabetes-related mortality, is a key challenge in diabetes care. Furthermore, monotherapy's low long-term durability and the unfavorable side effects of currently available anti-diabetic medications highlight the urgent need for new therapeutic options.[1]

Diabetes mellitus (DM) is becoming one of the most significant burdens on world health and economies, with a prevalence of 8.8% in adults (20–79 years).[2] A 50 per cent increase is expected globally. Diabetes mellitus (all kinds) is ranked ninth among the leading causes of morbidity and mortality with a significant impact on life expectancy.[4] Although the exact classification of diabetes is still debated due to the complicated nature of its pathophysiology, three basic subtypes are universally recognized: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM).[3] The present epidemic of T2DM has demonstrated a strong global escalation, accounting for nearly 90% of diabetes cases,[5] along with the increasing influence of genetic abnormalities, chemical toxicity, sedentary lifestyle, and ageing. Furthermore, a slew of microvascular and macrovascular consequences adds to the disease's mortality and global economic toll. Although a variety of factors have a role in the development of diabetes and its consequences, innate immunity has been identified as a key driver in the disease's pathogenesis.[6]

Autoimmunity is important in eliciting an inflammatory response in pancreatic islet cells, which leads to -cell failure in T1DM. Similarly, during the onset of T2DM and its progression to micro/macro-vascular problems, systemic low-grade inflammation plays a role as a shared mediator.[7] Inflammation-targeted treatments show significant advantages in T2DM hyperglycemia, -cell dysfunction, and insulin resistance, according to an increasing body of evidence from clinical investigations.[8,9]

Over the last ten years, the prevalence of T1DM in children and adolescents has risen dramatically in both developing and industrialized nations, accounting for 5% of all diabetic patients.[10] The major mediator in the generation of decreased -cell survival and faulty insulin secretion is an autoimmune response resulting from the interaction of a wide number of genetic and environmental variables.[11] T1DM has been demonstrated to significantly increase the infiltration of pancreatic islets by effector immune cells such as CD4+ and CD8+ T cells, macrophages, dendritic cells, and B cells.[12] Cytotoxic T cells, in particular, are thought to be the primary players, primarily beginning and increasing the progression of T1DM. T1DM patients' monocytes and macrophages produce more pro-inflammatory cytokines, which is consistent with results from rodent models that demonstrate a significant rise in circulation levels of proinflammatory cytokines (IL-1, IL-6, and TNF-).[13] Cytotoxic effects on pancreatic-cells are mediated by inflammatory cytokines. Pancreatic cells, unlike cells, have many receptors specific for cytokines, which contributes to increased vulnerability to cytokine-induced cytotoxicity and cell death.[14]

Metabolic inflammation in the development of T2DM

T2DM is the most common type of diabetes, accounting for approximately 90 per cent of all.[15] It has been identified as the world's third most common risk factor for disability-adjusted life years.[16] Furthermore, T2DM-related medical cost in low- and middle-income countries is expected to increase thrice compared to the general population.[17]

T2DM has a complex etiology. Insulin resistance in the peripheral tissues causes increased glucose synthesis in the liver and decreased glucose consumption in skeletal muscle and adipose tissue. Hyperglycemia is caused by this, as well as significant -cell dysfunction.[18] Increased levels of glucose and free fatty acids may stimulate the inflammatory response in pancreatic islet cells, leading to increased production of pro-inflammatory cytokines. IL-1 produced by macrophages can enhance insulin production, which compensates for insulin resistance, and enhance -cell proliferation at first. IL-1, on the other hand, will cause the production of a wide

range of cytokines and chemokines, including IL-6, IL-8, and IL-33, if it becomes prolonged or excessive. These attract macrophages and immune cells to the islet, further triggering an IL-1 auto-stimulation loop.[19] Furthermore, these macrophages can release a high amount of IL-1 and cytotoxic substances, which, when combined with molecular pathways, results in a significant reduction in -cell mass and reduced function.[20,21]

The discovery of a fundamental relationship between metabolic diseases and inflammation in recent decades has given rise to the idea of "metaflammation." Metaflammation.[7,22,23] Metaflammation is a type of low-grade systemic and chronic inflammation caused by an overabundance of nutrients and energy. Diabetes is increasingly becoming recognized as an inflammatory illness.[23] Long thought to be an inflammatory illness, type 1 diabetes (T1DM) is characterized by autoimmune-mediated death of pancreatic cells and inadequate insulin production.[23]

Type 2 diabetes (T2DM) was not related to inflammatory response until the early 1990s.[8] T2DM is characterized by insulin resistance and abnormal insulin production in peripheral organs such as adipose tissue, liver, and muscle, as well as persistent low-grade inflammation. There has been a growing body of research associating obesity and insulin resistance to inflammation in recent decades.[23] T2DM is currently being classified as an immunological illness because of the important role inflammation plays in its etiology.[24–26] Inflammation has been linked to a variety of metabolic diseases, including diabetes.[7]

T1D is an autoimmune disease characterized by the selective and specific death of insulin-producing pancreatic beta cells without additional Langerhans cells showing pathological changes.[27] T1D, on the other hand, exhibits great variation in terms of onset age, severity of autoimmune response, and therapeutic success, and it has been shown that both humoral and cellular immunity are involved in the pathogenesis of T1D.[28,29] Even though the first event is still unknown, the original theories about predisposition support that environmental trigger variables in early life, such as infections, nutrition, and substances that might activate self-targeting immune cascades, remain applicable.[30]

Understanding the pathogenesis of T1D has progressed in lockstep with developments in immunology. The most widely accepted explanation is that beta cell pancreatic islets in T1D patients become inflamed, a condition known as insulitis, as the disease progresses. Failure of both central and peripheral immunological tolerance mechanisms contributes to the development of autoreactive T cells in the periphery of non-obese mice with diabetes, according to Anderson et al.[31] Evidence from animal models has revealed that both CD4+ and CD8+ T cells (effector T-cells/Teff) are involved in the development of T1D because they target multiple beta cell autoantigens and associated peptide epitopes.[32] T-cell subtypes have also been shown to be capable of producing damaging peri-islet inflammatory infiltration and overt diabetes in T1D mice via adoptive T-cell transfer.[33] Human research employing pancreas samples acquired postmortem from people diagnosed with recent-onset T1D confirmed this.[34]

According to Wilcox et al.,[28] the immunological B cell (CD20+) profile varies with illness progression, as early investigations indicated they correspond closely with CD8+ T cell migration, following two different patterns, either high or low infiltration in islets.[35] Because of their ability to secrete cytokines like Interleukin 1 beta (IL-1beta) and tumour necrosis factor alpha (TNF-alpha) and create reactive oxygen species, macrophages are important mediators of islet inflammation (ROS).[36]

Additional research has found that lymphocytes and neutrophils are numerous in the surrounding pancreatic exocrine tissue in T1D, suggesting that these cells may play a role in disease progression.[37,38] Dendritic cells, natural killer (NK) cells, and NKT cells have been detected in the islet infiltration in certain studies and may play a role in the overall process, although it appears that the interplay between different cell types influences diabetes progression overall.[39,40]

Several pathophysiological studies have added to our knowledge of insulin resistance and secretion throughout the onset and progression of disease.[41,42] T2D patients have an initial state of insulin resistance that is compensated by insulin hypersecretion in the beta cells. However, as the disease progresses, this pancreatic functional reserve becomes unable to deal with the requisite insulin production, and beta cells are no longer able to secrete enough insulin by the time diabetes is diagnosed.[43]

Even though the relative contribution of beta cell dysfunction and insulin resistance varies in people with T2D, it is generally accepted that abnormal insulin sensitivity precedes the clinical diagnosis of diabetes by up to 15 years.[44] As a result, more recent research has focused on the pathways leading to beta cell dysfunction in addition to mechanistic studies investigating mechanisms forming the basis of insulin resistance.[45]

We have conducted several studies that showed type 1 diabetes is associated with some inflammatory biomarkers in the white matter of diabetic rats such as inducible nitric oxide synthase.[46] We have also found that the use of anti-inflammatory medications as aspirin is significantly associated with less occurrence of diabetic neuropathy.[47] The use of aspirin was also effective in reducing lipid profiles in diabetic type 2 patients.[48] We have also reported that the use of 5 mg tadalafil helps in reversing prediabetes.[49–52] In type 1 diabetic model using rats, we localized the existence of human papilloma virus (HPV) and Cytomegalovirus (CMV) in the adipose tissue of uterus of female rats.

Conclusion

In clinical practice, the inflammatory nature of diabetes is missing which may increases the progression of diabetes.

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Conflicts of interest

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