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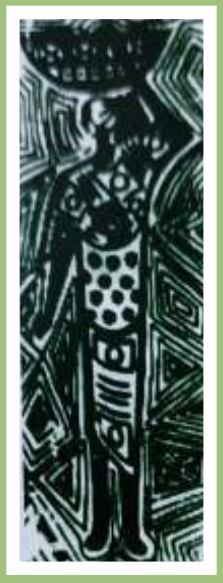

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REVIEW

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Putative Mechanisms of Immune Dysfunction in the Pathogenesis of Type 1 Diabetes Mellitus: A Scoping Review

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Abstract
Type 1 Diabetes Mellitus is a complex disorder characterized by autoimmune destruction of insulin-producing pancreatic beta cells. Immune dysfunctional mechanisms underlying its pathogenesis remain elusive. Immuno-toxic lifestyle habits (poor diet, inadequate sleep and lack of exercise) contribute to the pathogenesis of Immune-Mediated Inflammatory Diseases (IMIDs). There are disease models of T-cell dysfunction that describe the systemic inflammatory disease processes that underlie IMIDs. These disease models do not highlight the roles of immunotoxins in the disease pathogenesis. Online searches were conducted on databases such as Google Scholar, PubMed, Biomed Central, and SciELO. Articles were reviewed using keywords such as Immune optimization/dysfunction, T cell activation/dysfunction, cytokines, Type 1 DM, cellular adhesion molecules and inflammatory pathogenesis. This review proposed a putative immune dysfunctional disease model for Type 1 DM, which multi-omic studies may validate. Insights from the putative disease model can guide effective therapeutic interventions.

Keywords: Type 1 Diabetes mellitus, Immune dysfunction, Inflammatory cytokines, Multiomics.

Introduction

Type 1 Diabetes Mellitus (Type 1 DM) is the manifestation of an autoimmune disease that destroys insulin-producing pancreatic beta cells. [1] About 5% to 10% of people with diabetes mellitus have the Type 1 form. In 2021, about 8.4 million individuals were living with Type 1 DM; by 2024, the number is projected to increase to 17.4 million.[2] Immuno-toxic lifestyle habits like poor diet, lack of sleep and exercise are implicated in the aetiopathogenesis of Immune-Mediated Inflammatory Diseases (IMIDs), which are enhanced by proinflammatory and pro-proliferative immune dysfunctional processes. [3, 4]

In terms of health and disease, immune optimization and dysfunction may enhance or undermine the immune system. Immune-optimized/dysfunctional states determine, to some extent, the phenotypic expressions of genetically predisposing IMIDs. [4] Type 1 DM is enhanced by immune dysfunction and falls within the spectrum of IMIDs. Environmental toxicants may perturb an optimal/dysfunctional immune system. Since IMIDs and Type 1 DM are enhanced by immune dysfunction, they share similar immune dysfunctional pathogenesis. Inflammatory cytokines play pivotal roles in the disease processes, with their immunopathogenesis often mirroring each other. The biology and correlation of inflammatory cytokines in relation to immune

dysfunction and disease genesis are well established. [4, 5] Although insights into inflammatory dysfunctional immune processes concerning IMIDs and Type 1 DM exist, the actual inflammatory dysfunctional disease mechanisms remain unknown.

Environmental factors like diet contribute to the initiation of autoimmune processes destroying beta cells of the pancreas. [6] Epigenetic activation of T cells by dietary factors can alter their permeability and induce signal transductions. [7] Diet-mediated dysfunction of T cells in IMIDs is consolidated by inflammatory cytokines generated from other promoters of immune dysfunction like inadequate sleep and exercise. [4] Dysfunctional T cells play a central role in the immunopathogenesis of IMIDs. Trans-endothelial migration of dysfunctional T cells in disease pathogenesis is mediated by Cellular Adhesion Molecules (CAMs), regulated by proinflammatory cytokines in immunological processes. [3]

The rising incidence of Type 1 DM is a public health concern. The mortality rate underscores the limitations of current treatment approaches. Discussing our putative T cell immune dysfunction model of IMIDs using Type 1 DM as an example could highlight its pathogenesis concerning immunotoxic lifestyle habits. Insights from the putative disease model can guide effective therapeutic interventions.

Methods

Online searches were conducted on databases such as Google Scholar, PubMed, Biomed Central, and SciELO. Articles were reviewed using keywords such as Type 1 diabetes mellitus, Disease mechanisms, cellular adhesion molecules, Immune optimization/dysfunction, T lymphocyte activation/dysfunction, and inflammatory cytokines.

Results

Of the 237 articles identified from databases, 31 were duplicates, and 11 which did not highlight the role of immuno-toxins in the pathogenesis of IMIDs were excluded. Of the 195 articles assessed for legibility, 25 articles described immunopathogenesis of T cell dysfunction secondary to immunotoxins, discussed preventive and adjunctive therapeutic roles of immune optimization interventions on IMIDs and were included in the review [Figure 1].

Key Findings

1) Immuno-toxic lifestyle habits serve as initiators and consolidators of immune dysfunctional mechanisms underlying IMIDs and Type 1 DM.
2) Similar immune dysfunctional mechanisms underlie a spectrum of IMIDs and Type 1 DM.
3) Immune Optimization Interventions could be preventive and therapeutic adjuncts for managing IMIDs and Type 1 DM.

Immunopathogenesis of T Cells in Immune-Mediated Inflammatory Diseases

The immune system's components work concertedly to carry out rapid, specific and protective responses against harmful pathogens and their biological products. The mechanisms of immunity function across a broad spectrum of clinical conditions. [8] There are two broad divisions of the immune system: innate and adaptive. The protective effect of the innate immune system is mainly mediated through physical barriers like epithelial cell layers. The adaptive immune system's protective effect is mediated through complex interactions between cells of the immune system like B cells, T cells and subsets of leukocytes with cytokines produced by these cells. They also have receptors for different substances that can act as antigens. [9, 10]

Inflammation is the process by which leukocytes and plasma proteins are drawn from the blood to specific body areas, where they become activated to elicit adequate immune

responses. Many of these reactions involve cytokines. [11] Cytokines are hormone-like substances which act in a paracrine fashion to regulate immune responses.

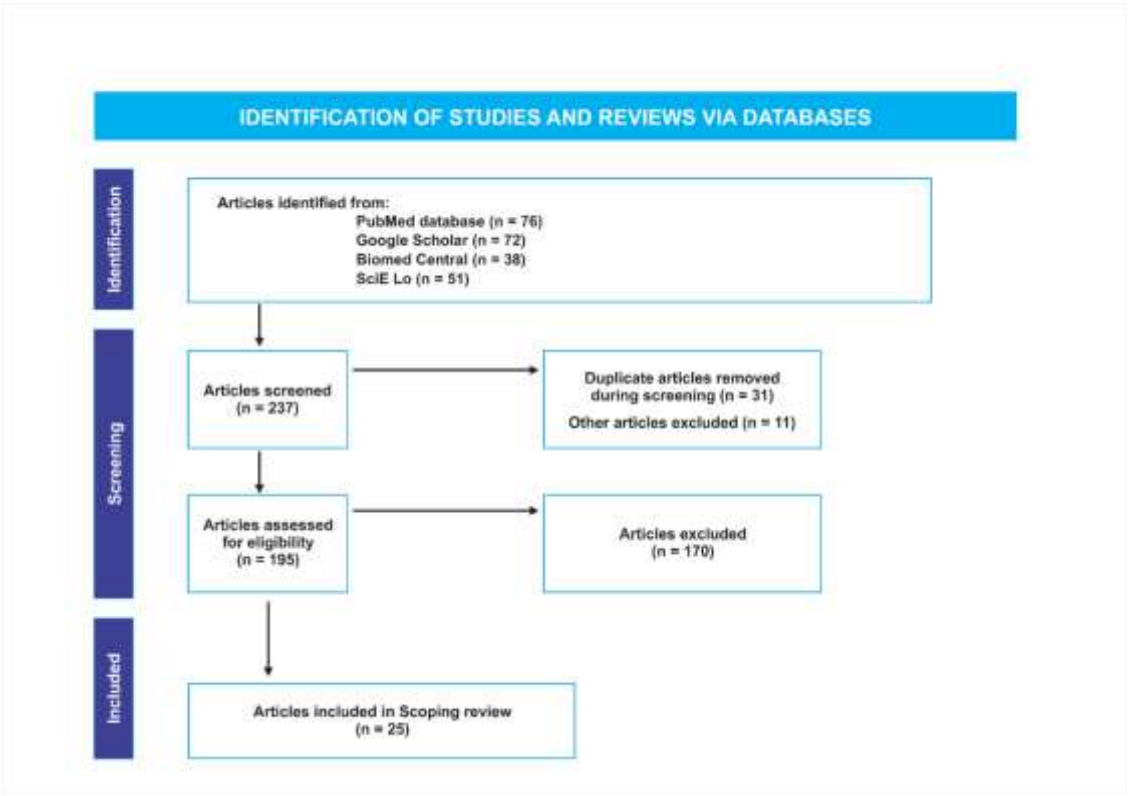

Figure 1: PRISMA flow diagram for the Mini review detailing the database searches and the number of articles screened.

They are either pro-inflammatory (IL-6, IL-7, TNF alpha) or anti-inflammatory (IL-13, IL-11, TGF-Beta).[4] T cells are crucial for immune functions. They maintain a homeostatic milieu and prevent disease. Their development occurs in a stepwise process in the thymus, which mainly generates CD4+ and CD8+ T cell subsets. [12] Depending on the cytokine milieu present in the disease microenvironment and specific transcription factors, CD4+ T cells can differentiate into several subsets of effector T cells such as T helper 1 (Th1) cells, T helper 2 (Th2) cells, T regulatory cells (Treg) or cytotoxic T cells. [7] Through a maze of complex interactions, subsets of T cells mediate anti-inflammatory and proinflammatory immune-mediated health and disease conditions. T cells have been shown to play a crucial role in the pathogenesis of hypertension, an IMID. Mice lacking T cells are resistant to blood pressure elevation, implying their distinct contributory roles in the pathogenesis of hypertension. [9, 13, 14] Products and effects of immune response may be controlled by genetic predisposition, which orchestrates and determines the homing of activated dysfunctional T cells to different body sites in disease states. They may also mediate different disease phenotypes in other sites of the body as well as worsening of clinical symptoms as described by Okafor *et al.* [7]

Common genetic and environmental factors underlie and enhance the pathogenesis of IMIDs. Furthermore, they have epidemiological associations and share similar immune inflammatory dysfunctional pathways. [13] Interactions of genes and the environment may lead to epigenetic changes. Epigenetic activation and subsequent dysfunction of T cells can be provoked by dietary factors, which

can alter their permeability and signal transduction processes.

Immune Dysfunction in Type 1 Diabetes Mellitus

Different immune system cellular components are involved in the immunopathogenesis of IMIDs and their diseases, like Type 1 DM. Moreover, the literature regarding the abovementioned immunopathogenesis has outpaced the known immune dysfunctional mechanisms underlying type 1 DM. In keeping with the objective of this review and for brevity, this review focused on T-cell immune dysfunction in Type 1 DM.

Specific subtypes of T-cells (Tregs) have their primary function geared towards the suppression or regulation of immune response. Defects in Tregs have been shown to play a role in autoimmune disorders like Type 1 DM. [15, 16] Defects in $FOXP3^+$ Tregs can elicit Type 1 DM in most individuals, thus highlighting its role in maintaining islet-specific tolerance. [17] T-cell receptor (TCR) signalling influences the development of self-reactive T-cells, which drive the progression of Type 1 DM. Furthermore, TCR signalling affects epigenetic and transcriptional regulation. Aberrant epigenetic changes in T-cells have been noted in T-cells in numerous autoimmune diseases. [18] Auto-reactive T-cells are the principal drivers of beta-cell destruction. Once T-cells enter the islets of Langerhans, the environment becomes increasingly proinflammatory. [19]

Putative Immunopathogenesis of T-Cell Dysfunction in Type 1 Diabetes.

Activated dysfunctional T cells (DTCs) are conceived to mediate distinct disease phenotypes depending on genetic predispositions, migrating to diverse places in the body during an immunological dysfunctional state as described by Okafor *et al.* [7] They move and adhere with the help of Cellular Adhesion Molecules (CAMs) through chemotaxis driven by inflammatory cytokines generated by DTCs, participating in cross-talks with the pancreas microenvironment in those susceptible to Type 1 DM, as shown in Figure 2. When dangerous food substances trigger diet-mediated epigenetic activation of T cells, their membranes may become unusually permeable, allowing signal transduction food molecules to enter and cause malfunction. [7] Furthermore, diet-mediated epigenetic post-translational modification of proteins, which are enzyme substrates for cytokine production by DTCs, may result in aberrant production of inflammatory cytokines. Enzymes involved in processing inflammatory cytokines are potential targets for novel drug designs. [20] Cross-talks between inflammatory cytokines produced by DTCs and the extracellular matrix of the disease site may exacerbate clinical symptoms, as observed in ovarian hyperstimulation syndrome. [21]

Aided by CAMs, DTCs migrate and adhere to the islet cells of Langerhans in the pancreas in Type I DM. Cross-talks between DTCs, inflammatory cytokines, and the organ microenvironment leads to chronic fibrotic changes, resulting in decreased insulin production. In an immune-optimized state, the integrity of T cell membranes is maintained in homeostatic states. Disruption and permeation of their membranes by harmful food substances, leading to the influx of molecules that prematurely activate them and prompt migration to disease-predisposing sites, are consequently mitigated. Additionally, diet-mediated T cell activation and dysfunction may be exacerbated by cross-talks between inflammatory cytokines generated from other immune dysfunctional states caused by inadequate sleep and lack of exercise. In other words, diet-mediated immune dysfunction initiates the activation and dysfunction of T cells, while other immune dysfunctional states promoted by inadequate sleep and lack of exercise consolidate this dysfunction. Poor diet and inadequate sleep/lack of exercise may be considered initiators and consolidators of immune dysfunction underlying Type 1 DM, respectively.

The suggested putative T cell dysfunction disease mediating model for Type 1 DM may be postulated as an IMID/autoimmune condition whereby genetic predisposition determines, to some extent, the disease phenotype. The discussed putative disease model may apply to the pathogenesis of Type 2 DM, other IMIDs and autoimmune disease conditions. It is important to note that the phenotypic expression of IMIDs based on genetic predispositions may vary across its spectrum.

Immune optimization interventions with immune optimizers such as a good diet, adequate sleep, and moderate-intensity exercise should be alluring adjunctive therapeutic strategies to prevent and mitigate immune dysfunction underlying IMIDs. Although immune optimization interventions are alluring disease preventive strategies, their efficacy as therapeutic adjuncts and immunoprophylaxis may vary. Therefore, IMIDs with strong genetic predisposition may be less amenable to immune optimization interventions as adjunctive therapeutic interventions. Unlike Type 2 DM, which has strong genetic associations, Type 1 DM may be more amenable to immunoprophylaxis and adjunctive, therapeutic immune optimization interventions.

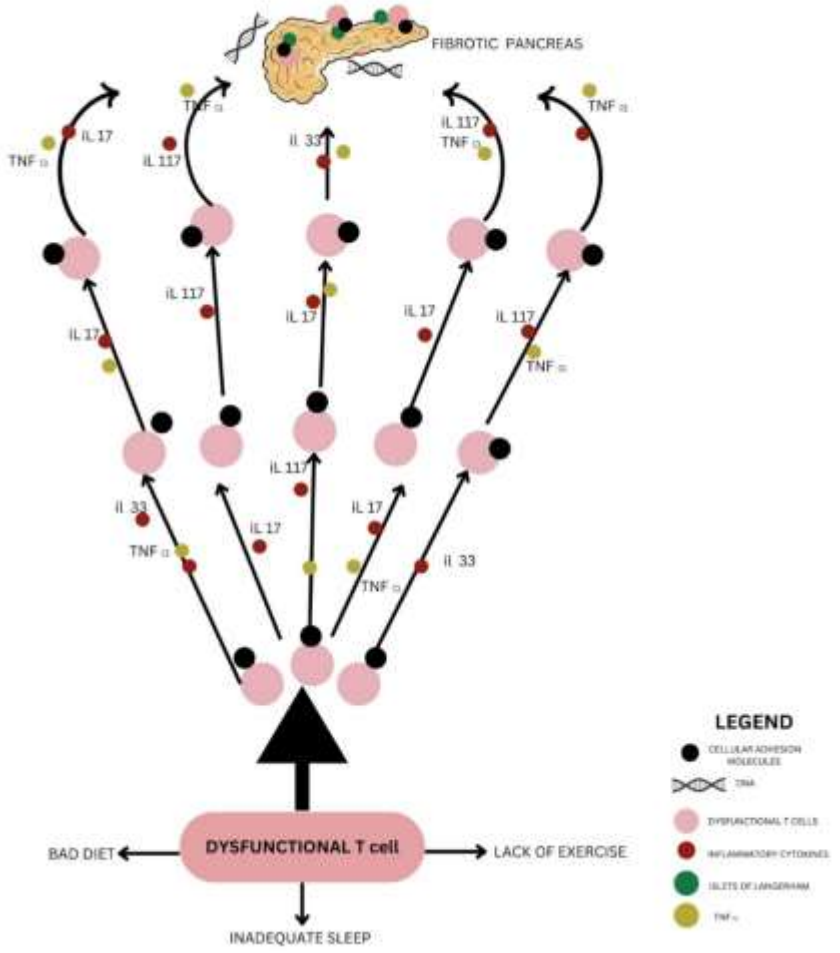

Figure 2: Putative Immuno-toxiepigenetic disease model of Type 1 Diabetes Mellitus

Roles of Multiomic Studies for Validation of Putative Immunotoxiepigenetic Model of Type1 DM

Immune optimization interventional Multiomic (genomic, transcriptomic, proteomic, metabolomic) studies can be used to investigate Type 1 DM disease mechanisms and validate our putative disease model. Gene expression studies may support and partly validate the putative theory of non-expression of disease phenotypes in an immune-optimized state despite Type 1 DM genetic predispositions. Studies on the proliferation and migration of DTCs may validate our theory of migration of DTCs to islets of Langerhans in Type 1 DM in immune dysfunctional states. An array of gene transcript signatures relative to adverse environmental exposures through epigenetic mechanisms may be highlighted by correlative transcriptomic and DTC studies. Differentially Expressed Genes (DEG) like SPINK9, TRDN, PVRL4, MYO3A, PDLIM1, KIAA1614 and GRP have been identified in Type 1 DM using whole transcriptomics. [22]

Comprehensive and correlative analysis of the proteasome for post-translational modifications of substrate enzymes for cytokine production by DTCs may validate and support the putative theory of inflammatory cytokine production by DTCs. The protein glutathione peroxidase is highly expressed and associated with fasting C-peptide/glucose, especially after the first year of Type 1 DM diagnosis. [23]

Metabolomic studies evaluating the gut microbiome and other biological specimens may highlight metabolites of environmental toxicants suspected to drive adverse gene expressions. Research has shown that dysbiosis of the gut microbiota triggers a spectrum of IMIDs. [24] Furthermore, biological specimens may highlight metabolites associated with T cell dysfunction and further validate the theory of its dysfunction by environmental toxicants through epigenetic mechanisms. Metabolomics analysis of serum and urine in Type 1 DM patients shows increased metabolites in the tryptophan metabolism pathway. The metabolites include 5-hydroxy-L-tryptophan, 5-methoxyindoleacetate and 4AD [4-(2-aminophenyl)-2, 4-dioxobutanoate)]. [25]

Study Limitation: This mini-review did not discuss the diagnostic and monitoring roles of multi-omic studies for Type 1 DM.

Conclusion

This scoping review has discussed a putative Immunotoxiepigenetic disease model of Type 1 DM and the role of multi-omic studies for the validation of the disease model. Insights from this disease model should guide therapeutic interventions for IMIDS and its disease spectrum, like Type 1 DM. Furthermore, it could pave the way for an emerging field in therapeutics: "immunotoxiepigenetic therapeutics", which takes into account immune dysfunctions underlying IMIDs and the institution of appropriate adjunctive therapeutic immune optimization interventions. Rational use of drugs entails drug prescriptions and proscriptions commensurate with patients' clinical and laboratory parameters. Immunotoxiepigenetic therapeutics is envisaged to prescribe/proscribe therapeutic interventions in line with the rational use of drugs, clinical/laboratory needs of patients and waxing/waning phenotypic expressions of IMIDs like Type 1 DM.

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