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REVIEW ARTICLE

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Major metabolic and metabolomic approaches of dietary therapy in the control of inflammatory obesity processes in COVID-19: a concise systematic review

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Abstract

Introduction: Obesity stands out as a multifactorial disease that can cause several public health problems. Currently, more than 30% of the world's population is overweight or obese. By 2020, it is estimated that over 60% of the world population will be overweight or obese. 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 pandemics such as COVID-19. The optimal immune response depends on proper diet and nutrition to keep the infection under control. **Objective:** This study analyzed the main interactions of dietary therapy in the control of obesity and its comorbidities, especially meta-inflammation. **Methods:** This study followed a systematic review model. The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases, using scientific articles from 2009 to 2021. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 105 studies were analyzed and submitted to eligibility analysis, and then 42 high to medium quality studies were selected. Biases did not compromise the scientific basis of the studies. Research has shown that unbalanced dietary patterns, such as the Western diet, rich in simple sugars, refined carbohydrates, saturated and trans-fatty acids, lead to chronic inflammatory responses, increased fat deposition, and future comorbidities associated with overweight and obesity. In addition, some nutrients have important effects in decreasing the inflammatory response and in metabolic restoration, reducing oxidative stress. Therefore, adequate dietary interventions for the management of overweight and obesity are needed, especially starting early in children and adolescents for healthy growth, preventing comorbidities in adulthood.

Keywords: Obesity. Inflammatory processes. Meta-inflammation. Dietary therapy. COVID-19.

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 people with overweight and obesity 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 for 2.8 million people a 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, to 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 fertility, 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 pandemic such as COVID-19 [9-12]. Thus, the optimal immune response depends on proper diet and nutrition to keep the infection under control. As an example, sufficient protein intake is crucial for optimal antibody production.

Furthermore, the 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. Also, dietary constituents with anti-inflammatory and antioxidant actions are highlighted by vitamin C, vitamin E, carotenoids, and polyphenols [13].

In this sense, 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 the angiotensin-2 converting enzyme (ACE2). Dietary fiber and short-chain fatty acids also showed anti-inflammatory effects [13].

Therefore, this systematic review study analyzed the main interactions of dietary therapy in the control of obesity and its comorbidities, mainly meta-inflammation.

Methods

Study Design

The present study followed a concise systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and meta-analysis-HTTP: //www.prisma-statement.org/).

Search Strategy and Search Sources

The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases, using scientific articles from 2009 to 2021, using the MeSH Terms (descriptors) *Obesity; Inflammatory processes; Meta-inflammation*; *Dietary therapy and COVID-19*, and using Booleans "and" between MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument.

Results

Summary of Findings

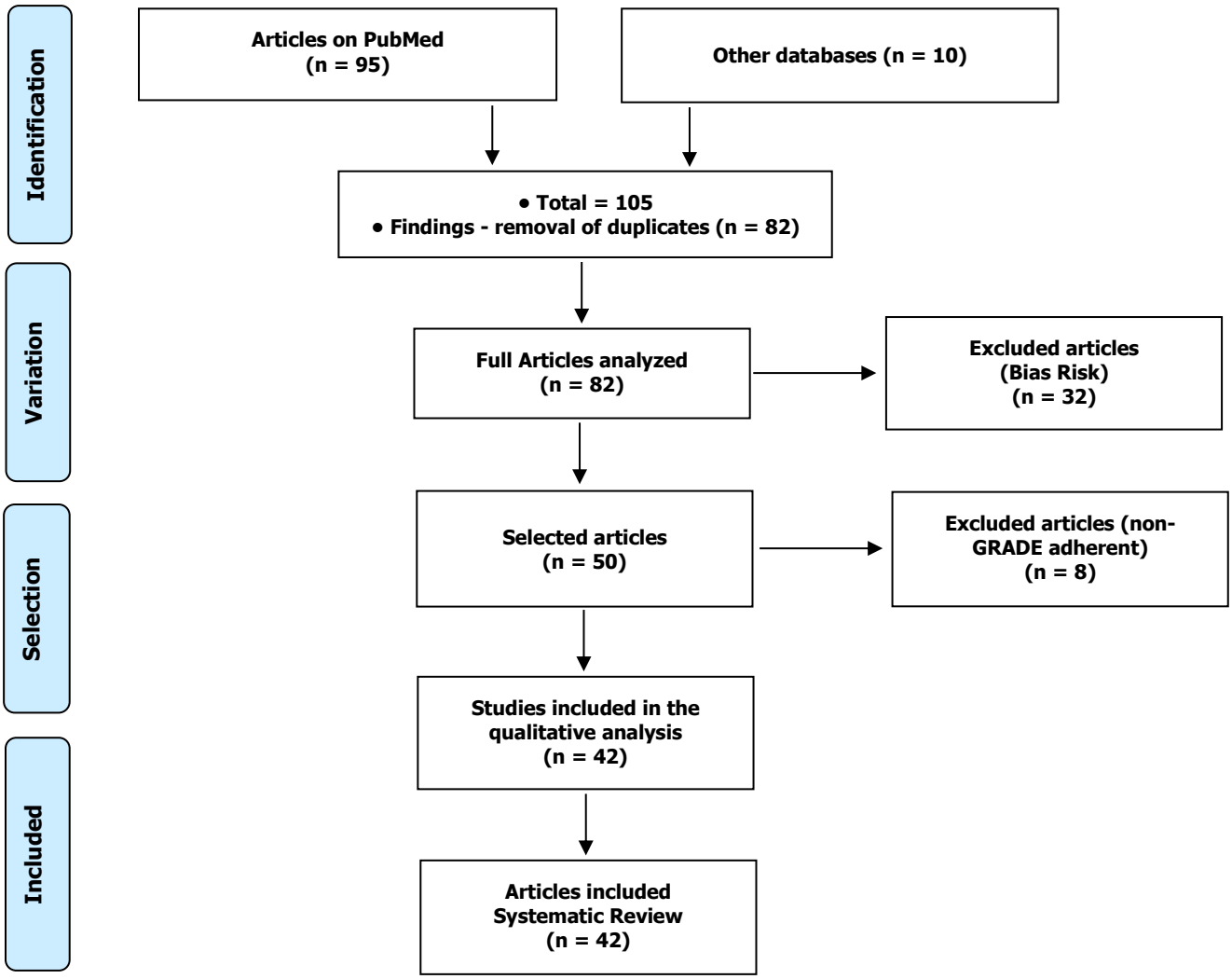
As a corollary of the literary search system, 105 studies were analyzed and submitted to eligibility analysis, and then 42 high to medium quality studies were selected (**Figure 1**), considering, in the first instance, the level of scientific evidence of studies in type of study such as meta-analysis, randomized, prospective and observational. Biases did not compromise the scientific basis of the studies.

Main Obesity Information

Worldwide, obesity is recognized as the most important non-infectious epidemic and is considered a chronic, serious and multifactorial disease. Overweight and obesity are already seen from the age of five onwards, in all income groups and regions of Brazil, although socioeconomic factors are also determinant [3]. Studies highlight that obesity is related to several diseases, such as type II diabetes, hypertension, cardiovascular disease, dyslipidemia, atherosclerosis, and some forms of cancer, among others. In people with a BMI between 18 and 25 (ideal weight), there are about 8.0% diabetics. In individuals with a BMI above 40 (severe obesity), this percentage reaches 43.0 % [6].

According to the last assessment carried out by ISFO in 2017, overweight and obesity are established risk factors for 13 types of cancer. In 2015, in France, 5.4% of cancer cases were attributed to being overweight, corresponding to 18,600 cases, including 3400 colon cancer, 2600 kidney cancer, 4,500 breast cancer, and 2,500 endometrial cancer [1]. Obesity in children and adolescents has also been linked to an increased risk of cancer in adults.

Figure 1. Flowchart showing the article selection process.



In this sense, one of the main causes of obesity is an imbalance in energy balance favored by a diet rich in processed foods, red meat, trans and saturated fatty acids, foods and beverages with a high glucose content, and poor in fruits and vegetables, vegetables and whole grains. The main national and international recommendations to reduce the prevalence of obesity are to have a balanced diet and regular physical activity [1].

In this sense, studies indicate the main risks of diseases with increased weight (**Table 1**) [2,8].

Table 1. WHO classification for obesity based on BMI [2,8].

Diagnosis	BMI (kg/m^2)	Disease Risk	Disease Risk
		WC (cm)* Males ≤ 94	**WC(cm)* Male *>94* Female *>80***
Underweight	**< 18.5**		
Normal weight	**18.5–24.9**		
Overweight	**25–29.9**	Increased	Increased
Class I obesity (moderate obesity)	**30–34.9**	High	High
Class II obesity (severe obesity)	**35–39.9** **≥ 40**	Very High Extremely High	Very High Extremely High

*Within each BMI category, disease risk may vary depending on the fat distribution reflected in waist circumference (WC).

Obesity and Inflammatory Processes

The circulating level of cytokines and acute-phase proteins associated with inflammation is elevated in obese patients. Thus, adipocytes secrete several cytokines and acute-phase proteins that increase the production and circulation of factors related to inflammation. 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]**.

In this context, the association between obesity and inflammatory disease stands out. There are three possibilities, the first one 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 adipocytes themselves are an immediate source of some or several, of these inflammatory markers **[16-18]**.

In this sense, 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]**. In this context, some studies have shown low concentrations of anti-inflammatory adipokine (adiponectin) associated with the occurrence of different types of cancer and high concentrations with the inhibition of tumor growth. Adiponectin and leptin are the most abundant adipokines synthesized by adipose tissue, although there are 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, excess adipose tissue increases the production of several adipokines that 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 stand out, situations strongly correlated with cardiovascular disease **[15]**. Anti-inflammatory adipokines are the IL1 receptor antagonist (IL-1ra), transforming growth factor-β (TGF-β), those produced by Th2 cells (IL-4, IL-5, and IL -10), and adiponectin **[18]**. The imbalance between pro-and anti-inflammatory cytokines can induce inflammatory or hypersensitivity responses (allergies). Also, high plasma adiponectin concentrations are associated with a reduced risk of myocardial infarction in men. Adiponectin is inversely proportional to the concentration of C-reactive protein (CRP). It can down-regulate the gene expression of PCR in adipocytes **[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 in inflammatory genes, and a downregulation in anti-inflammatory genes **[19]**. However, it is not only in the adipose tissue that this change in cells of the innate immune system occurs. Thus, the authors demonstrated that the circulating mononuclear cells of obese individuals are also in a pro-inflammatory state, with an increase in intranuclear factor κB (NF-κB) and, consequently, with an increase in the transcription of pro-genes. inflammatory drugs regulated by it **[20]**. As a corollary, the innate immune response in obese patients is altered, resulting in an imbalance in the line of defense against infections, an increase in the inflammatory response, and abnormal activation of T lymphocytes. 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]**.

Obesity and COVID-19 - Meta-Inflammation

Meta-inflammation describes the junction of inflammation with 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 C reactive, cytokines, chemokines, macrophages, and TNF-α. The imbalance in inflammatory mediators induced by excess nutrients is the basis of meta-inflammation in obesity, considered a low-grade chronic inflammatory state. Similar to that seen in acute inflammatory diseases, obesity can cause multiple organ dysfunction. Meta-inflammation leads to myocardial dysfunction by direct damage to inflammatory mediators, as well as by dysfunction of other organs **[7]**.

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 picture of hyper inflammation with a cytokine storm. As a corollary to the exacerbated inflammatory process, the coagulation cascade is unregulated, causing hypercoagulability. Therefore, the endothelial

dysfunction caused by SARS-CoV-2 justifies why patients with comorbidities related to blood vessels such as cardiovascular disease, hypertension, diabetes, and obesity are more likely to develop severe conditions of COVID-19, even death [21].

Post-mortem histological studies revealed lymphocytic endothelium in the lungs, heart, kidneys, and liver, as well as cellular necrosis and the presence of microthrombi, which, in the lungs, worsens respiratory failure. Thus, authors found in autopsies evidence of direct viral infection of SARS-CoV-2 in the endothelial cell and diffuse inflammation. The ACE2 receptor is also widely expressed on multiorgan endothelial cells [22].

In this sense, other authors performed an autopsy study that compared the lungs of patients who died from COVID-19 versus those who died from Influenza A (H1N1). The histological pattern in the periphery of the lung was diffuse alveolar lesion with perivascular T-cell infiltrate. The lungs of patients with COVID-19 also showed distinct vascular characteristics, consisting of severe endothelial damage associated with the presence of intracellular virus and ruptured cell membranes. Histological analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were nine times more prevalent in patients with COVID-19 than in patients with influenza ($p<0.001$) [23].

In addition, respiratory failure caused by COVID-19 is related to inflammatory and coagulation process changes in the alveolar microcirculation. Thus, alveolar thrombotic microangiopathy is a primary thrombosis triggered in COVID-19 and differs from pulmonary arterial thrombosis, as there is a direct action of the virus on the endothelium, causing diffuse endothelium. Thus, it is suggested that the action of SARS-CoV-2 provides endothelial denudation due to inflammation, leading to significant exposure of tissue factors, activating the coagulation cascade, and subsequent pulmonary thrombotic microangiopathy [24].

In this sense, this process of local cytokine activation can complicate the evolution of pneumonia caused by COVID-19, especially in obese patients, as the micro thrombosis state causes post-thrombotic endothelial dysfunction, activates the complement system, and release cytokines. And when these systems are activated, a continuous state of hypercoagulability occurs. As scientific evidence, authors have demonstrated the relationship between obesity and a higher risk of intubation and mechanical ventilation, in addition to higher hospital mortality. In this series, 46% of the 1150 patients hospitalized with severe COVID-19 were obese, and invasive mechanical ventilation was required in 79% of the 257 patients who progressed to the critical form of the disease [25].

This was also reported in a multicenter study involving 5,700 hospitalized patients in metropolitan New York. Obesity was described as the second most frequent comorbidity, being present in approximately 40% of patients with COVID-19. During hospitalization of the 2634 patients, 14.2% were treated in the ICU and 12.2% received invasive mechanical ventilation. Mortality for those who required mechanical ventilation was 88.1% [26].

Still, other authors observed the relationship between obesity and the development of severe respiratory manifestations when analyzing 103 patients hospitalized with COVID-19. They reported that 47% of these patients were obese. In this study, patients who presented a BMI of 30 kg/m2 were among those most in need of ICU admission and mechanical ventilation [27].

Dietary Therapy in the Control of Meta-Inflammation

Nutritional status can have a significant impact on an individual's general health, reduction of comorbidities, and reduced susceptibility to the development of infections such as COVID-19. However, according to the WHO, there is still no single food or natural remedy with proven scientific evidence to prevent COVID-19 infections [28]. Despite this, based on previous studies, it is known that nutritional status plays a significant role in patient outcomes [29]. Therefore, it is necessary to follow a diet characterized by anti-inflammatory properties to benefit or prevent COVID-19 [30-33].

In this sense, evidence suggests that dietary patterns and individual nutrients can influence systemic markers of immune functions. Thus, maintaining the nutritional status at this time is significant, given that the fight against COVID-19 can last a long time. Also, to maintain a healthy immune system, special attention must be paid to maintaining a healthy diet, lifestyle, and exercise regimen [34].

Also in this scenario, there are nutritional deficiencies of calcium, vitamin C, vitamin D, folate, and zinc among elderly populations [35], making them immunodepression [36]. 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 [37].

In this context, a review study examined the usefulness of early intervention with micronutrients,

with a focus on zinc, selenium, and vitamin D, to alleviate the increase in COVID-19. The results revealed that there is direct evidence for associations between zinc, selenium, and vitamin D, and COVID-19. An adequate supply of zinc, selenium, and vitamin D are essential for resistance to other viral infections, immune function, and reduced inflammation [38].

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 epigenetics 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 nutrients in the diet can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate, 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 [39].

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact the cellular state by modulating the activity of the signaling pathway. A clear example is through the mechanistic target 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 activation of mTORC1 by blocking Rag GTPase-mediated mTORC1 recruitment to the lysosome where it can be activated by Rheb GTPase [39].

Another way that nutrients are detected to impact the cellular state is through the 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 regulates cell growth and autophagy. Furthermore, transcription factors can be directly regulated by metabolites. Kynurenine tryptophan is an endogenous agonist for the aryl hydrocarbon receptor and alpha-ketoglutarate (α-KG) which binds and activates IKKβ and initiates NF-κβ signaling [39].

Thus, nutritional health acts directly on the human intestinal microbiota, impacting the metabolism and the immune system for tissue regeneration. Recent discoveries on the role of the "nutrological microbiota" in mechanisms involved in tissue regeneration, in particular skin, liver, bone, and nervous system regeneration [40].

In this aspect, in the inflammatory phase, vitamin A increases the release of cytokines, bromelain, and amino acids prevent prolonged inflammatory events, vitamin C increases neutrophil migration and lymphocyte activation. In the proliferative phase, vitamin C is needed for collagen synthesis, glucosamine increases the production of hyaluronic acid. Vitamin A, on the other hand, promotes the differentiation of epithelial cells. Zinc is needed 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 [41].

Finally, reduced age-related muscle repair efficiency contributes to the development of sarcopenia. Nutrients such as amino acids, polyunsaturated fatty acids, polyphenols, and vitamin D can enhance skeletal muscle regeneration by targeting key functions of immune cells, muscle cells, or both [42].

Conclusion

Research has shown that unbalanced dietary patterns, such as the Western diet, rich in simple sugars, refined carbohydrates, saturated and trans-fatty acids, lead to chronic inflammatory responses, increased fat deposition, and future comorbidities associated with overweight and obesity. In addition, some nutrients have important effects in decreasing the inflammatory response and in metabolic restoration, reducing oxidative stress. Therefore, adequate dietary interventions for the management of overweight and obesity are needed, especially starting early in children and adolescents for healthy growth, preventing comorbidities in adulthood.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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