Review Article

Preventive and Therapeutic Adjunctive Roles of Immune Optimization on Inflammatory and Infectious Diseases: A Mini Review

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Abstract

Inflammatory and infectious diseases encompass a wide array of pathologic processes underscored by inflammatory immune dysfunction and infections. They are commonly caused by immuno-toxic lifestyle habits (poor diet, inadequate sleep, lack of exercise) and infectious agents. Management of the disease spectrum is challenging. Immune dysfunction enhances their pathogenesis and clinical symptoms. Hence, immune optimization interventions are useful for their prevention and management. T-cell dysfunction disease mediating models describing inflammatory and infective disease processes underlying inflammatory and infectious diseases exist. However, they do not highlight inflammatory and infective dysfunctional processes underlying the diseases concerning toxin-mediated epigenetic T-cell dysfunction. 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 lymphocyte activation/dysfunction, cytokines, inflammatory/infectious pathogenesis, therapeutic adjunct, and disease prevention. There is a putative T cell toxin-mediated dysfunction disease model for Immune-Mediated Inflammatory Diseases (IMIDs), which may apply to inflammatory and infectious diseases. The putative disease model may highlight the actual inflammatory/infective immune dysfunctional processes underlying T cell disease mediation in inflammatory and infectious diseases. We proposed putative inflammatory and infectious disease models that highlight inflammatory and infectious dysfunctional processes underlying T cell dysfunction disease mediation which may be validated by multi-omic studies. Validation of the putative disease models using inflammatory and infective heart diseases as classic examples should pave the way for a better understanding of the pathogenesis of inflammatory and infectious diseases. Insights from these putative disease models can guide effective interventions.

Keywords: Disease prevention, infectious/inflammatory diseases, therapeutic adjunct

Introduction

The cardiovascular disease spectrum contains inflammatory and infective heart diseases (IIHDs), which manifest as pericarditis, myocarditis, and endocarditis. Inflammatory heart diseases are autoimmune or auto-inflammatory and have similar causative non-infective factors like immuno-toxic lifestyle habits, air pollutants, etc. Inflammatory immune dysfunction underlines the pathogenesis of inflammatory heart diseases.[1] Viruses are the main infective causative agents of pericarditis and endocarditis, while myocarditis is caused by bacteria. Genetic predisposition may explain rare heart inflammation in young people.[2]

The immune system in health and disease may be enhanced by immune optimization (IO) and dysfunction, respectively. An optimized immune system dissuades inflammatory and infective disease processes. Immune dysfunction enhanced by toxin/infectious agents may reflect a spectrum of IIHDs that share similar immune dysfunctional pathogenesis. Inflammatory cytokines play pivotal roles in the disease processes. The biology and correlation of inflammatory cytokines (IL-6, IL-1, IL-33, TNF-alpha, IL-10, and IL-8) concerning IIHDs is well known.[3] However, the actual

Access this article online

Quick Response Code:

Website: www.njbcs.net

DOI: 10.4103/njbcs.njbcs_36_24

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Submitted: 26-Apr-2024 **Revised:** 17-Jun-2024
Accepted: 19-Jun-2024 **Published:** 25-Sep-2024

How to cite this article: Okafor MT, Ghasi SI. Preventive and therapeutic adjunctive roles of immune optimization on inflammatory and infectious diseases: A mini review. Niger J Basic Clin Sci 2024;21:185-9.

inflammatory dysfunctional disease mechanisms are unknown.

Inflammatory heart diseases have autoimmune and auto-inflammatory etiology.[1] They share similar inflammatory pathways with dysfunctional T cells playing central roles in their immunopathogenesis. Transendothelial migration of T cells is mediated by cellular adhesion molecules (CAMs), which are regulated by pro-inflammatory cytokines produced by T cells in immunological processes.[4] Viruses bind to CAMs to gain entry to the host cell. Bacterial surface proteins are frequently recognized and bound to by CAMs.[5,6] In contrast to jet lesions, which predispose heart valve colonization by bacteria, infection of non-bacterial thrombotic vegetation requires a predisposition that is partially operative amidst T cell dysfunctional activities.[7]

The combined incidence of inflammatory and infectious diseases, which affects all systems of the body, is alarming and should be a dire public health concern. Furthermore, their rising incidence, morbidity, and mortality underscore the limitations of current drug treatment modalities. Moreover, these drugs are not without side effects. Immune optimization (IO) interventions with immune optimizers such as a good diet, adequate sleep, and moderate intensity should be alluring preventive and adjunctive therapeutic strategies to mitigate immune dysfunction—a forerunner to inflammatory and infectious diseases. Hence, this review aims to highlight IO as a preventive and therapeutic adjunct for the management of inflammatory and infectious diseases. Additionally, discussing a putative T cell immune dysfunction model of inflammatory and infectious diseases using inflammatory and infective heart diseases as classic examples should pave the way for a better understanding of the preventive and therapeutic adjunctive roles of immune optimization for the management of inflammatory and infectious diseases.

Materials and Methods

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 lymphocyte activation/dysfunction, inflammatory cytokines, disease prevention, and therapeutic adjunct.

Results

Of the 314 articles identified from databases, 41 were duplicates and 13 not related to the review topic were excluded. Of the 260 articles assessed for legibility, 16 articles were included in the Mini review [Figure 1].

Putative Immuno-toxic lifestyle mediated T-cell dysfunction in inflammatory and infectious diseases

According to Okafor *et al.*,[8] activated dysfunctional T cells (DTCs) migrate to different sites of the body in an immune dysfunctional state to mediate different disease phenotypes based on genetic predispositions. Diet-mediated epigenetic activation of T cells by egregious food substances may lead to their dysfunction by abnormally permeating their membranes with the influx of signal-transduction food molecules.[8] Furthermore, diet-mediated epigenetic post-translational modification of proteins that are enzyme substrates for cytokine production by DTCs may cause aberrant production of inflammatory cytokines. Enzymes that process

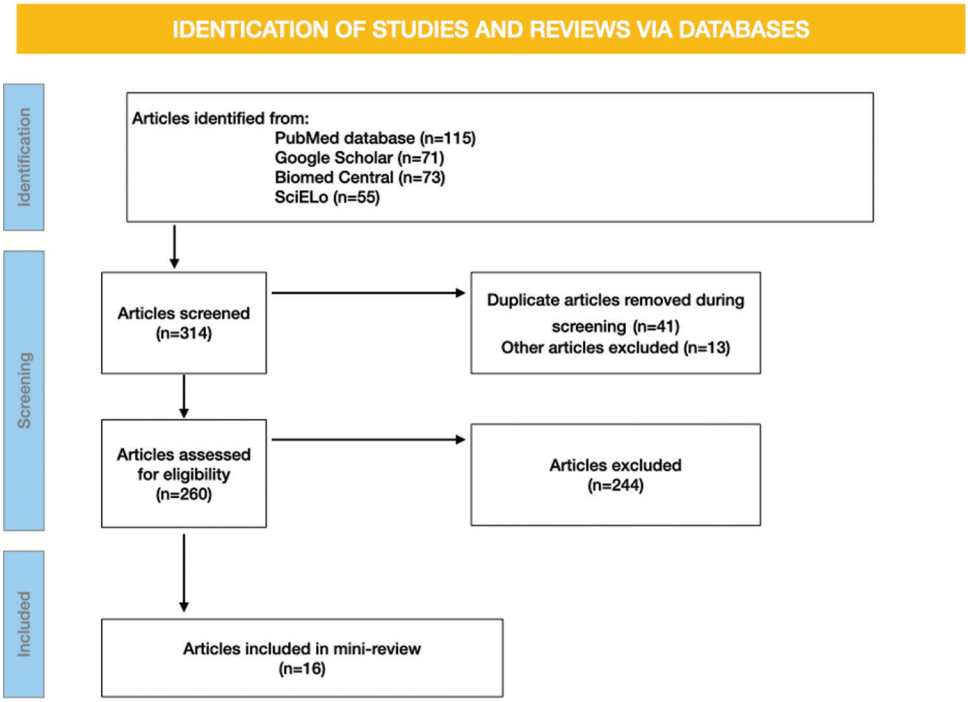

Figure 1: PRISMA flow diagram for the Mini review detailing the database searches and the number of articles screened

inflammatory cytokines are targets for novel drug designs.[9] For inflammatory heart diseases, following exposure of T cells to toxicants in diet, they become dysfunctional. Pro-inflammatory cytokines released by DTCs aid their migration through chemotaxis to the microenvironment of the pericardium, myocardium, and endocardium. Genetic predisposition to inflammatory heart disease manifests as an autoimmune phenotype, while its absence manifests as auto inflammatory phenotype as shown in Figure 2. For infective heart diseases, carditis-causing viruses and bacteria express receptors for CAMs and form respective ligands with DTCs. DTC ligand complexes with viruses and bacteria then migrate via chemotaxis to the pericardium, myocardium, or endocardium to mediate infective disease processes. Cytotoxic activities of T cells towards infecting viruses and bacteria are sub-optimal in immune dysfunctional states. T cell dysfunction may be exacerbated by cross-talks between inflammatory cytokines generated from other promoters of immune dysfunctional states like inadequate sleep and lack of exercise. In other words, diet-mediated immune dysfunction initiates activation and dysfunction of T cells while other immune dysfunctional states promoted by inadequate sleep and lack of exercise consolidates its dysfunction. Bad diet and inadequate sleep/lack of exercise may be referred to as the initiators and consolidators of immune dysfunction underlying IIHDs. Good diet, adequate sleep, and moderate-intensity exercise may be conceived as gatekeeping and caretaker triumvirates with respect to disease prevention and adjunctive therapeutic intervention roles. In an immune-optimized state, the integrity of the membrane of T cells is in a homeostatic state, there is no disruption and permeation of their membrane by environmental toxicants to activate their disease-mediating behaviors. Cytotoxic activities of T cells towards infecting organisms are optimal and prevent infections ab initio. There is no expression of aberrant CAMs for attachment of infecting organisms. Furthermore, the aberrant release of inflammatory cytokines by DTCs, which aids migration via chemotaxis of infective organisms and DTCs to disease-predisposing sites is abated. Our putative T cell dysfunction inflammatory heart disease model may be postulated as autoimmune (with characterizing antibodies) and auto-inflammatory diseases (lacking characterizing antibodies) with similar underlying T cell epigenetic-mediated dysfunction, whereby genetic predisposition determines the disease phenotype. Afore discussed putative disease model may apply to the pathogenesis of other autoimmune and auto-inflammatory disease conditions. There is clinical evidence of positive adjunctive therapeutic diet-mediated IO effects on some immune-mediated inflammatory diseases (IMIDs), which may be due to T cell dysfunction abatement.[10-12] As regards infectious heart diseases, our putative disease model may be postulated as infectious disease processes exacerbated by T cell epigenetic mediated dysfunction. Putative aforementioned T cell dysfunction disease models may also apply to the pathogenesis of other infectious diseases.

Roles of multi-omic studies in the validation of putative inflammatory and infectious 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 genetic predispositions. DTC proliferation and migration studies may validate the

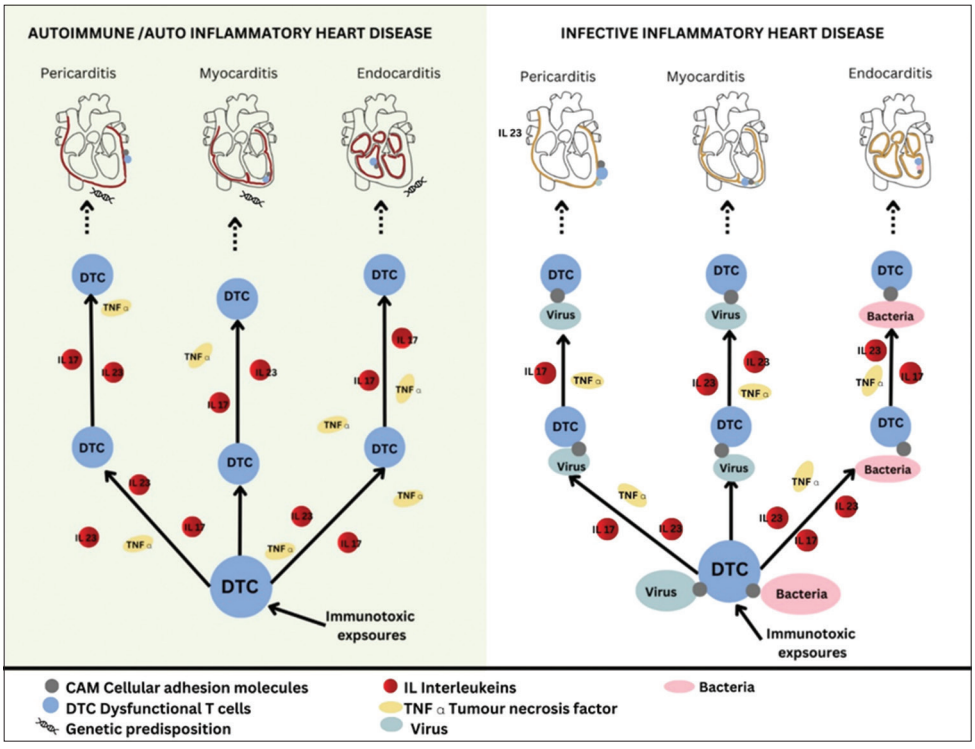

Figure 2: Putative Immunotoxic epigenetic T cell dysfunction model of inflammatory and infective heart diseases

theory of migration of DTCs to disease-predisposing body sites in immune dysfunctional states. Correlative polymerase chain reaction (PCR) for viral load and bacterial count studies with DTC migration/proliferative studies, may highlight our DTC/infective organism interactions in the pathogenesis of infective heart diseases. Multiomic studies can be used to investigate disease mechanisms and validate putative disease models. An array of gene transcript signatures relative to adverse environmental exposures, by epigenetic mechanisms may be highlighted by correlative transcriptomic and DTC studies. Also, 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 following exposure to environmental toxicants. 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 diseases.[13] Also, biological specimens may highlight metabolites associated with T cell dysfunction and further validate the theory of its dysfunction by environmental toxicants in an epigenetic mechanism.

Immune optimization as a preventive and therapeutic adjunct for the management of inflammatory and infectious diseases

Drug treatment of inflammatory heart diseases is mainly immunosuppressive. Steroids can suppress immune dysfunction but do not address the cause. Furthermore, it may complicate comorbid disease conditions like diabetes mellitus and other IMIDs. As a therapeutic adjunct, IO probably due to T cell dysfunction abatement has been shown to reduce the drug treatment requirement of some IMIDs.[10,11] IO may also reduce episodes of idiopathic recurrent pericarditis and steroid treatment requirements. Inflammatory heart diseases are, to some extent, mirror images of one another in terms of their pathogenesis. IO strategies applicable to one may apply to the other and may also translate to reduced drug treatment requirements for their management and that of comorbid conditions. Furthermore, IO may translate to reduced clinical symptoms of diseases. Concerning the aforementioned, interactions between DTCs and the disease site may worsen clinical symptoms of the disease due to hypersecretion.[8] Pleural effusion following DTC and pericardium interaction may be reduced following IO. IO can translate to better efficacy of antimicrobials used in infective heart diseases from improved gut microbiota. Better efficacy of antimicrobials addresses drug resistance. It is important to note that IO should not replace drug treatments of IIHDs but should suffice as a therapeutic adjunct, which may translate to an overall reduction in drug intake and consequent side effects.

Immune optimizers such as a good diet, adequate sleep, and moderate-intensity exercise have been recognized as immune optimizers from time immemorial. Abating immune dysfunction, even in the presence of genetic predisposition to inflammatory heart diseases, should be both preventive and therapeutic. Tinkering with our genetic makeup through genetic engineering may offer little hope for disease-predisposing inflammatory heart disease gene–environment interactions. After all, evolution confers genetic variations on organisms as a survival advantage. It is important to note that genetic predisposition to a disease may not translate to its phenotypic expression in an immune-optimized state. Genetic testing for inflammatory heart disease genes should better profile individuals who are more susceptible to early institutionalization of immune optimization preventive measures.

Egregious food substances interact with transcription factors such as NF-kB, yielding inflammatory processes.[8] Our putative T cell dysfunction highlights probable disease mechanisms caused by epigenetic diet-mediated dysfunction of T cells. A Personalized Food Avoidance Dietary Approaches for Management of IMIDs (PFA-DAMI) addresses primary and secondary immune intolerance to food substances and has been shown to have positive effects on obesity and other IMIDs.[10,11,14]

Moderate-intensity exercise has a positive effect on hypertensives in a clinical longitudinal study to improve immune functionality.[11] Adjunctive therapeutic roles of moderate-intensity exercise are limited in some heart diseases due to functional pathologies. Close monitoring of cardiac indices like Left Ventricular Ejection Fraction (LVEF) with echocardiography may inform a gradual increase in exercise tolerability. Ongoing clinical trials of the effect of a Personalized Food Avoidance Dietary Approach to Stop Hypertension (PFADASH) have shown improvements in echocardiographic cardiac indices in study participants with reduced ejection fraction as well as exercise tolerance.[15]

Inadequate sleep is associated with dysfunctional immune functions. Recent studies have shown associations between disrupted sleep, sleep deprivation, and inflammatory processes, although the physiological mechanisms underlying this association are unclear.[16]

Study limitation

This mini-review did not discuss the diagnostic and monitoring roles of multi-omic studies for inflammatory and infectious diseases.

Conclusion

We conclude with this aphorism: The number of days for preventive and adjunctive treatment approaches other than immune optimization for “mending of broken hearts” caused by immune dysfunction and infective organisms are numbered.

Authors’ contribution

This manuscript has been read and approved by the author. The requirements for authorship were met as outlined below.

MTO: Concept, design, definition of intellectual content, literature search, article screening, manuscript preparation,

manuscript editing, and manuscript review. Also, take responsibility for the integrity of the content of this manuscript. MTO: Literature search, article screening, data acquisition, manuscript preparation, manuscript review. SIG: manuscript preparation, manuscript editing, manuscript review. SIG: A manuscript review.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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