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Impact of obesity on immune function and depressive disorder: integrative review

Impacto da obesidade na função imune e no transtorno depressivo: revisão integrativa

Impacto de la obesidad en la función inmunitaria y el trastorno depresivo: revisión integradora

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ABSTRACT

Objective: This integrative review aims to search and analyze scientific evidence on the relationship between obesity, immune function, and depressive disorder. **Methods:** The present study is a descriptive review of literature concerning the keywords: obesity, depression, immunologic, inflammation, psychoneuroimmunology and cytokines. The inclusion criteria were: articles published in english; articles referring to the integrative review and articles published and indexed in the PubMed database in the last 17 years. **Results:** A large amount of evidence indicates that immune function seems to be compromised in obesity and has, through this, a relationship in the trigger of depressive symptom. However, more evidence is still needed to better elucidate the pathophysiology components of depressive incidences through obesity and associated immunological alterations. **Conclusions:** The pathophysiological scenario of obesity is closely related to changes in immune function, and these may promote depressive symptoms through various physiological mechanisms and thus negatively impact mental health status.

Keywords: depressive disorder, immune system, obesity, inflammation, cytokines

RESUMO

Objetivo: Esta revisão integrativa tem como objetivo pesquisar e analisar evidências científicas sobre a relação entre a obesidade, a função imune e o transtorno depressivo. **Métodos:** O presente estudo é uma revisão descritiva da literatura referente às palavras-chave: obesidade, depressão, imunológico, inflamação, psiconeuroimunologia e citocinas. Os critérios de inclusão foram: artigos publicados em inglês, artigos referentes à revisão integrativa e artigos publicados e indexados no banco de dados PubMed nos últimos 17 anos. **Resultados:** Uma grande quantidade de evidências indica que a função imunológica parece estar comprometida na obesidade e possui, através desta, relação com desencadeamentos de sintomas depressivos. Entretanto, ainda são necessárias mais evidências para melhor elucidação dos componentes fisiológicos de etiologia das incidências depressivas através da obesidade e das alterações imunológicas associadas. **Conclusões:** O cenário fisiopatológico da obesidade está intimamente relacionado a alterações na função imunológica e estas podem promover desencadeamentos de sintomatologias depressivas através de mecanismos fisiológicos diversos e desta forma impactar negativamente o estado de saúde mental.

Palavras-chave: desordem depressiva, sistema imunológico, obesidade, inflamação, citocinas

RESUMEN

Objetivo: Esta revisión integradora tiene como objetivo buscar y analizar la evidência científica sobre la relación entre obesidad, función inmune y trastorno depresivo. **Métodos:** El presente estudio es una revisión descriptiva de la literatura relativa a las palabras clave: obesidad, depresión, inmunológico, inflamación, psiconeuroinmunología y citocinas. Los critérios de inclusion fueron: artículos publicados en inglês, artículos referentes a la revisión integrativa y artículos publicados e indexados en la base de datos PubMed en los últimos 17 años. **Resultados:** Una gran cantidad de pruebas indica que la función inmunitaria parece estar comprometida en la obesidad y está relacionada con los síntomas depresivos. Sin embargo, aún se necesitan más pruebas para dilucidar mejor los componentes fisiológicos de la etiología de las incidencias depresivas a través de la obesidad y las alteraciones inmunológicas asociadas. **Conclusiones:** El escenario fisiopatológico de la obesidad está

estrechamente relacionado con los cambios en la función inmunitaria y éstos pueden promover el desencadenamiento de síntomas depresivos a través de diversos mecanismos fisiológicos y, por tanto, repercutir negativamente en el estado de salud mental.

Palabras clave: trastorno depressivo, sistema inmune, obesidade, inflamación, citoquinas

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Introduction

Depressive disorder is a multifactorial disease of high pathophysiological complexity [1]. In 2019, the Global Burden of Disease, Injury, and Risk Factors (GBD) study ranked depression among the twenty-five diseases with the highest burden and disability worldwide [2]. The prevalence of global obesity has grown in recent decades and has established itself as a significant public health problem worldwide [3]. Despite the impact of depression and obesity in the global health context, the mechanisms of etiology of both diseases remain not fully understood.

The prevalence of mental diseases has substantially increased. It has grown in correlation with changes in the dietary profile of the human diet with increased consumption of ultra-processed and energy-dense foods [4] and consequent weight gain. Obesity and other chronic diseases are associated with alterations in immune response, leukocyte counts and cellular immune response components [5], and various physiological changes.

Studies estimate that obese individuals have around a 55% of chance of developing depressive symptoms throughout life [6]. In this sense, studies have shown that obesity and its metabolic and immunological alterations positively correlate with incidences of depression [7]. In addition, growing evidence has demonstrated that abdominal adiposity and a food consumption profile predominantly based on proinflammatory and high-energy foods, common in the population affected by obesity, may influence the onset of depressive disorder [8 - 10].

Bidirectional associations between obesity and depression have been reported, demonstrating that individuals affected by depressive disorder become more susceptible to weight gain induced by reduced-quality food choices [6]. However, the holistic understanding of immune mechanisms associated with gut-brain communication in the triggering of depressive disorders remains to be fully elucidated.

Dysregulation in immune response has been associated with depressive symptoms through multifactorial inflammatory mechanisms and interaction with the central nervous system (CNS) via the hypothalamic-pituitary-adrenal axis [7]. Dietary and obesity patterns have been strongly linked to alterations in the profile of cytokine secretion, including elevated production of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), triggering neuroinflammatory processes and metabolic disorders that may result in depressive incidences [11].

Therefore, there is increasing evidence reporting the influence and impact of obesity on immune response and the incidence of psychic alterations. However, there is still a need for further studies to elucidate this intercommunicating scenario. In this context, this review aims to establish a survey of evidence and a better understanding of the impact of obesity on immune function and in triggering depressive disorders.

Methods

The present study is a descriptive review of literature based on PubMed database. The scientific publications on obesity and depressive disorders, with highlights to immune mediators involved in both diseases, were selected based on the keywords: Obesity, Depression, Immunologic, Inflammation, Psychoneuroimmunology, and Cytokines. The inclusion criteria defined for the selection of articles were: articles published in English; articles referring to the integrative review and articles published and indexed in the referred database in the last 17 years.

Results

Obesity and the immune system

Obesity is characterized by chronic low-grade inflammation related to local origins in adipose tissue and subsequent systemic inflammatory state [5]. Positive associations between obesity and changes in inflammatory cytokines such as TNF-α, IL-6, and C-reactive protein (CRP) have been reported [12 - 14] [Figure 1]. Indeed, an increase in serum concentrations of complement components, including C3 and C4, and CRP has been observed in obese adolescents aged 13-17 years [14], and elevated serum levels of IL-6 and TNF-α have been described in obese Korean adults [12]. Abdominal fat accumulation, assessed by waist circumference measurement, is positively correlated with proinflammatory markers such as complement C3, CRP, IL-6, and retinol-binding protein (RBP) [13]. These findings indicate a possible link between the profile of body fat distribution and immune function alterations.

The communicative links between nutritional status and immune competence have been supported in the literature through the reported association of malnutrition with impaired immune function. Malnutrition leads to increased vulnerability to infections in underweight populations. However, understanding obesity as a disorder of nutritional status has also been associated with diverse immunological impairments, including association with increased ectopic lipogenesis in primary lymphoid organs, distinct innate and adaptive cell populations in adipose tissue, and increased serum levels of inflammatory mediators [15].

The adipose tissue of obese individuals has a more significant accumulation of macrophages, T cells, B cells, and mast cells than the adipose tissue of lean individuals [16, 17]. Indeed, innate and adaptive cells in the obese adipose tissue show a proinflammatory profile, which favors the maintenance of inflammation [16].

Obese adipose tissue has an increased population of resident macrophages, which comprise up to 40% of total tissue cells [15, 18]. The profile of macrophages in obese adipose tissue is characterized by a predominance of the M1 subtype, which produces proinflammatory cytokines favoring inflammation, in contrast to the M2 subtype, predominantly found in lean adipose tissue, which is associated with an anti-inflammatory response [15]. Inflammatory pathways are sustained in obesity and promote the elevated secretion of proinflammatory cytokines, such as TNF-α and IL-1β, which may have local and systemic effects,

promoting metabolic dysregulation associated with insulin resistance [18]. However, differences are found in a distinct type of adipose tissue, subcutaneous and visceral. Macrophages produce more proinflammatory cytokines in visceral adipose tissue than in subcutaneous tissue [19]. Indeed, more detrimental metabolic and systemic effects are observed when body fat distribution is predominantly visceral rather than subcutaneous.

Yang et al. [16] observed that subcutaneous adipose tissue harbors significantly higher numbers of CD4 and CD8 T cells, with excessive secretions of proinflammatory cytokines in obese women (BMI>40, n=6) compared to lean women (BMI<24, n=6). Moreover, reduced T cell receptor (TCR) diversity was also identified in lymphocytes from subcutaneous and visceral adipose tissue of obese mice compared to lean mice, demonstrating a possible reduction in thymopoiesis and compromised immune surveillance associated with overweight [16].

Differences in CD4 T cell (Th) subpopulations, including Th1, Th2, and regulatory T cells (Treg), are found in obese individuals. The predominance of the Th1 population, impaired Treg number and activity are observed in obese individuals [18] [Figure 2]. Furthermore, the reduction of Treg in obesity has been associated with impaired immuneregulation, increased proinflammatory mediators, and the development of metabolic diseases in experimental studies [20].

Neuroinflammation and depression in obesity

Neuroinflammatory factors have been associated with significant impacts on the interaction between neurobiological trigger mechanisms of major depressive disorder, including reductions in serotonin concentration and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [21].

Clinical studies have demonstrated an association between serotonin metabolism in depressive patients, depletions in tryptophan amino acid (TRP) concentration, and incidences of depressive symptoms [22]. Serotonin (5HT) is synthesized through a metabolic route characterized by the action of the tryptophan hydroxylase enzyme on the tryptophan amino acid (TRP); however, changes in tryptophan catabolism through metabolic ways alternative to serotonin synthesis and precursors of metabolic products that generate oxidative stress have been strongly associated to proinflammatory cytokines and neuroinflammation [21, 23, 24].

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Presumably, TRP conversion into its metabolite product, kynurenine (KYN), reduces serotonin availability in the CNS, which is essential in regulating mood states [25 - 27].

Considering that obesity is characterized by a state of low-grade inflammation, the impact of its inflammatory manifestations has been increasingly investigated as a link to incidences of mood disorders and psychiatric pathologies. Experimental and clinical models have demonstrated a correlation between mood disorders with diseases in which pathophysiology evokes inflammatory mechanisms [27, 28]. The depressive etiology is linked to the expression of inflammatory cytokines with influence on the HPA axis, promoting changes in glucocorticoid secretions and endocrine negative feedback loops [23, 29].

Hyperactivity of the HPA axis determined by elevations in cortisol levels is the breakthrough for the neurobiology adjacent to psychiatric disorders, as it has been shown that prolonged exposure to high levels of circulating cortisol may promote damage in limbic brain regions, including the amygdala and hippocampus, which are responsible for regulating mood states [30]. Interestingly, hyperactivation of the HPA axis and increased cortisol levels have been found in obese individuals with mental disorders [31].

The bidirectional intercommunication between obesity and depression has multifactorial origins [Figure 3]. Among them, homeostatic dysregulation in the HPA axis and immune-inflammatory activations are among the communicating factors for the etiological understanding of alterations in mood states [32] reflected in obese individuals.

Considering that inflammatory mediators strongly modulate the HPA axis, Milaneschi et al. suggest that chronic inflammation typical of obesity may provide perturbations in glucocorticoid and cortisol binding receptors, thus triggering persistent elevations in plasma glucocorticoid concentrations in obese individuals [32] and may provide depressive symptoms through the glucocorticoid-sensitive mesolimbic neurofunctional.

As reported by Troubat et al. and supported by previous studies, abnormalities of the HPA axis are observed in depressive illness and corroborate with studies demonstrating higher salivary and urinary glucocorticoid concentrations in patients diagnosed with the depressive disorder [21].

Milaneschi et al. reported that patients diagnosed with atypical subtype of depression, marked by hypoactivity, mood reactivity, hyperphagia, hypersomnia, and extreme severe paralysis [33], had a higher predisposition to overweight and obesity (BMI ≥ 24.9) and high levels of CRP [34]. Indeed, this subtype of depression has been associated with inflammatory factors, such as increased IL-2 and reduced IL-4 serum levels [35].

The relationship between obesity and depression has also been more recently supported through the strong association between waist-to-hip ratio in individuals with increased abdominal adiposity and depressive incidences, with a prevalence of ratios on the order of 1.38 (95% CI, 1.22-1.57) [36].

High levels of CRP in depressed individuals were reported in a cohort study between 1999-2004 [37]. Indeed, increased levels of CRP are found in approximately 25% of individuals diagnosed with major depression, and elevations in circulating levels of IL-6 are also reported, highlighting that patients with chronic inflammatory-based pathologies may present increased rates of attempted suicidal ideation [38]. In this way, clinical interventions with anti-inflammatory drugs may become strategies to prevent severe cases of depression [38].

The primary immunological characterization of obesity concerns the profile of chronic low-grade inflammation and its associations with cellular and humoral immune responses. Among the alterations of immune activity, activation of the inflammasome, a sensor of the innate immune system, has been attributed as one of the mechanisms involved in depression [39].

The inflammasome protein complex, formed in the cytoplasm in response to pathogens recognition or cellular damage, recruits caspase-1, a protease responsible for cleaving the immature form of pro-IL-1β and pro-IL-18, into mature forms of IL-1β and IL-18 cytokines. Interestingly, an experimental study with mice reported that caspase-1 inhibition has a protective effect on anxious and depressive behaviors [40]. Indeed, the secretion of IFN-γ by resident adipose tissue T cells has been associated with increased expression of the caspase-1 and NLRP3 inflammasome in adipocytes from obese individuals, favoring proinflammatory pathways that sustain the chronic inflammation typical of obesity [32, 39, 41] and may thus comprise an etiological way of incidence for depressive pathology.

Conclusion and future perspectives

Dysregulation in neuroendocrine pathways and neurotransmitter production with direct physiological importance for mood state maintenance are strongly correlated with proinflammatory cytokines and patters of immune cell activation, which are also found in obesity. The connection of inflammation, obesity and depressive disorders has been identified in observational studies assessing the high incidence of depression in obese individuals, while inflammation in obesity explains in part the depressive symptomatology. However, despite advances in understanding the integrative pathophysiology between obesity and depression onset through immune dysfunctions, more evidence is still needed to evaluate and elucidate ideal clinical and pharmacological management for the prevention and treatment of depressive conditions in obese individuals.

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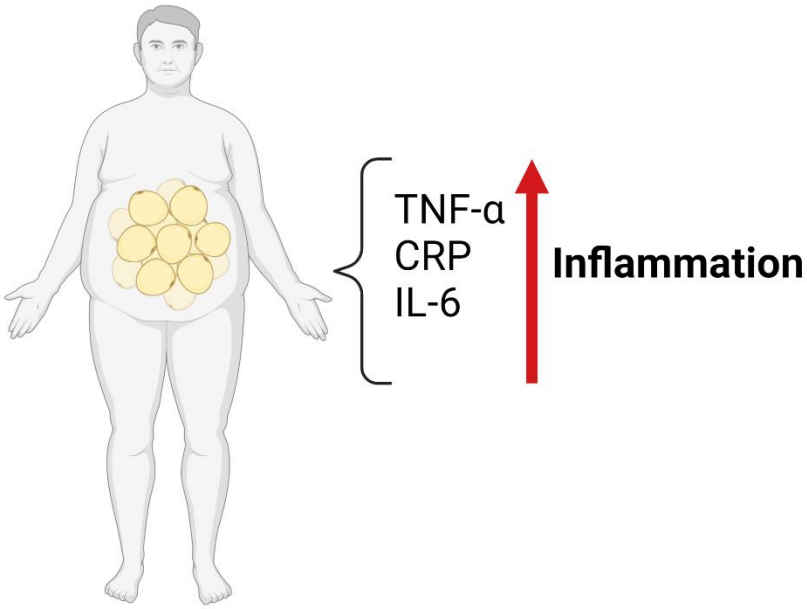

Figure 1. Inflammatory mediators associated with obesity. Obesity is related to increased secretion of inflammatory cytokines, including TNF-α, IL-6 and CRP (C - reactive protein)
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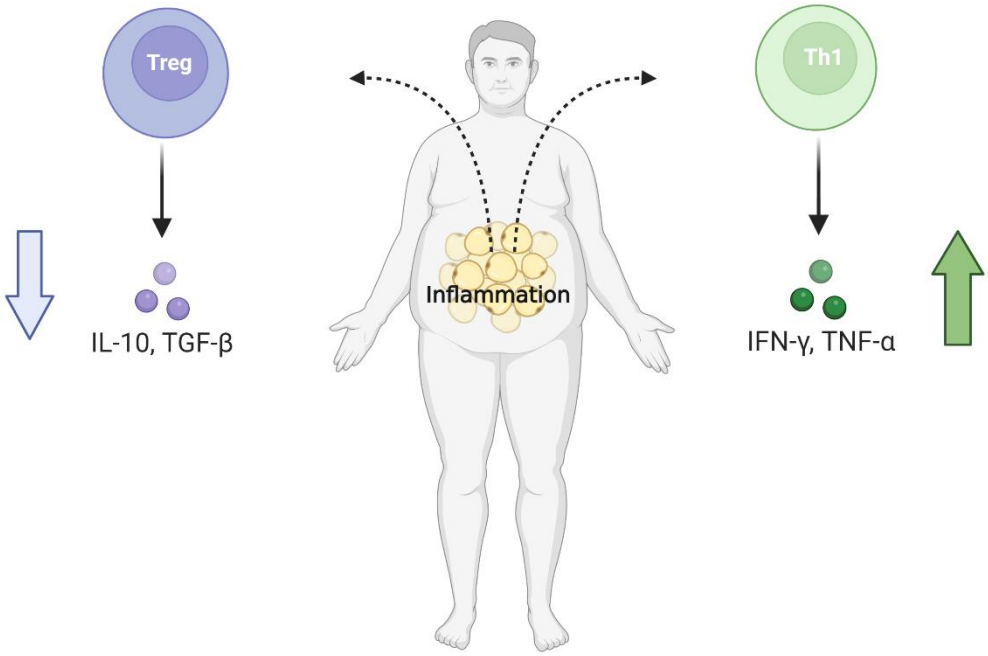

Figure 2. CD4 T cell population associated with obesity. Predominance of Th1 and reduction of Treg cell population are characteristic of inflammation in obese individuals.
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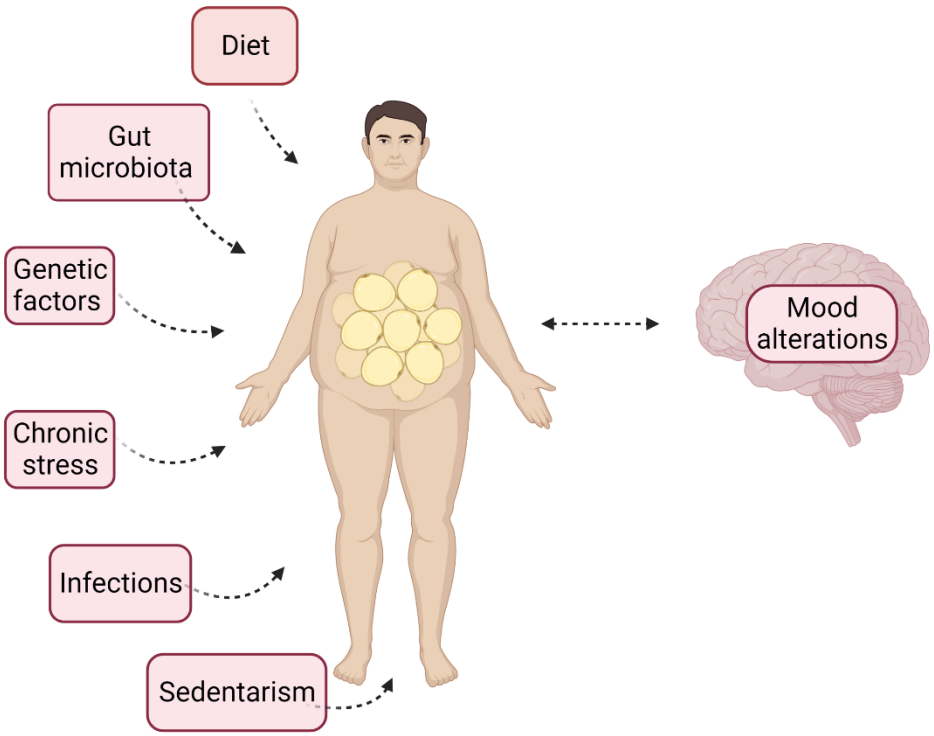

Figure 3. Multifactorial aspects associated with obesity and mood alterations. Social, genetic, dietary, and individual habits are associated with mood changes and the onset of depressive symptoms.
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