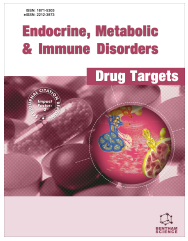
MINI-REVIEW ARTICLE

The Inflammatory Response in Metabolic Syndrome



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Abstract: Metabolic syndrome (MS) encompasses a cluster of metabolic disorders that significantly increase the risk of developing cardiovascular diseases and type 2 diabetes mellitus. While the precise etiology of MS remains unclear, it is widely recognized as a multifactorial condition influenced by environmental, lifestyle, and genetic factors. Inflammation, a fundamental physiological response designed to maintain homeostasis, plays a central role in MS. When the body detects foreign substances or cellular stress, the immune system is activated, synthesizing signaling molecules, such as cytokines and chemokines. However, prolonged or dysregulated immune activation can result in chronic low-grade inflammation, a hallmark of MS. This persistent inflammatory state contributes to the pathophysiology of MS by promoting insulin resistance, endothelial dysfunction, and adipose tissue remodeling. The diagnostic criteria for MS, including central obesity, dyslipidemia, hyperglycemia, and hypertension, are all associated with inflammatory processes mediated by the activation of both innate and adaptive immune systems.

This review explores the intricate relationship between each diagnostic criterion of MS and the inflammatory response. By delving into the immunological mechanisms underpinning MS, we aim to understand how inflammation links metabolic dysregulation to disease progression comprehensively. This knowledge could pave the way for targeted therapeutic interventions and lifestyle modifications to mitigate the global burden of MS.

Keywords: Metabolic syndrome, immune system, cytokines, inflammation, cells, etiology.

1. INTRODUCTION

Metabolic syndrome (MS) refers to clinical and metabolic disorders predisposing to cardiovascular disease and diabetes mellitus type 2. Although the exact pathophysiology of MS remains complex and poorly understood, its etiology is widely recognized as multifactorial, involving a dynamic interplay between genetic predisposition and environmental factors [1, 2].

The diagnostic criteria for MS have evolved. In 2009, a significant milestone was reached when six prominent organizations, including the International Diabetes Federation (IDF), American Heart Association (AHA), National Heart, Lung, and Blood Institute (NHLBI), World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity, published a joint scientific statement on the harmonization of MS criteria. This harmonized definition has since become the most widely accepted diagnostic standard. According to this definition, the presence of three or more of the following five metabolic disturbances is required for a diagnosis of MS: 1) increased waist circumference (population and country-specific), 2] hypertension, 3] hyperglycemia (>100 mg/dL), 4] low levels of high-density lipoprotein or HDL (<40 mg/dL in males and <50 mg/dL in females), and 5] elevated triglycerides (>150 mg/dL) [3].

The global prevalence of MS is alarmingly high. In the United States, a 2020 study reported a prevalence of 34.7%, with Hispanics identified as the second ethnic group with the highest prevalence [4]. In Mexico, the prevalence of MS

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varies significantly depending on the diagnostic criteria used. Notably, a 2018 study found that 56.31% of Mexican adults met the harmonized criteria for MS [5].

Given the multifactorial etiology and significant global prevalence of MS, understanding the underlying mechanisms driving its progression is essential. Among these mechanisms, the role of chronic low-grade inflammation stands out as a critical contributor to the metabolic disturbances characteristic of MS. Adipose tissue dysfunction, a hallmark of MS, actively promotes an inflammatory state through the secretion of pro-inflammatory molecules, such as leptin and cytokines, linking metabolic dysregulation to systemic inflammation. Exploring the inflammatory response in MS provides crucial insights into its pathophysiology and highlights potential targets for therapeutic intervention [6, 7].

2. METHODOLOGY

The databases used for the literature of this article were PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/). The terms used included "metabolic syndrome", "inflammation" AND "metabolic syndrome", "metabolic syndrome" AND "etiology", "inflammation" AND "obesity", "inflammation" AND "hyperglycemia", "inflammation" AND "dyslipidemia", and "inflammation" AND "hypertension". Only articles published in English language between 2015 and 2024 were included. The selected studies focused mainly on the relationship between metabolic syndrome and immunology, excluding those not providing experimental, clinical trials, or meta-analyses. Reviews and case report articles were excluded unless they provided relevant theoretical background.

2.1. The Inflammatory Response

Inflammation is a physiological response crucial for maintaining homeostasis in the organism. It is a protective mechanism activated by various stimuli, including invading pathogens or endogenous signals from damaged or stressed cells. The primary goals of inflammation are to eliminate the underlying cause of injury, remove necrotic cells, and facilitate tissue repair. This process begins when host cells recognize conserved molecular patterns on pathogens, called pathogen-associated molecular patterns (PAMPs), or endogenous stress signals known as danger-associated molecular patterns (DAMPs). These molecular signals are detected by specialized receptors called pattern recognition receptors (PRRs) [8]. PRRs are expressed across a broad range of cells, including innate immune cells, such as monocytes, macrophages, neutrophils, and dendritic cells, as well as non-immune cells, such as lymphocytes, fibroblasts, and epithelial cells. When PRRs detect PAMPs or DAMPs, they activate signaling pathways that stimulate transcription factors, like nuclear factor-kappa B (NF-κB), AP-1, and IRF3. These transcription factors drive the production of pro-inflammatory molecules, including cytokines, chemokines, and adhesion molecules, which coordinate the inflammatory response [9].

Cytokines, such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), regulate the immune system and modulate cell behavior at local, tissue, and systemic levels. They enhance the activation of endothelial cells, increasing vascular permeability and allowing immune cells to migrate from the bloodstream to the site of injury. Chemokines, another group of signaling molecules, play a key role in guiding immune cells, like neutrophils and monocytes, to the affected area, where they engage in processes, such as phagocytosis and pathogen elimination [10, 11].

While inflammation is typically a controlled and self-limiting process, persistent stimulation can result in chronic inflammation. This occurs when the initial inflammatory trigger is not resolved, leading to prolonged activation of immune pathways. Chronic inflammation is characterized by a sustained production of pro-inflammatory molecules and ongoing recruitment of immune cells, which can lead to tissue damage and dysregulation of normal physiological processes [12, 13]. In the pathogenesis of metabolic syndrome (MS), chronic low-grade inflammation is critical. Understanding the inflammatory mechanisms underlying MS is essential for developing targeted interventions. The following sections delve deeper into the connections between inflammation and the individual diagnostic criteria of MS, shedding light on how immune dysregulation contributes to this multifaceted syndrome.

2.2. Inflammation and Obesity

Obesity results from a combination of factors that cause an imbalance between caloric intake and energy expenditure [14]. In individuals with obesity, adipose tissue undergoes extensive cellular and structural remodeling, characterized by the infiltration of immune cells. This process contributes to sustained low-grade chronic inflammation and a disruption of metabolic homeostasis [15]. Adipocytes, the adipose tissue's primary cells, secrete various adipokines that regulate inflammatory and immune responses, glucose metabolism, and lipid homeostasis [16, 17]. Chronic inflammation in obesity is marked by macrophage infiltration into adipose tissue. Over time, other immune cells, including lymphocytes, eosinophils, and neutrophils, have been identified as key contributors to adipose tissue metabolism and the inflammatory milieu [15, 18, 19].

Macrophages in adipose tissue are broadly categorized into two types based on their cytokine secretion profiles: M1 and M2. M1 macrophages, often called "pro-inflammatory", secrete cytokines, such as IL-6, IL-1β, monocyte chemoattractant protein-1 (MCP-1), and TNF-α. Conversely, M2 macrophages, activated by anti-inflammatory cytokines, like IL-4 and IL-13, are associated with tissue repair and the resolution of inflammation [20-23]. In patients with MS, an increased prevalence of M1 macrophages and elevated levels of MCP-1 have been strongly linked to systemic inflammation and metabolic dysfunction [24, 25]. Interestingly, interleukin-32 (IL-32) is a pro-inflammatory cytokine that plays a key role in various inflammatory and immune responses.

Recent studies have shown that serum levels of IL-32 are significantly lower in obese individuals compared to those with normal weight. This finding suggests that chronic inflammation in obesity may trigger the downregulation of IL-32 expression as an adaptive mechanism to minimize the harmful effects of sustained inflammation. However, further research is needed to understand this regulatory process fully and its implications [26].

Obesity is associated with increased intestinal permeability and elevated circulating lipopolysaccharide (LPS) levels, which activate pattern recognition receptors (PRRs), such as toll-like receptor-4 (TLR4), in adipose tissue cells, initiating a pro-inflammatory cascade. Additionally, free fatty acids (FFAs), elevated in obesity and high-fat diets, exacerbate inflammation by indirectly activating TLR4 and promoting cytokine production [27-30]. TLR4 contains a toll-interleukin-1 receptor (TIR) domain in its cytoplasmic tail, which is activated by the LPS binding, causing conformational changes that are activated and facilitated by proteins, such as MD2 and CD14, which recruit adapters, such as TRIF, initiating MyD88-dependent and independent pathways. In the MyD88-dependent pathway, IRAK1/4, TRAF6, and TAK1 are activated, promoting IkB phosphorylation, which allows the translocation of NF-kB to the nucleus to induce the transcription of proinflammatory genes, such as TNF-α, IL-6, and IL-1β. In the TRIF-independent pathway, IRF3 is activated, promoting the production of type 1 interferon [31-33].

Emerging evidence suggests that specific nutrients and dietary compounds may possess anti-inflammatory properties capable of mitigating the effects of MS. For example, riboflavin (vitamin B2) has been shown to reduce pro-inflammatory mediators, like TNF-α, IL-6, and MCP-1, in adipocyte-macrophage co-cultures, potentially improving insulin sensitivity and alleviating chronic inflammation [30, 34-36]. Similarly, dietary polyphenols, particularly those found in fruits, vegetables, and also *Camellia sinensis* tea polysaccharides, have demonstrated the ability to inhibit adipogenesis, modulate gut microbiota, and attenuate inflammation, as well as antioxidative activity and antitumor properties [37-39]. In another study, microcystin-LR (MC-LR) was reported to activate the PI3K/AKT/mTOR/SREBP1 signaling pathway that promotes overexpression of lipid synthesis and inhibits fatty acid β-oxidation in obese mice and also induces and aggravates the state of serum oxidative stress, which may exacerbate the obesity process [40]. These findings emphasize the importance of dietary strategies in preventing and managing MS, although further clinical studies are needed to establish their efficacy and mechanisms of action.

2.3. Inflammation and Hyperglycemia

Hyperglycemia is a central feature of metabolic syndrome (MS) and a defining characteristic of diabetes mellitus. Persistent high glucose levels in the bloodstream trigger a cascade of pathological processes contributing to inflammation and systemic dysfunction. One principal pathway involves accumulating reactive oxygen species (ROS) and advanced glycation end-products (AGEs). These AGEs interact with their receptors (RAGE), activating the NF-κB signaling pathway, which upregulates the production of pro-inflammatory cytokines, such as IL-6 and TNF-α. These cytokines further impair insulin signaling, exacerbating insulin resistance and disrupting systemic homeostasis, ultimately contributing to the pathogenesis of diabetes and its associated complications [41, 42].

Chronic hyperglycemia amplifies ROS production by activating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway. In neutrophils, increased glycolytic activity in the pentose phosphate pathway generates NADPH, which serves as a substrate for NADPH oxidase, facilitating the production of superoxide, a key ROS molecule involved in inflammatory processes [43, 44]. This oxidative stress not only promotes inflammation, but also induces significant immune dysfunction. Hyperglycemia is associated with decreased recruitment of granulocytes to the alveolar airspace and reduced production of key cytokines, including CXCL1, CXCL2, IL-1β, and TNF-α. Additionally, it downregulates the expression of toll-like receptor 2 (TLR-2) and the toll/IL-1R domain-containing adaptor protein (TIRAP), both essential for pathogen recognition and the initiation of innate immune responses [45-48]. At the tissue level, hyperglycemia drives inflammation in adipose tissue and the liver. TNF-α, free fatty acids, and ROS activate IκB kinase β (IKKβ) and c-Jun N-terminal kinase 1 (JNK1), leading to the transcriptional upregulation of genes involved in the inflammatory response. This contributes to insulin resistance and metabolic dysregulation [41, 49, 50]. Moreover, chronic hyperglycemia induces significant immune alterations, including increased apoptosis in immune cells and an imbalance between pro-inflammatory (*e.g.*, Th17) and anti-inflammatory (*e.g.*, regulatory T cells, Tregs) populations. Impaired differentiation and function of Tregs further tip the balance toward a pro-inflammatory state, perpetuating systemic inflammation and disrupting the delicate interactions between innate and adaptive immunity. These processes aggravate the pathological effects of hyperglycemia, contributing to vascular and metabolic complications [48, 51-53].

Hyperglycemia also compromises immune defense mechanisms, reducing the production of cytokines, such as IL-12 and interferon-gamma (IFN-γ), impairing leukocyte recruitment, and diminishing neutrophil phagocytic activity. Delayed neutrophil apoptosis and a pro-inflammatory shift in macrophages and monocytes exacerbate systemic inflammation. Natural killer (NK) cell activity is also reduced, compromising immune function. These immune dysfunctions increase susceptibility to infections, impair wound healing, and contribute to complications, such as diabetic foot ulcers and sepsis [48, 54-56].

Addressing hyperglycemia is critical for managing glucose levels and improving immune system resilience. Targeting the inflammatory and oxidative pathways associated with hyperglycemia could mitigate immune dysfunction, reduce complications, and improve outcomes for diabetic patients.

2.4. Inflammation and Dyslipidemia

Dyslipidemia, a hallmark feature of metabolic syndrome (MS), is characterized by abnormalities in lipid and lipoprotein profiles. These typically include elevated triglyceride (TG) levels, reduced high-density lipoprotein (HDL) cholesterol, and elevated low-density lipoprotein (LDL) cholesterol. Dyslipidemia contributes significantly to the pathophysiology of MS by disrupting metabolic homeostasis, promoting glucose dysregulation, enhancing TG synthesis, and increasing hepatic secretion of very low-density lipoproteins (VLDL). This leads to triglyceride accumulation in the liver (hepatic steatosis) and systemic dyslipidemia, which are closely linked to chronic low-grade inflammation [17, 57, 58].

The underlying mechanisms of dyslipidemia often involve a hypercaloric diet that promotes adipocyte hypertrophy and lipolysis, releasing free fatty acids (FFAs) into circulation. Elevated FFAs disrupt extracellular homeostasis and act as damage-associated molecular patterns (DAMPs). These DAMPs are recognized by pattern recognition receptors (PRRs), particularly toll-like receptors (TLRs), expressed on macrophages and other immune cells. The activation of TLRs triggers signaling cascades, such as the NF-κB pathway, leading to the secretion of pro-inflammatory cytokines, like TNF-α, IL-6, and IL-1β. These inflammatory mediators exacerbate insulin resistance, endothelial dysfunction, and atherosclerosis, thereby perpetuating cardio-metabolic disorders [57, 59, 60].

Recent studies have highlighted additional mechanisms by which dyslipidemia drives inflammation. Oxidized LDL (ox-LDL) particles and cholesterol crystals activate the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome in macrophages. This activation leads to the cleavage of pro--caspase-1 into its active form, caspase-1, which processes pro-IL-1β and pro-IL-18 into their mature, pro-inflammatory forms. These cytokines are secreted by immune cells within atherosclerotic plaques, promoting local inflammation and contributing to plaque instability and cardiovascular events [61-63].

Activating TLRs and NLRP3 inflammasome further amplifies inflammatory signaling by engaging pathways, such as c-Jun N-terminal kinase (JNK) and inhibitor of nuclear kappa-B kinase subunit β (IκKβ). This results in the production of a wide range of pro-inflammatory cytokines, including IL-1β, IL-18, IL-6, IL-8, and TNF-α, all of which play central roles in the progression of cardio-metabolic diseases caused by dyslipidemia [64, 65].

Moreover, dyslipidemia and inflammation act synergistically over time, significantly increasing the risk of type 2 diabetes and other metabolic disorders. Elevated LDL and reduced HDL cholesterol levels correlate with higher inflammatory markers, such as IL-6 and C-reactive protein (CRP), underscoring the link between lipid abnormalities and systemic inflammation. FFAs further exacerbate inflammation by binding to TLR4, intensifying cytokine secretion and metabolic dysfunction [66].

Targeted interventions addressing dyslipidemia and inflammation hold promise for managing MS. Statins and novel lipid-lowering agents improve lipid profiles and reduce inflammation by attenuating TLR activation and cytokine production. Inhibiting NLRP3 inflammasome activation offers another potential strategy to combat chronic inflammation, improving outcomes in cardio-metabolic diseases.

2.5. Inflammation and Hypertension

Low-grade chronic inflammation plays a pivotal role in hypertension pathophysiology, with innate and adaptive immune systems contributing to its progression. Hypertension is characterized by a gradual increase in systemic vascular resistance, often mediated by vasoconstriction and oxidative stress [67]. Key mediators, including angiotensin II, activate NADPH oxidase 1 (NOX1) through the AT1R-Gβγ-PI3Kγ pathway, generating superoxide, which facilitates the entry of Ca^{2+} through non-selective cation channels (NSCCs) and promotes smooth muscle contraction, contributing to the acute pressor response. Subsequently, NOX1 is sustainably activated by the angiotensin II type 1 receptor Gαq/protein kinase C-phospholipase-11 (AT1R-Gαq/11-PLC-PKCβ) pathway, further exacerbating ROS [68, 69]. Angiotensin II and other mediators, such as endothelin-1, prostaglandin H2, and angiotensin II, act as damage-associated molecular patterns (DAMPs), activating immune cells, such as T lymphocytes. This process enhances vascular tension and promotes the release of pro-inflammatory molecules, such as IL-6, IL-8, and ROS. Additionally, endothelial cells increase the expression of adhesion molecules, like vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1), facilitating immune cell infiltration and perpetuating vascular inflammation [67, 70, 71].

In the innate immune system, neutrophils and macrophages are key contributors to the inflammatory response in hypertension. These cells generate ROS, inducing oxidative stress and reducing the bioavailability of nitric oxide (NO), a critical vasodilator. This imbalance promotes endothelial dysfunction, increasing vascular resistance and blood pressure. The adaptive immune system is also heavily involved, with CD4+ T lymphocytes playing a central role. T helper 1 (Th1) cells secrete pro-inflammatory cytokines, like interferon-gamma (IFN-γ), while T helper 17 (Th17) cells produce interleukin-17 (IL-17) [72], which exacerbates hypertension through mechanisms, such as kidney injury and dysfunction. Regulatory T cells (Tregs), which represent approximately 10% of CD4+ T cells, play a protective role by modulating immune responses and maintaining vascular homeostasis. However, in hypertensive individuals, Treg activity is often diminished, tipping the balance toward a pro-inflammatory state [67, 73-75].

CD8+ T cells are significantly elevated in hypertension and contribute to vascular inflammation. These cells express the mineralocorticoid receptor (MR), whose activation promotes interactions with the nuclear factor of activated T cells 1 (NFAT1) and activator protein-1 (AP1). This signaling cascade drives the production of IFN-γ, further contribut-

ing to vascular inflammation and elevated blood pressure. MR overexpression in CD8+ T cells exacerbates hypertensive conditions, highlighting its importance in the pathogenesis of hypertension [74-77].

Cytokines, such as TNF-α and interleukin-1 (IL-1), also significantly regulate blood pressure in hypertensive states. TNF-α influences the immune system by activating NF-κB, which promotes the expression of IL-1. IL-1 receptor (IL-1R) signaling is critical in driving vascular remodeling and inflammation, further perpetuating endothelial dysfunction and vascular resistance [73, 76].

Addressing inflammation provides a promising therapeutic approach for managing hypertension. Therapies, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), not only reduce blood pressure, but also mitigate inflammatory signaling by decreasing angiotensin II-mediated cytokine production and oxidative stress [78]. Inhibitors of mineralocorticoid receptors (MR) may attenuate the inflammatory effects of CD8+ T cells. Experimental approaches targeting specific immune pathways, such as IL-17 or IL-1 blockade, also show potential for reducing vascular inflammation and improving blood pressure control [79, 80].

Lifestyle interventions, including dietary modifications and regular physical activity, reduce inflammation and improve vascular health.

As MS has increased over the years and, according to the estimated prevalence, will continue to increase, there is a need to know more about its etiology. Similarly, further investigation into additional cytokines involved in this disease is essential for developing future therapies; also, healthier eating habits and physical activity need to be promoted to prevent the progression of the condition. In this regard, studies have recommended including anti-inflammatory elements in the diet, such as curcumin and garlic, which help reduce abdominal obesity and LDL levels; this, combined with physical activity, can reduce levels of inflammatory markers [81–84].

This review has thus outlined the diagnostic criteria for MS and their intricate connections to immune system dysregulation (Fig. **1**).

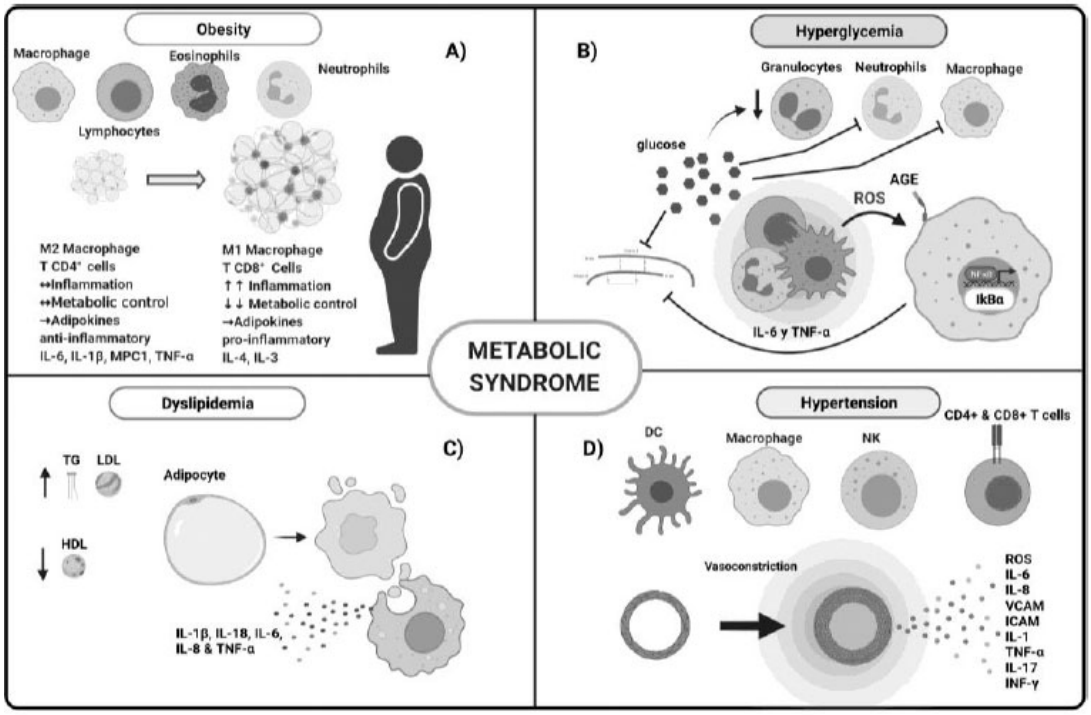

Fig. (1). Cells and molecules of the immune system are involved in the inflammatory development of each diagnostic criterion of metabolic syndrome. (**A**) Macrophages, lymphocytes, eosinophils, and neutrophils are the cells involved in adipose tissue. Macrophages are the protagonists, with the M1 or M2 inflammatory profile increasing or decreasing each parameter and expression of molecules. (**B**) When there is an increase in glucose, granulocytes reduce, resulting in a dysfunction of neutrophils and macrophages. ROS are also produced and activate transcription factors, promoting the inflammatory response, which results in insulin resistance and hyperglycemia. (**C**) Adipocyte hypertrophy increases TG and LDL-c and decreases HDL-c, activating macrophages, which release inflammatory cytokines. (**D**) Cells involved in hypertension are mainly DC, macrophages, NK, and T cells; when vasoconstriction occurs, ROS is released, producing inflammatory cytokines and adhesion molecules. Continuous arrows indicate activation and flat arrows indicate inhibition. *(A higher resolution version of this figure is available in the electronic copy of the article).*

Future multidisciplinary research should focus on identifying and characterizing additional cytokines and signaling pathways involved in MS to discover new therapeutic targets, such as the inhibition of some cytokines or receptors that compete with pro-inflammatory cytokines [85-87]. On the other hand, in recent years, studies on intestinal microbiota have emphasized the use of probiotics, prebiotics, and synbiotics, as the composition of the microbiota increases systemic inflammation in obesity [88-90], which is one of the main characteristics of MS. Likewise, it has been mentioned that there are genetic factors that could increase the risk of developing this disease [91-93]. Consequently, MS must be studied from an interdisciplinary research approach to unravel this pathology's heterogeneity. Moreover, public health initiatives promoting healthier eating habits and increasing physical activity are essential to mitigate the risk of MS and its related complications. These preventive measures, combined with a deeper understanding of the molecular and immunological mechanisms of MS, could significantly reduce its impact on global health.

CONCLUSION

MS is characterized by a state of chronic low-grade inflammation involving both innate and adaptive immune responses. As its prevalence continues to increase, further research is needed to understand better its etiology, including the role of cytokines, immune signaling pathways, and genetic predisposition. Future therapeutic strategies should explore cytokine inhibition, dietary interventions with anti-inflammatory components, and microbiota-targeted approaches, such as probiotics and prebiotics, to mitigate systemic inflammation. Furthermore, interdisciplinary research is essential to address the complexity of MS, while public health initiatives promoting healthier diets and increased physical activity need to be implemented to prevent and manage this condition.

AI DECLARATION

The article's English language was improved with ChatGPT. The authors partially generated this text with GPT-3, OpenAI's large-scale language-generation model. Upon generating draft language, the authors reviewed, edited, and revised the language to their liking and take ultimate responsibility for the content of this publication.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: writing of the paper: Luz Andrea Martínez-Perez; investigation: Grecia Denisse González-Sánchez; data collection: Julieta Becerra-Ruiz, Fernando Martínez Esquivias; study concept or design: Juan Manuel Guzmán-Flores. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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