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Review

Systemic Chronic Inflammation: Integrative Strategies for Health Improvement and Prevention of Inflammatory Receptor Overexpression

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Abstract: The body's physiology during physical injuries and diseases depends heavily on the function of acute inflammation. On the other hand, many variables, including iatrogenic, immune system deficiencies, lifestyle, and social and environmental factors, are significant in developing systemic chronic inflammation (SCI). SCI is a major contributor to many diseases and a global cause of death and disability. Therefore, in the present article, we suggest integrative strategies for preventing SCI by addressing receptor overexpression and promoting health improvement. With the objective of reducing chronic inflammation by regulating cytokines, chemokines, and receptor modulation to try to reduce the risk of developing systemic chronic inflammatory diseases (also known as chronic-degenerative diseases, such as diabetes mellitus, cancer, cardiovascular disease, stroke, chronic kidney disease, neurodegenerative disorders, autoimmune diseases, and psychiatric disorders), the strategies we suggest are dietary modifications, exercise, and meditation. Accordingly, the prevention of SCI can be approached holistically with the help of the previous strategies, which may substantially impact public health.

Keywords: systemic chronic inflammation; disease etiology; immune response; receptor damage; meditation; exercise; autoimmune diseases; health food; oxidative stress; cancer

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1. Introduction

The understanding of inflammation or its descriptions dates back to various ancient cultures, where it was considered an early component of the healing process after an injury or event, safeguarding the integrity and survival of the organism. The current view of inflammation is similar (acute inflammation) since it has been characterized as a short-lived manifestation of an irritant or injury that contributes to the reorganization, self-organization, restoration, repair, and recovery of the affected tissues [1,2], generating symptoms of redness, heat, swelling and pain [3].

Inflammation is a well-established evolutionary process within our organism. Its purpose to maintain a dynamic balance to prevent disease due to bacteria, fungi, toxins,

viruses, and infections. The intrinsic regulation mediated by inflammation prevents the multiplication of these organisms, preserving the system's balance and the organism's life [1]. Therefore, the body's physiology during physical injuries and diseases depends heavily on the function of acute inflammation, which is a dynamic, complex, systemic, and multifactorial process.

On the other hand, systemic risk factors such as social factors, environmental factors, infections, physical inactivity, poor diet, exposure to psychological stress, iatrogenic, environmental, and industrial toxicants [4] can lead to the establishment of long-lasting acute inflammation, which occurs locally, and can progressively lead to loss of function in the affected tissue [3] and gradually spread to other tissues and organs, becoming Systemic Chronic Inflammation (SCI). This state of SCI is low-grade and persistent (observed in chronic diseases and in some cases in aging) where there is an activation of immune components that are different from those existing in an acute immune response [5], e.g., carrying a short to long-lasting response causing immune alterations and induction of oxidative stress, as well as, modifications in metabolism, reorganization, and function of cells, tissues, and organs [1,6].

In this sense, SCI has been linked to being the root cause of several chronic-degenerative diseases and systemic chronic inflammatory diseases, such as cancer, diabetes mellitus, cardiovascular disease, stroke, chronic kidney disease, neurodegenerative diseases (e.g., Alzheimer's disease), autoimmune diseases (e.g., rheumatoid arthritis), psychiatric disorders (anxiety and depression), and others, which have been identified as the leading cause of disability and mortality globally [1,4,7–10].

In some cases, chronic inflammatory processes are associated with immunological, endocrine, enzymatic, neurochemical, and metabolic changes in energy expenditure. Chronic inflammation triggers a metabolic shift from efficient oxidative phosphorylation to less efficient glycolytic energy production, while simultaneously reducing insulin sensitivity and glucose availability, it also alters sleep patterns and circadian rhythms [6,11]. When this metabolic change occurs, it generates energy-saving behavioral effects related to reduced food intake and libido, fatigue, and depressive symptoms such as sadness, anhedonia, sleep disturbance, and social isolation [11].

In addition, multiple studies have tried to describe systemic chronic inflammation's molecular behavior, including processes mediated by cytokines, chemokines, and their receptors. In this sense, most studies agree that under these conditions, high levels of proinflammatory Toll-like receptors (TLRs) begin to be expressed, including tumor necrosis factor receptors (TNFR), sphingosine-1-phosphate receptors (S1PRs), interleukin-1 receptor (IL-1R), and the activation of other signaling pathways by transcription factors such as nuclear factor κβ (NF-κβ), mitogen-activated protein kinase (MAPK), and cyclooxygenase-2 (COX-2) expression. In addition, the induction of genes that promote inflammation has also been observed, such as the consequent release of proinflammatory cytokines (interleukins), tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), and chemokines (MCP-1, IL-18, RANTES, MIP-2, CXCL1 and CXCL10), as well as other substances and processes [12–14]. It is important to note that SCI-related processes can be present for long periods and even throughout life, without the development of disease, because these processes are not necessarily pathological. However, in certain cases, the imbalance of these processes leads to pathology; they can trigger diseases associated with SCI, such as cancer, diabetes mellitus, rheumatoid arthritis, and others [1,4,7–10].

All of the above tells us about the complexity and self-organization of nature and the physiology of the body [2], in both inflammatory processes and life, receptors, and mediators are only one of many components involved; thus, addressing the individual components in an SCI process can be complex and, at times, insufficient. Therefore, instead

of focusing on each receptor separately, we could consider integrative strategies that focus on restoring the functionality of the damaged receptors involved in SCI, as well as the interrelationships with other affected body systems, so the present article aims to show how dietary modifications, exercise, and meditation can help to improve and restore health in SCI-related diseases.

2. Effects of an Inadequate Diet on Some Receptors and Signaling Pathways Involved in Inflammation

In recent years, food and its health implications have become increasingly important. The growing demand for food and crops, coupled with the planet's overpopulation, has driven the development of more abundant, pest-resistant, and longer shelf-life crops, which are usually achieved with genetically modified foods. These food modifications have been made to meet consumer needs. Still, often, the nutritional quality of the food needs to be addressed, which significantly impacts the physiological state of the people who consume it. In addition, the transportation of these foods contributes considerably to greenhouse gas emissions [15,16]. It should be clarified that foods exposed to pesticides hurt the immune system and human health. In addition, they play an essential role in SCI, affecting both the activation and function of inflammation-modulating receptors.

On the other hand, local or bioregional pesticide-free foods can offer us a new perspective to take care of the planet and our health. For example, some dietary components, such as fatty acids, omega-3, antioxidants, phytochemicals, and fiber, have been shown to have anti-inflammatory effects and can modulate the inflammatory response [17]. A fiber-rich diet of fruits, vegetables, legumes, whole grains, and omega-3 fatty acids in foods such as fish can prevent damage that triggers inflammation. In addition, it can benefit inflammation by modulating the composition of the intestinal microbiota and improving the health of the gastrointestinal tract [17], since the intestinal microbiota plays a central role in anti-inflammatory processes.

Fatty acids are essential sources of energy for the body. They have a generic structure based on a hydrocarbon chain with a reactive carboxyl group at one end and a methyl group at the other [18]. Long-chain polyunsaturated fatty acids (PUFA), such as omega-6 (n-6: arachidonic acid) and omega-3 (n-3: eicosapentaenoic acid and docosahexaenoic acid) [19], are considered important components of breast milk and are present in the membranes of immune system cells and act through multiple mechanisms to influence immune function [20,21] and; therefore, have anti-inflammatory effects.

However, fatty acid intake influences inflammatory cells function and coherence, thus impacting inflammatory process response. Some of their functions are summarized below:

- Fatty acid intake can affect the structure and concentrations of lipids, lipoproteins, metabolites, and hormones, directly influencing inflammatory processes [22].
- Non-esterified fatty acids can act directly on inflammatory cells through surface or intracellular "fatty acid receptors". The latter can include transcription factors involving peroxisome proliferator-activated receptors, and thus directly impacting inflammatory signaling pathways [23].
- PUFA can be oxidized (enzymatically or non-enzymatically), and derivatives of lipid peroxidation can act directly on inflammatory cells via surface or intracellular receptors [24], directly impacting SCI processes.

In addition, fatty acids exhibit important biological activities such as the regulation of the structure and function of the building blocks of cell membrane phospholipids, regulation of intracellular signaling pathways, activity of transcription factors and gene expression, regulation of the production of bioactive lipid mediators, modulation of intracellular signaling in immune cells including neutrophils, monocytes, macrophages, dendritic

cells, T-cells, and B-cells. The role of PUFAs with respect to immune function is that it acts as an important substrate for the generation of bioactive lipid mediators [19]. However, as mentioned above, when fatty acids are damaged, either by lipid peroxidation (a metabolic process that degrades lipids by the action of free radicals and reactive oxygen species) [24] or by an excessive saturated fat diet, they ultimately affect the activation of transcription factors and gene expression mentioned above.

However, a diet rich in saturated fats, refined sugars, and ultra-processed foods can promote SCI and lead to changes in the functionality of receptors in other organs and tissues (pancreas, kidney, liver, adipose tissue, muscles, heart, and brain), in some cases contributing to an increased risk of chronic inflammatory diseases, e.g., obesity, which is a significant factor in the development of metabolic syndrome, characterized by metabolic complications including visceral adiposity, hypertension, high circulating cholesterol, and elevated blood glucose. This combination often leads to insulin resistance and type 2 diabetes and is associated with a sustained inflammation profile [18]. In summary, a healthy diet is crucial to modulate the chronic inflammation seen in various diseases. By preventively reducing this inflammation, changes in the functionality of receptors (depending on the tissue and organ) will not occur, thus preventing the development of chronic degenerative diseases. Therefore, a balanced diet rich in anti-inflammatory foods may promote long-term health by preventing conditions related to SCI.

2.1. The Connection Between Microbiota and Nutrition as an Alternative for Treating Systemic Chronic Inflammation

The microorganisms that inhabit the human gastrointestinal tract comprise the intestinal microbiota, a dynamic community composed mainly of species of the prokaryotic domain, composed of bacteria and other unicellular microbes lacking specialized organelles. To a lesser extent, fungi, parasites, archaea, and viruses are also present [25].

The interaction between the microbiota and the human host is complex and begins at birth, significantly impacting the development of a newborn's immune system [26]. This is a vulnerable period, as the gut is a critical site for various interactions between host and microbiota throughout life [17]. This tells us about an ecological relationship between two parts generating an environment where the ecosystem is the co-organizer and co-programmer of the living system to which it belongs. This relationship is not between two closed entities but a relationship between two open systems [2], where the microbiota and the host do not cease to be part of each other; that is, they need a constant exchange of energy to maintain their structure. This exchange allows the ecosystem to continue in its process of self-organization, to transform and evolve during the life of the human being.

Therefore, energy metabolism serves as a critical point for the interaction between the microbiota and the host since the intestinal microbiota not only receives energy from the host to maintain average growth but also supplies energy to the host through the release of enzymes, metabolites, short-chain fatty acids, amino acids, bile acids, protease B, caseinolytic and lipopolysaccharides (LPS), among other substances [25].

Diet has been shown to influence gut microbiota diversity, health, and SCI processes. In comparison, a Western diet characterized by a high intake of carbohydrates and red meat and a low intake of plant fiber is identified as one of the risk factors for developing inflammatory bowel disease (IBD). Low fiber intake has been associated with a lower diversity of gut microbiota; studies of Western populations identified that the risk of developing Crohn's disease (CD) was 40% lower in women with a high fiber intake in the long term, which is related to a higher diversity of gut microbiota. In turn, a high intake of sugar, sucrose, soft drinks, and red meat consumption was associated with an increased risk of developing IBD and ulcerative colitis (UC), diseases related to SCI. However, this is not the case in the Asian population, where daily intake of tea or coffee is associated with

a lower risk of developing IBD. In contrast, high fiber and tea consumption is associated with lower cases of CD and UC in this population [27].

On the other hand, it has been observed that food can affect the rheostasis of the intestinal microbiota, the immune system, and circadian cycles, which provides an idea of the effects of nutrition on human health. In this sense, when an imbalance is present in the organism, it self-organizes to regulate itself; for example, when there is an excess of energy, this is stored in adipocytes in the form of lipids (triglycerides), resulting in hyperplasia and hypertrophy of fatty tissue, leading to oxygen depletion and the establishment of a condition of cellular stress; this leads to the differentiation of monocytes into macrophages and the recruitment of M1 macrophages at the systemic level (Figure 1) triggering an inflammatory response [13], which, if prolonged over time, can lead to the development of chronic degenerative diseases.

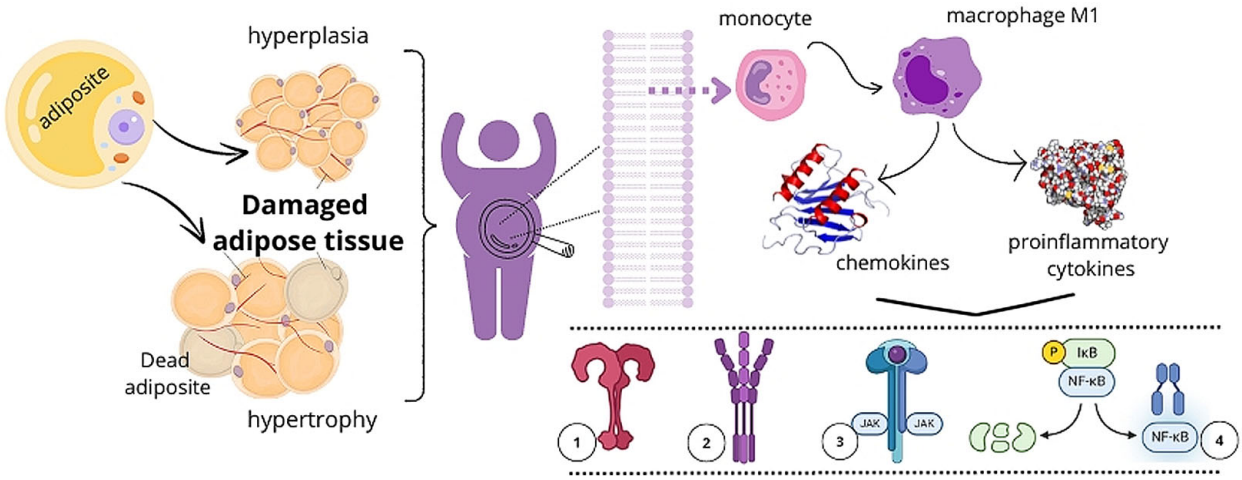


Figure 1. Recruitment of M1 macrophages by damaged fatty tissue. The figure shows the expression of high levels of proinflammatory receptors ((1) Toll-like receptors, (2) tumor necrosis factor receptors, (3) interleukin-1 receptor, and (4) activation of nuclear factor κβ (NF-κβ) transcription factors) for proinflammatory molecules leading to acute or chronic inflammation.

In addition, excess lipids that are not stored in adipose tissue are deposited in other organs (such as the liver, skeletal muscle, and blood vessels). This chronic condition can establish a vicious circle characterized by increased central adiposity, intrahepatic fat accumulation, vascular inflammation, impaired endothelial function with cardiovascular sequelae, alterations in the central nervous system (CNS), and disorders in various organs and tissues [13].

On the other hand, the intestinal microbiota responds to dietary patterns and macronutrients; for example, the presence of certain foods induces changes in bacterial diversity by the abundance of *Bacteroides* and phylum *Firmicutes* (microorganisms beneficial for the human intestinal flora), while an imbalance of these bacteria can produce health problems in the host organism induced by a dysbiosis in the intestinal flora; therefore, proper communication in the gut–brain axis is crucial for different processes, signaling pathways and neurotransmission systems [26].

In addition, Gram-negative bacteria can produce the endotoxin LPS (the main component of their cell wall). Under SCI conditions, activating the TLR signaling pathway (a group of receptors that recognize different pathogen-associated molecular patterns) can increase this endotoxin's permeability in cells. LPS can move into the systemic circulation via the uptake of dietary factors (transcellular) or tight junctions of compromised enterocytes (paracellular). Translocation of LPS into the circulation can activate proinflammatory pathways, including NF-κβ and MAPK pathways, leading to increased production of

inflammatory mediators [14]; therefore, a diet that reduces the presence of this type of bacteria in the host can reduce SCI [28].

When the intestinal microbiota imbalance persists for a prolonged period, the inflammatory state can affect other tissues and systems, potentially leading to SCI. In this sense, it is crucial to maintain a healthy balance in the intestinal flora since, depending on its composition, signals are sent that will activate various physiological mechanisms, given that the microorganisms present in the intestine send information to the brain and other systems, for example:

If *Bacteroides* predominate over *Firmicutes*, the intestine is less efficient in obtaining energy from food; however, if *Firmicutes* bacteria are in the majority, the body can absorb more calories [29].

A greater diversity in the diet may favor the availability of different nutrients in the host. As a result, the predominant strains in the digestive system will change depending on the predominant type of food, which will generate dynamic processes in the microbiota. On the other hand, it has been reported that people who consume more meat in their diets have significantly different intestinal microbiomes than those with predominantly vegetable diets due to the fact that there are certain bacteria that thrive on an abundance of protein [30]; therefore, people with a higher intake of animal protein would have a higher risk of developing SCI-related diseases.

In addition, an ethnographic study looked at the effect of diet on gut microbiota, where culture, collective enterotypes, and bioregion significantly influence the foods consumed by people [31–33], this has a significant impact on the bacterial colonies in our gut; for example:

- *Prevotella* is an enterotype and is usually associated with a high fiber intake and is sometimes seen in people who follow a vegetarian diet where plant-based foods predominate. It can also be observed in Asian populations with a high consumption of starchy foods such as rice [30].
- *Bacteroides* are an enterotype that is usually detected in those people who follow a high-protein or high-fat diet, as is the case of athletes; therefore, many foods of animal origin are consumed. A positive association with anaerobic microorganisms and specific genera, including *Bacteroides* and *Bilophila*, has been observed in Western diets, which are rich in saturated fats but low in unsaturated fats [34]. Therefore, the presence of this type of bacteria can exert alterations in the macro and micronutrients of the intestine, in addition to the fact that the additives present in the ultra-processed foods commonly found in this diet negatively alter the intestinal microbiota and enhance the processes of chronic inflammation in various diseases [35,36].
- *Ruminococcus* is one of the most common enterotypes, and its presence is related to the moderate and balanced consumption of foods of animal and vegetable origin. Therefore, there is greater diversity and microbial richness. Enterotypes of these populations are characterized by a remarkably high abundance of *Bifidobacterium*, a probiotic currently often given as a treatment to restore the intestinal flora. This genus is known for producing large amounts of starch-metabolizing enzymes [37].

Therefore, the microbiota–diet relationship is crucial to generate health processes, where a healthy diet based on the consumption of fresh, seasonal, or bioregional foods and to a lesser extent the consumption of ultra-processed foods could improve the diversity of our intestinal microbiota and in parallel reverse SCI-related diseases.

2.2. Impact and Alternatives in the Consumption of Hypercaloric or Ultra-Processed Foods

On the other hand, increased postprandial glucose, oxidative stress, and inflammatory biomarkers is a physiological process that occurs in people with diabetes, e.g., mitochondrial emission of H_2O_2 after energy substrate processing leads to a reduction in cellular

glutathione content and an increase in reactive oxygen species (ROS) generation, establishing a more oxidized redox state; as a result, transcription factors, such as NF-κβ, are activated to induce proinflammatory genes and subsequent positive regulation of proinflammatory cytokines (such as various interleukins (IL), TNF-α and IFN-γ), chemokines (such as MCP-1, IL-18, RANTES, MIP-2, CXCL1, and CXCL10), expression of COX-2, and inducible nitric oxide synthase [12].

In hypercaloric states, the high consumption of ultra-processed foods or diseases such as diabetes can lead to SCI processes in which glucose intake induces increased activity of the significant proinflammatory transcription factor, NF-κβ, and reduced expression of Ikβα, its inhibitor. This translates into increased expression of TNF-α (a proinflammatory cytokine), monocyte chemotactic protein-1, and intercellular adhesion molecule-1, in this sense, leads to a manifestation of inflammation. However, when there is an isocaloric intake of lipids, proteins, and glucose, some differences between macronutrients can be observed, with proteins being the least effective in inducing oxidative stress and fats inducing the highest ROS response [38].

Elevated plasma concentrations of inflammatory mediators significantly increase the risk of atherosclerotic complications related to cardiovascular diseases. In contrast to the proinflammatory effects of high-fat, high-calorie (HFHC) meals, the intake of equicaloric meals rich in fruits and fiber does not induce an increase in ROS generation or inflammation at the cellular and molecular levels [38], thus reducing the risk of developing SCI-related diseases.

Therefore, HFHC meals are essential in the biological substrate and pathogenesis of the proinflammatory states of insulin resistance, obesity, and type 2 diabetes, as they predispose to visceral adiposity and intrahepatic fat accumulation, creating the environment for inflammation, which leads to insulin resistance, as well as intrahepatic fat accumulation; this correlates with the metabolic disorders associated with obesity compared to visceral adiposity. In contrast, fiber-rich meals exert anti-inflammatory effects that can significantly suppress the inflammation caused by HFHC meals when compared to these meals. Moreover, central adiposity increases with age, so alternatives such as a healthy diet with adequate macronutrient composition, caloric restriction, and increased physical activity should be found [38].

Diets rich in polyphenols, flavonoids, and phytoestrogens (abundant in various fruits, vegetables, and legumes) are anti-inflammatory and potentially anti-atherogenic [39–41]. For example, orange juice contains two major flavonoids, naringenin, and hesperidin, which contribute to its ability to inhibit ROS generation, NF-κβ binding, proinflammatory cytokine expression, endotoxemia, and TLR-4 expression induced by an HFHC meal [42,43].

Furthermore, it was comprehensively demonstrated that adding fiber to the HFHC meal prevents oxidative stress, reduces chronic inflammation, promotes post-meal insulinogenesis, and reduces glycemic rise. Dietary fiber also reduces endotoxemia and the induction of TLR-4 and TLR-2, the receptors for endotoxins and Gram-positive bacterial products. Fiber induces reductions in the expression of proinflammatory cytokines, such as TNF-α and IL-1β, which significantly increase after an HFHC meal. While TNF-α interferes with insulin signaling, IL-1β is toxic to β-cells. Thus, this demonstrates the critical role of dietary modifications in reversing these processes and preventing SCI-related diseases such as type 2 diabetes. Therefore, energy-dense foods should be replaced by fiber-rich foods, such as fruits, vegetables, legumes, whole grains, etc. The benefits of fiber-rich foods have been demonstrated in addition to preventing type 2 diabetes and atherosclerosis [44].

Notably, increased secretion of inflammatory mediators by macrophages and T-cells, such as IL-6, is mediated by hepatocyte stimulation and C-reactive protein (CRP) release. This acute-phase protein is beneficial for detecting acute tissue injury when expressed at

high concentrations (i.e., greater than 10.0 mg/L). Still, it has recently been considered a marker of subclinical chronic inflammation when measured at minor variations or minimal levels (i.e., high-sensitivity CRP). In addition, it is worth noting that there are now some new markers for SCI such as the soluble urokinase plasminogen activator receptor (suPAR), which has been shown to be a better marker than IL-6 and CRP for SCI [45]. In this regard, an increase in high-sensitivity CRP and inflammatory biomarkers has been detected in the consumption of ultra-processed foods, which correlated with the presence of SCI-related diseases [46]. The circulating level of CRP has also been considered a risk factor for developing cardiovascular disease and is associated with an increased risk of certain cancers and neurodegenerative disorders. CRP exerts proinflammatory effects on several cell lines, including endothelial cells, leukocytes, and platelets, by activating various signaling pathways [13]. However, consuming fiber, carotenoids, flavonoids, fruits, vegetables, legumes, and cereals has been shown to exert anti-inflammatory effects and inhibit the production of CRP and systemic markers of chronic inflammation compared to Western, North American, and Northern European dietary patterns [47].

On the other hand, as previously mentioned, when there is a diet rich in fats and sugars, in addition to the presence of an unbalanced intestinal flora, several chronic degenerative diseases, gastrointestinal pathologies, and cancer can develop; these conditions are related to inflammation and the activation of the signaling pathway of the receptor SphK/S1P/S1PR [48]. For example, inflammatory gastrointestinal diseases are associated with increased cancer-related morbidity and mortality, where gastrointestinal tumors and inflammatory cells contain activated sphingolipid-metabolizing enzymes, including sphingosine kinase 1 (SphK1) y SphK2, generating sphingosine-1-phosphate (S1P), a highly bioactive compound, which is linked to many inflammatory responses, including lymphocyte trafficking, that are driven by circulating S1P, present in high concentrations in both plasma and lymph of cancer patients. Overexpression and activation of SphK1 facilitate the development and progression of esophageal, gastric, and colon cancers. The SphK/S1P axis is a mediator of inflammation in the tumor microenvironment and has recently been defined as a target for the treatment of gastrointestinal diseases, including inflammatory bowel disease and colitis, as several SphK1 inhibitors and S1PR antagonists have been developed and proposed as novel anti-inflammatory and anticancer agents [48], in this sense, an adequate diet is essential to avoid these mediators and signaling pathways that develop SCI processes.

3. Exercise's Anti-Inflammatory Benefits in Several Systemic Chronic Inflammation-Related Illnesses or Conditions

It is widely acknowledged that physical activity is crucial for maintaining and enhancing health. Physical inactivity initiates a vicious cycle of inflammation. Evidence supports that exercise may improve health status in chronic degenerative diseases [49]. Furthermore, physical activity is fundamental in preventing at least 35 chronic conditions [50]. Exercise can function as a preventive measure for various diseases, including psychiatric, neurological, metabolic, cardiovascular, pulmonary, and musculoskeletal disorders, as well as certain types of cancer, all of which are characterized by an SCI state. Regular physical activity reduces the risk of chronic diseases, partly due to its anti-inflammatory effects. These effects may be mediated by a reduction in visceral fat mass, leading to decreased adipokine release and the creation of an anti-inflammatory environment with each about of exercise [51].

The impact of exercise on SCI is influenced by the type, intensity, and duration of exercise training, as well as individual or tissue-specific differences [52]. Regular moderate-intensity physical activity can foster an anti-inflammatory state, whereas high-intensity

physical activity or competition has been shown to activate the inflammatory response [53]. Increasing evidence from animal and clinical studies suggests that structured and appropriate exercise can induce an anti-inflammatory phenotype [54].

Exercise induces anti-inflammatory effects with each session, reducing the SCI pattern; for example, it has been observed that IL-6 is released exponentially from muscle into the bloodstream during exercise. In contrast to the cytokine response triggered by an infection, exercise leads to an increase in IL-6 without a preceding increase in TNF-α and IL-1β [55]. The following sections will delve into the relationship between exercise and non-communicable diseases.

3.1. Abdominal Adiposity and Visceral Fat

Abdominal adiposity is linked to cardiovascular diseases, type 2 diabetes, dementia, colon cancer, and breast cancer [56]. Both increased abdominal adiposity and physical inactivity have adverse health consequences; however, physical inactivity is not always related to obesity, as it can be a consequence of chronic fatigue or trauma, without generating the side effects caused by abdominal adiposity. Low fitness and physical inactivity are associated with higher visceral fat, independent of body mass index [57,58]. Actually, it is discussed if the effect of exercise training protects against abdominal adiposity is mediated by IL-15 [59]. In mice, overexpression of IL-15 offers protection against visceral fat accumulation [60]. Muscle mass also protects against abdominal adiposity, with myokines such as IL-4, IL-6, IL-7, IL-15, and myostatin playing roles in muscle growth and maintenance [61]. Visceral fat accumulation activates inflammatory pathways, promoting insulin resistance, atherosclerosis, and neurodegeneration [62], contributing to various chronic diseases associated with SCI and physical inactivity. Physical training reduces visceral adipose tissue and lowers the risk of developing SCI [63–65].

3.2. Type 2 Diabetes

Evidence suggests that SCI is pivotal in the pathogenesis and progression of type 2 diabetes mellitus (T2DM) [66,67]. A meta-analysis reports that increased physical exercise significantly improves glucose control in individuals with type 2 diabetes, with an average reduction in hemoglobin A1C ranging from 0.4% to 0.6% [68]. In addition, elevated IL-1β levels contribute to β-cell damage [69], while TNF-α is critical in mediating insulin resistance [70]. Exercise may enhance insulin sensitivity, in part, by inhibiting TNF-α. Furthermore, exercise-induced upregulation of circulating interleukin-1 receptor antagonist (IL-1RA) may confer protection against IL-1β-induced β-cell cytotoxicity [62]. On the other hand, gastric emptying is a crucial regulator of postprandial glucose levels, and delayed gastric emptying is an essential mechanism by which short-acting glucagon-like peptide-1 (GLP-1) analogs improve glycemic control in clinical practice. In this context, preclinical research in mice revealed that exercise-induced IL-6 promotes the secretion of GLP-1 from both intestinal L cells and pancreatic β-cells (and pancreatic alpha cells), leading to increased insulin secretion [71]. Lang Lehrskov et al. [72] showed that increased IL-6 concentrations under exercise, delayed gastric emptying, and reduced postprandial glycemia.

Finally, a recent meta-analysis by Papagianni et al. [73] demonstrated that exercise training significantly improves inflammatory markers and adipokines in patients with T2DM. The study showed reductions in SCI due to a decrease in CRP, resistin, IL-6, and TNF-α, alongside improved glycemic control.

3.3. Cardiovascular Disease

Studies have demonstrated that a lack of IL-6 facilitates atherosclerosis, whereas it is promoted by TNF-α, indicating the role that SCI mechanisms play in these circumstances [63]. Elevated levels of TNF-α lead to increased triglyceride levels, increased

synthesis of light-density lipoprotein, and reduced levels of high-density lipoprotein [74]. It has been suggested that TNF-α may also induce endothelial dysfunction and subsequent atherosclerosis [75]. TNF-α blockers and exercise appear to prevent intima-media thickness progression in patients with inflammatory arthritis [76]. Finally, certain cardiovascular risk factors have been linked to the increased production of ROS or reduced plasma glutathione levels, leading to oxidative damage implicated in chronic inflammation [77], which exercise reverses.

3.4. Oxidative Stress

An increase in the systemic inflammatory state, which is mainly mediated by an increase in oxidative stress and a deterioration in antioxidant defense, is associated with an increase in the production of ROS, such as superoxide anion radicals ($O_2 \cdot^-$), hydroxyl radical (·OH), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$) [78]. This cascade activates nuclear transcription factors sensitive to redox status, notably NF-κβ, resulting in the upregulation of proinflammatory cytokines like TNF-α and IL-1β [79], which causes deregulating inflammatory responses under certain disease states.

It is well known that acute exercise generates ROS [80]; however, strong evidence shows that regular exercise upregulates endogenous antioxidants in muscles [81], but also in other tissues or organs such as the brain, liver, heart, blood, kidney, and stomach vessels [82]. Exercise training decreases oxidative stress by augmenting antioxidant defenses consisting of enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and nonenzymatic antioxidants, including glutathione [83].

3.5. Anti-Inflammatory Effects of Physical Activity and Exercise in Depression

Major depressive disorder (MDD) is classified as an affective disorder, characterized by one or more depressive episodes due to physiological changes in brain structure and function [84], the above is related to a systemic substrate, both internal and external (social, environmental, lifestyle, etc.) that converge in its physiopathology. The latter hypothesis places the role of glial cells and the associated presence of chronic neuroinflammation at the center of MDD pathogenesis. Clinical data showed that levels of the peripheral and CNS proinflammatory markers CRP, TNF-α, and IL-6 are significantly increased in MDD patients compared to healthy controls [85,86].

A study Agudelo et al. [87] revealed that enhancement of the skeletal muscle peroxisome proliferator-activated receptor gamma coactivator (PGC-1) by exercise training protected mice from stress-induced depression in an inflammation-dependent manner. It has been proposed that enhanced expression of PGC-1 following exercise significantly reduces depressive behaviors and hippocampal expression of MCP-1 (monocyte chemoattractant protein-1), TNF-α, IL-1, and IL-6 [88]. Furthermore, a study found that exercise-induced improvements in the symptoms of depression correlated with a significant decline in serum concentration of IL-1 [89]. This suggests that circulating IL-1 might serve as a potential biomarker for MDD, with a decrease in IL-1 indicative of MDD improvement and a reduction in the SCI. Several other clinical investigations have underscored the high efficacy of exercise in alleviating clinical symptoms and reducing the recurrence rate of MDD episodes [90–92], which tells us that an exercise-induced reduction in SCI plays a vital role in preventing the pathophysiology of MDD.

3.6. Alzheimer

Scientific literature has demonstrated inflammatory responses accompanied by the activation of immune cells in the brains of early clinical AD (Alzheimer's disease) patients and postmortem pathological tissues, as well as animal models of AD (such as APP/PS1, TLR4M, CRND8 transgenic mouse models, among others) [93].

Studies on naturally aging animals and healthy people of different ages found that lifelong exercise can effectively alleviate SCI by inhibiting proinflammatory factors and increasing anti-inflammatory factors [94,95]. The anti-inflammatory properties of exercise can suppress AD's inflammatory state and ameliorate AD's pathophysiological characteristics [96]. A study conducted with senescent individuals with an average age of 71 years revealed a three-fold decrease in the number of proinflammatory monocytes CD14 and CD16 in the blood after leg and chest resistance training [97]. In addition, prolonged exercise can also affect the number of different T cells, including regulatory T cells, that influence the immune system [98]. Therefore, exercise may be one of the crucial ways to regulate immune and inflammatory responses under an advanced age state, which is characteristic of AD, in addition to reducing SCI in patients with AD.

4. Effects of Meditation on Systemic Chronic Inflammation

Historically, meditation has been considered the heart of Eastern and Buddhist practices, it is linked to specific qualities of consciousness and awareness that can be cultivated and strengthened through continuous practice. It focuses on training attention to increase awareness and achieve a relationship with mental processes, thinking [99], relationship with the body, breathing, and the suspension of prejudices [100], among other methods, which depend on the type of meditation and times since there is an extensive repertoire to perform this practice. Meditation has not only been shown to contribute to improving mental and physiological health but also facilitates the deep understanding of nature and the processes of personal identity and, in a parallel way, cultivates psychological processes. Meditation explores what we perceive, being aware of our actions, emotions, feelings, ideas, and images in the present [101,102].

In Western culture, meditation (mindfulness) is often interpreted as a psychological practice, commonly described as the ability to intentionally self-regulate attention in the present moment. However, it is detached from its philosophical and cultural roots [100]. Some practices include concentration, relaxation, induction of altered states of consciousness, suspension of logical thinking, and maintaining an attitude of self-observation. In addition, meditation has been conceptualized as an activity that promotes constant attention and the expansion of self-awareness, favoring a greater sense of personal and collective integration and cohesion [103].

Various methodologies have been developed to promote the practice of meditation and explore its benefits for human health and well-being. One of the most recognized programs in this field was created in the 1970s. It is a stress reduction program based on secularized teachings derived from various historical meditation traditions, especially Eastern humanistic contemplative traditions [104]. It should be clarified that the teachings focus on being accessible and relevant in contemporary contexts without adherence to any specific religious affiliation.

Numerous scientific investigations have been conducted to support the benefits of meditation-centered practices, demonstrating their ability to heal and alleviate the effects of stress and anxiety, improve mood, increase motivation, and promote the overall well-being of individuals. In sum, meditation and other techniques, such as breath regulation, have the potential to increase altruistic traits in humans, such as empathy and self-transcendence [105,106]. Rojas-Gómez et al. [107] mentioned that studies conducted by several renowned universities, including the University of Madison, Princeton, Harvard, and Berkeley, have reported that meditation increases brain neuroplasticity, generating well-being levels, attention capacity, cognitive improvement, and strengthening of the immune system.

The benefits of meditation for the health and coherence of the organism appear to be similar in magnitude to those achieved by other conventional methods (psychoactive medications, psychotherapy, health education, and behavior modification) used to treat stress, pain, and various illnesses. Explorations have been conducted with meditation in patients with chronic pain, fibromyalgia, cancer, anxiety disorders, and major depression, as well as in contexts such as medical schools and prison settings [108–110], which was related to improved quality of life for participants.

Currently, there is a growing interest in the effects of meditation on chronic diseases and psychophysiological factors, mainly in diseases such as acquired immunodeficiency syndrome (AIDS), multiple sclerosis, cardiovascular diseases, fatigue states, sleep disturbances, and stress [110]. Thus, meditation has been shown to reduce symptoms in various chronic degenerative diseases, as well as to exert an effect on inflammatory markers in the body and their gene expression, for example, in cytosines, chemokines, and CRP, which play a crucial role as extracellular messengers during the immune response [109,111].

A relative reduction in IL-6 levels after meditation has been observed in patients with breast cancer. Meanwhile, in patients presenting with ulcerative colitis, a decrease in IL-10 and increased antibody production was observed [109,112] by performing eight weeks of meditation and aerobic exercise. Thus, in both cases, meditation is shown to reduce the degree of inflammation under these conditions.

On the other hand, a study was conducted on participants who underwent image of magnetic resonance scans before and after completing an eight-week meditation program. The results showed increased gray matter density (neuronal somas) in regions linked to self-awareness and compassion, such as the hippocampus (area related to learning and memory), posterior cingulate cortex, and the cerebellum; structures that are also linked to the synthesis and release of neurotransmitters, which are essential in mediating inflammation. In addition, a decrease in gray matter density was observed in the amygdala (a structure related to fear, anxiety, stress, and the induction of oxidative stress), which correlated with stress reduction in the participants. These changes were not observed in the group that did not perform the meditations, indicating that they were not simply attributable to the passage of time but that evidence suggests that changes in brain structure and function associated with meditation may underlie the reduction in symptoms of anxiety and depression (conditions characterized by neuroinflammation), as well as, contribute to the observed benefits in emotional regulation, attention, and memory [113,114].

In addition, neurodegenerative diseases such as AD and frontotemporal dementia are characterized by gray matter loss, where this loss is related to the presence of SCI [93]; therefore, performing meditation practices could ameliorate the pathophysiological characteristics of AD by restoration of gray matter in oxidative stress inhibition promoting structures [96,113,115], which, could be related to the reduction in SCI by induction of meditation practice [96,109,112].

On the other hand, when studying DNA it has been observed that telomeres tend to shorten with aging and this has been associated with the presence of diseases such as hypertension, atherosclerosis, diabetes mellitus type 2, cancer, cardiovascular diseases, cognitive impairment and dementia; diseases closely linked to SCI, but people who practice meditation constantly tend to maintain a percentage of longer telomeres compared to people who do not practice it. It should be clarified that longer telomeres are associated with increased longevity, reduced oxidative stress and therefore this could be related to a reduction in SCI [106,116,117]. In addition, meditation has been associated with improved mental health, decreased ROS, and reduced stress, which could contribute to the prevention of cellular aging [116] and therefore to the reduction in SCI.

A study carried out by Black and Slavich [109] examined the effect of meditation on several immunological parameters, including the production of inflammatory proteins, cytokines, and other markers related to the immune response; tentative evidence was found suggesting that meditation may modulate some of these parameters, which favors a healthier immune profile. Specifically, a reduction in the proinflammatory pathway and protection against cellular aging were observed.

Bushell et al. [118] stressed the importance of understanding the inflammatory state of an organism in the face of an infection or the presence of a virus, such as SARS-CoV-2, where SCI is a crucial factor in the development of serious complications due to this coronavirus. In this sense, meditation, yoga, and pranayama practices have been shown to be a complementary treatment that exerts anti-inflammatory effects and reduces the activity of proinflammatory cytokines. Therefore, these practices have the potential to modulate the inflammatory response of the organism improving the quality of life of people going through an SCI-related illness.

The study by Dada et al. [106] provides significant evidence of the therapeutic effect of meditation in glaucoma disease, observing at the physiological level an increase in antioxidant capacity, reduction in intraocular pressure, and reduction in proinflammatory biomarkers (IL-6, TNF-α, and ROS). In addition to the physiological effects described above, meditation was also associated with an improvement in the overall well-being of the participants.

The above information tells us about the implications of meditation on mental and physiological health, which provide a precedent to address new integrative approaches for various diseases related to SCI, which guides us towards new avenues that have been rarely explored and have gained scientific relevance at present.

5. Conclusions

The accumulated background data shows that SCI is a state resulting from chronic physiological stimulation of the immune system caused by conditions both external (epigenetic, e.g., low physical activity and consumption of hyperpalatable processed foods high in fat, sugar, salt and flavor additives) and internal to an organism. This generates important changes in cellular metabolism, as well as in the molecular mechanisms underlying inflammatory processes, but if this process is sustained over a long period, it can lead to the development of chronic degenerative diseases and their progression, which are present in the world with a high mortality rate. In this sense, the present work shows evidence of how meditation, a healthy diet (consumption of fresh, seasonal, or bioregional foods and to a lesser extent the consumption of ultra-processed foods) and exercise [119–123], can restore the functionality of the inflammatory process under SCI, and thus improve the quality of life of individuals and in some cases reverse symptomatology. Finally, the impact of this paper is promising for biomedical and public health research projects that seek to address inflammation in a systematic way and not from a reductionist viewpoint [124], so that the systemic approaches we propose can restore the operability of the inflammatory process and reduce SCI.

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