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REVIEW ARTICLE

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Major evidence of nutrological regulation in obese patients with meta-inflammation: a systematic review

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Abstract

Introduction: Obesity stands out as a multifactorial disease that can cause several public health problems. There are 2.0 billion overweight and obese people in the world, and Brazil ranks fifth in the world. A healthy nutritional status promotes immune function and can prevent the onset of a serious inflammatory process and severe infections, especially in times of a pandemic such as COVID-19. **Objective:** It was to highlight the main clinical considerations of nutrological and dietary regulation in obese patients with marked inflammatory processes and meta-inflammation through a systematic review. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from August to September 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 127 articles were found. A total of 74 articles were fully evaluated and 29 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 32 studies at high risk of bias and 25 studies that did not meet the GRADE. Research has shown that unbalanced dietary patterns, such as the Western diet, rich in simple sugars, refined carbohydrates, and saturated and trans fatty acids, lead to chronic inflammatory responses, increased fat deposits, and future comorbidities associated with overweight and obesity. Caloric restriction decreased polymerase chain reaction (PCR) in obese patients and diet administration over 12 weeks had a beneficial effect. Furthermore, obese patients with antioxidant supplementation had lower values of BMI, waist circumference, fasting blood glucose level, and insulin resistance homeostasis model assessment when compared to the placebo group, as well as lower total cholesterol levels, triglycerides, LDL, malondialdehyde and tumor necrosis factor-alpha. Supplementation of n-3 PUFA can significantly reduce serum PCR, tumor necrosis factor α (TNFα), and interleukin 6 (IL-6) concentrations.

Keywords: Obesity. Inflammatory processes. Meta-inflammation. Dietary therapy. nutritional regulation.

Introduction

Obesity stands out as a multifactorial disease that can cause several public health problems **[1]**. Currently, more than 30% of the world's population is overweight or obese. By 2020, it is estimated that more than 60% of the world population will be overweight or obese **[1]**. In the current scenario, there are 2.0 billion overweight and obese people in the world, and Brazil is in fifth place in the world ranking, with an estimated 18.0 million people **[3]**. In the United States, the prevalence of obesity is greater than 30.0% for both sexes, and obesity is the cause of death of 2.8 million people per year, affecting 26% of adults **[4]**. In Europe, it is estimated that 10 to 20 % of men and 15 to 25 % of women are obese **[5]**.

In this context, concerning the cause of obesity,

there is a complex relationship between biological, psychosocial, and behavioral factors, including genetic composition, socioeconomic status, and cultural influences **[6]**. Furthermore, obesity has been associated with microorganisms, epigenetics, increased maternal age, greater fecundity, lack of sleep, endocrine disruptors, pharmaceutical iatrogenesis, and intrauterine and intergenerational effects **[6,7]**. Comorbid conditions and their treatments may also be a factor in the development of obesity **[8]**.

In this regard, it has been postulated that a healthy nutritional status promotes immune function and can prevent the onset of a severe inflammatory process and severe infections, especially in times of a pandemic such as COVID-19 **[9-12]**. Thus, the optimal immune response depends on an adequate diet and nutrition to keep the infection under control. As an example, sufficient protein intake is crucial for optimal antibody production. Furthermore, a low level of micronutrients, such as vitamin A or zinc, is associated with an increased risk of infection, as this deficiency promotes inflammatory processes and oxidative stress. Furthermore, dietary constituents with anti-inflammatory and antioxidant actions are highlighted by vitamin C, vitamin E, carotenoids, and polyphenols **[13]**.

Thus, several of these dietary elements can interact with transcription factors, such as NF-kB and Nrf-2. An important example is vitamin D, which protects tissue against viral cellular infection through angiotensin-converting enzyme 2 (ACE2). Dietary fiber and short-chain fatty acids have also shown anti-inflammatory effects **[13]**.

Therefore, this study highlighted the main clinical considerations of nutrological and dietary regulation in obese patients with marked inflammatory processes and meta-inflammation through a systematic review.

Methods

Study Design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*Obesity. Inflammatory processes. Meta-inflammation. Dietary therapy. Nutritional regulation*". The research was carried out from August to September 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality and Risk of Bias

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

Results and discussion

Summary of Literary Findings

A total of 127 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 74 articles. A total of 42 articles were fully evaluated and 29 were included and developed in the present systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 32 studies at high risk of bias and 25 studies that did not meet the GRADE.

Figure 1. Flowchart showing the article selection process.

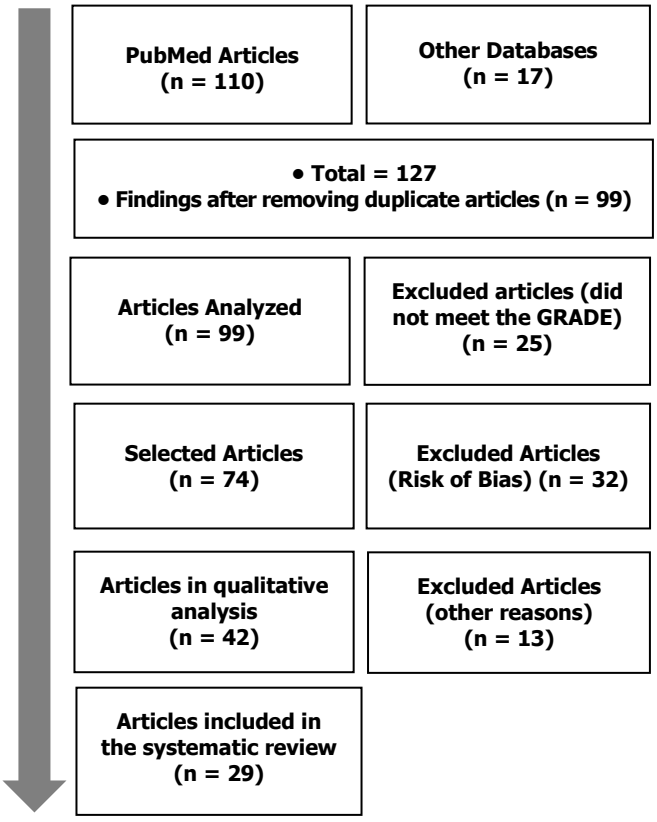
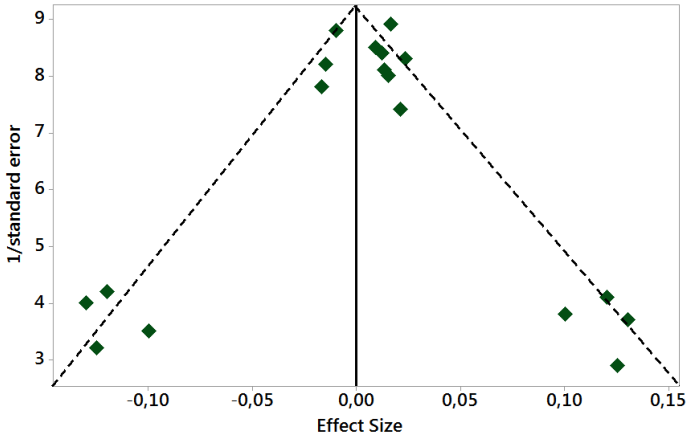


Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the

difference) using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are presented in the upper region.

Figure 2. The symmetrical funnel plot suggests no risk of bias between the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (Ntotal=29 studies evaluated in full in the systematic review).



In the obesity scenario, the circulating level of cytokines and acute phase proteins associated with inflammation is elevated. Adipocytes secrete several cytokines and acute-phase proteins that increase the production and circulation of inflammation-related factors. The inflammatory process may be due to resistance to insulin action and other disorders associated with obesity, such as hyperlipidemia and metabolic syndrome **[14,15]**.

There are three possibilities, the first reflects the production and release from organs other than adipose, mainly the liver and immune cells. The second explanation is that white adipose tissue secretes factors that stimulate the production of inflammatory markers by the liver and other organs. The third possibility is that the adipocytes themselves are an immediate source of some or several, of these inflammatory markers **[16-18]**.

In this context, it can be highlighted that the adipokines related to inflammatory processes are interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, and adiponectin **[17]**. Some studies have shown low concentrations of the anti-inflammatory adipokine (adiponectin) associated with the occurrence of several types of cancer and high concentrations with the inhibition of tumor growth. There are also others such as TNF-α, IL-6, IL-1, CC-chemokine ligand 2 (CCL2), a visceral adipose-tissue-derived serine protease inhibitor (vaspin), and retinol-binding protein 4 (RBP4) **[17]**.

In this aspect, adipokines have a great impact on various bodily functions. In this case, control of food intake and energy balance, immune system, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, and body homeostasis, situations strongly correlated with cardiovascular disease **[15]**. Furthermore, high plasma concentrations of adiponectin are associated with a reduced risk of myocardial infarction in men **[15]**.

In this context, obesity induces a change in the macrophage profile, with an increase in the M1 (pro-inflammatory) phenotype. This effect corresponds to an upregulation of inflammatory genes, and a downregulation of anti-inflammatory genes **[19,20]**. Furthermore, the primary increase in the inflammatory response in obese patients works as a predictor for the hyperinflammatory state observed in COVID-19. Therefore, this primary increase can be amplified by SARS-CoV-2 infection, increasing the production of cytokines such as TNF-α, IL-1, and IL-6 **[21]**.

As a corollary of this, meta-inflammation describes the junction of inflammation with the metabolic changes that occur in the body of obese patients **[5]**. Several toxic mediators that contribute to the inflammatory state and tissue damage are present in obesity, such as free fatty acids (FFA), toxic lipid derivatives, such as diacylglycerol, toxic nitric oxide metabolites, and inflammatory mediators, such as protein Reactive C, cytokines, chemokines, macrophages and TNF-α.

The imbalance in inflammatory mediators induced by excess nutrients is the basis of meta-inflammation in obesity. Obesity can cause dysfunction of multiple organs and meta-inflammation leads to myocardial dysfunction by direct damage to inflammatory mediators, as well as by dysfunction of other organs **[7]**.

In this scenario, obese patients stand out among the young population that progresses to the severe form of COVID-19. The unfavorable evolution is possible because these patients have a more inflamed and hyperreactive endothelium, which, under the stimulus of SARS-CoV-2, presents an excessive response, responsible for the hyperinflammation with cytokine storm. As a corollary to the exacerbated inflammatory process, the coagulation cascade is deregulated, causing hypercoagulability. Therefore, endothelial dysfunction caused by SARS-CoV-2 justifies why patients with blood vessel-related comorbidities such as cardiovascular disease, hypertension, diabetes, and

obesity are more likely to develop severe COVID-19, even death [21].

This was also reported in a multicenter study involving 5,700 patients hospitalized in the New York metropolitan area. Obesity has been described as the second most frequent comorbidity, being present in about 40% of patients with COVID-19. During the hospitalization of the 2634 patients, 14.2% were treated in the intensive care unit (ICU) and 12.2% received invasive mechanical ventilation. Mortality for those who required mechanical ventilation was 88.1% [22].

Still, other authors observed the relationship between obesity and the development of severe respiratory manifestations when analyzing 103 hospitalized patients with COVID-19. They reported that 47% of these patients were obese. In that study, patients with a BMI of 30 kg/m2 or more were among the most in need of ICU admission and mechanical ventilation [23].

Nutritional Regulation of Meta-Inflammation

Nutritional status can have a significant impact on an individual's overall health, reducing comorbidities, and reducing susceptibility to developing infections such as COVID-19. However, according to the WHO, there is still no single food or natural remedy with proven scientific evidence that prevents COVID-19 infections [24]. Nevertheless, based on previous studies, nutritional status is known to play a significant role in patient outcomes [25]. Therefore, it is necessary to follow a diet characterized by anti-inflammatory properties to benefit or prevent COVID-19 [26-29].

In this sense, evidence suggests that dietary patterns and individual nutrients can influence systemic markers of immune functions. Thus, maintaining nutritional status at this time is significant, given that the fight against COVID-19 can last a long time. Yet, to maintain a healthy immune system, special attention should be paid to maintaining a healthy diet, lifestyle, and exercise regimen [30].

Still in this scenario, there are nutritional deficiencies of calcium, vitamin C, vitamin D, folate, and zinc among elderly populations [31], making them immunosuppressed [32]. Thus, a healthy and balanced diet can provide the macro and micronutrients, prebiotics, probiotics, and symbiotics needed in the elderly that can restore and maintain immune cell function [33].

In this context, a review study analyzed the usefulness of early micronutrient intervention, focusing on zinc, selenium, and vitamin D, to alleviate the rise of COVID-19. The results revealed that there is direct evidence of the associations between zinc, selenium, and vitamin D and COVID-19. An adequate supply of zinc, selenium, and vitamin D is essential for resistance to other viral infections, immune function, and reduction of inflammation [34].

In this scenario of nutritional triggers to favor immune strengthening responses, as well as improving the performance of mitosis, meiosis, and all cellular functioning, all this functioning is directly integrated with the energy balance and nutritional status of the body. The metabolic by-products and substrates that regulate epigenetically and signaling pathways are considered to have an instructive, rather than an observer, role in regulating cell fate decisions. Metabolism encompasses the interactions between diet, the microbiome, and the cellular enzymatic processes that generate the chemical pathways necessary to sustain life. Furthermore, endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter the fate of the cell by controlling chromatin accessibility and downstream gene expression patterns. Thus, most substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways such as the tricarboxylic acid cycle, methionine cycle, folate cycle, glycolysis, β-oxidation and the hexosamine pathway [35].

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact the cellular state by modulating signaling pathway activity. A clear example is through the mechanistic targeting signaling pathway of rapamycin (mTOR) and, in particular, the mTOR 1 complex (mTORC1), which regulates cell growth only when nutrients and growth factors are present. Depletion of specific nutrients, including arginine, leucine, and S-adenosyl methionine, prevents growth factor-induced mTORC1 activation, blocking Rag GTPase-mediated recruitment of mTORC1 to the lysosome where it can be activated by Rheb GTPase [36].

Another way nutrients are detected to impact cellular state is through AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance and in the process regulate cell growth. and autophagy. Furthermore, transcription factors can be directly regulated by metabolites. Tryptophan kynurenine is an endogenous agonist for the aryl hydrocarbon receptor and alpha-ketoglutarate (α-KG) that binds to and activates IKKβ and initiates NF-κβ signaling [35].

Also, nutrological health acts directly on the human

gut microbiota, impacting metabolism and the immune system for tissue regeneration. Recent findings on the role of the "nutrological microbiota" in mechanisms involved in tissue regeneration, in particular skin, liver, bone, and nervous system regeneration **[36]**.

In this aspect, in the inflammatory phase, vitamin A increases the release of cytokines, bromelain, and amino acids to prevent prolonged inflammatory events, and vitamin C increases neutrophil migration and lymphocyte activation. In the proliferative phase, vitamin C is necessary for collagen synthesis, glucosamine increases the production of hyaluronic acid. Vitamin A promotes the differentiation of epithelial cells. Zinc is necessary for DNA and protein synthesis and cell division. In the remodeling phase, amino acids and proteins play a key role in stabilizing the wound scar **[37]**.

Finally, age-related reduced efficiency of muscle repair contributes to the development of sarcopenia. Nutrients such as amino acids, polyunsaturated fatty acids, polyphenols, and vitamin D can enhance skeletal muscle regeneration, targeting key functions of immune cells, muscle cells, or both **[38]**.

In this sense, epigenetic signaling pathways and transcription are affected by changing nutrient levels. Furthermore, the focus of the literature on stem cell metabolism is centered on central carbon metabolism and the balance between glycolysis and oxidative phosphorylation in the regulation of cell fate **[28]**.

As literary support, a double-blind, randomized, placebo-controlled clinical trial evaluated the effects of 8-week propolis supplementation (510 mg daily) on glucose homeostasis, lipid profile, liver function, anthropometric indices, and meta-inflammation in patients with non-alcoholic fatty liver disease (NAFLD). In this trial, 44 patients with NAFLD confirmed by ultrasound findings were randomly allocated to the "propolis" (n=23) or "placebo" (n=21) group together with a calorie-restricted diet group (-500 kcal d-1) for 8 weeks. Fasting serum levels of metabolic factors, liver enzymes, and inflammatory factors, as well as anthropometric indices, food intake, and appetite status, were assessed pre-and post-intervention. The hepatic fibrosis score, insulin resistance homeostasis assessment model (HOMA-IR), and quantitative insulin sensitivity verification index (QUICKI) were also calculated. Weight, body mass index (BMI), waist and hip circumferences, and waist/height ratio decreased significantly in both groups ($p<0.001$), while waist/hip ratio ($p=0.006$) and serum cholesterol level total ($p=0.038$) decreased only in the propolis arm. Fasting blood glucose ($p = 0.037$), serum insulin level ($p = 0.040$), HOMA-IR ($p = 007$), desire to eat sweets ($p = 0.005$) and NAFLD fibrosis score ($p = 0.013$) decreased significantly in the propolis group compared to the placebo group, post-intervention after adjusting for baseline values and potential confounders. However, QUICKI showed a significant increase ($p=0.015$) in the propolis arm compared to the placebo at the study endpoint. Although there were significant reductions in the serum levels of inflammatory factors, including tumor necrosis factor-α (TNF-α), toll-like receptor-4 (TLR-4), and monocyte chemotactic protein-1 (MCP-1), as well as such as liver enzymes and fatty liver severity, differences between groups were not statistically significant after adjusting for potential confounders **[39]**.

Furthermore, chronic inflammation in obese patients can be controlled through a calorie-restricted diet, characterized by a reduction in PCR. A review study based on randomized controlled trials evaluated the role of this diet in PCR. Results showed that caloric restriction decreased PCR in obese patients and diet administration over 12 weeks had a beneficial effect **[40]**.

In addition, a meta-analysis study showed heterogeneity in the beneficial effects of antioxidant supplementation in obese adults, exploring the differential effects of antioxidant supplementation on basic indicators of obesity, lipid metabolism, systemic antioxidant capacity, inflammatory biomarkers, and liver function. A total of 30 studies were included in this study with a sample of 845 obese patients in the antioxidant supplementation group and 766 obese patients in the placebo control group. The meta-analysis showed that obese patients with antioxidant supplementation had lower values of BMI, waist circumference, fasting glucose level, and insulin resistance homeostasis model assessment when compared to the placebo group. Furthermore, obese patients on antioxidant supplementation had lower levels of total cholesterol, triglycerides, LDL, malondialdehyde, and tumor necrosis factor-alpha when compared to the placebo group. In addition, obese patients with antioxidant supplementation had higher levels of HDL and superoxide dismutase when compared to the placebo group. Antioxidant supplementation did not affect other parameters analyzed, including waist-to-hip ratio, leptin, fat mass, interleukin-6, C-reactive protein, alanine transaminase, and aspartate transaminase in obese patients **[41]**.

Furthermore, a study with 32 meta-analyses demonstrated that n-3 PUFA supplementation significantly reduced serum C-reactive protein (PCR),

tumor necrosis factor α (TNFα), and interleukin 6 (IL-6) concentrations **[42]**.

Conclusion

Research has shown that unbalanced dietary patterns, such as the Western diet, rich in simple sugars, refined carbohydrates, and saturated and trans fatty acids, lead to chronic inflammatory responses, increased fat deposits, and future comorbidities associated with overweight and obesity. Caloric restriction decreased PCR in obese patients and diet administration over 12 weeks had a beneficial effect. Furthermore, obese patients with antioxidant supplementation had lower values of BMI, waist circumference, fasting blood glucose level, and insulin resistance homeostasis model assessment when compared to the placebo group, as well as lower total cholesterol levels, triglycerides, LDL, malondialdehyde and tumor necrosis factor-alpha. Supplementation of n-3 PUFA can significantly reduce serum PCR, tumor necrosis factor α (TNFα), and interleukin 6 (IL-6) concentrations.

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Ethics approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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