ARTÍCULO DE REVISIÓN

Obesity and depression: A molecular and epidemiological view of two comorbid disorders

Obesidad y depresión: una visión molecular y epidemiológica de dos trastornos comórbidos

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SUMMARY

Currently, depression and obesity are chronic disorders considered public health problems because of their association with functional impairment, ominous healthcare costs, and increased morbidity and mortality rates worldwide. However, based on the high prevalence of both pathologies, a possible relationship between obesity and depression has been presumed and studied in recent years, demonstrated through observational epidemiological studies and meta-analyses, positioning them as commonly comorbid chronic diseases. Thus, obesity increases the risk of depression, while depression can lead to obesity, thus establishing a bidirectional relationship between them. From a molecular point of view, depression and obesity are chronic diseases where immune disruption in the form of neuroinflammation or low-grade systemic inflammation are the hallmark disturbances in the central and peripheral tissues alongside the classic obesity-related metabolic disorders, characterized by insulin and leptin resistance and cortisol increase leading to hypothalamic-pituitary-adrenal axis dysregulation. However, how obesity and depression are linked at the pathophysiological level is not fully understood yet, so the present narrative review aims to determine the shared molecular basis of obesity and depression and the epidemiological evidence supporting the bidirectional link between these entities.

Keywords: Obesity, depression, epidemiological evidence, pathophysiology, molecular basis.

RESUMEN

Actualmente, la depresión y la obesidad son trastornos crónicos considerados problemas de salud pública por su asociación con el deterioro funcional, los ominosos costes sanitarios y el aumento de las tasas de morbilidad y mortalidad en todo el mundo. Sin embargo, en base a la alta prevalencia de ambas patologías, en los últimos años se ha presumido y estudiado una posible relación entre la obesidad y la depresión, demostrada a través de estudios epidemiológicos observacionales y meta-análisis, posicionándolas como enfermedades crónicas comúnmente comórbidas. Así, la obesidad aumenta el riesgo de depresión, mientras que la depresión puede conducir a la obesidad, estableciendo así una relación bidireccional entre ambas. Desde un punto de vista...
molecular, la depresión y la obesidad son enfermedades crónicas en las que las alteraciones inmunológicas en forma de neuroinflamación o inflamación sistémica de bajo grado son las alteraciones distintivas en los tejidos centrales y periféricos, junto con los clásicos trastornos metabólicos relacionados con la obesidad, caracterizados por la resistencia a la insulina y la leptina y el aumento del cortisol que conduce a la desregulación del eje hipotálamo-hipófisis-suprarrenal. Sin embargo, aún no se comprende del todo cómo se relacionan la obesidad y la depresión a nivel fisiopatológico, por lo que la presente revisión narrativa pretende determinar las bases moleculares compartidas de la obesidad y la depresión y las pruebas epidemiológicas que apoyan el vínculo bidireccional entre estas entidades.

INTRODUCTION

Depression and obesity are chronic diseases considered global public health problems due to increased morbidity and mortality rates over the last half-century and are associated with individual functional impairment and high healthcare costs (1–4). Depression is a common disorder worldwide, affecting approximately 3.8% of the population, including 5% of middle-aged adults and 5.7% of adults over 60 years, affecting about 280 million people globally (5). In Latin America and the Caribbean, 5% of the adult population has depression (6), while Ecuador exhibits a 4.6% prevalence (7). Thus, depression is the leading cause of disability in developed countries, with a clear association in the quality of life and functional impairment comparable to that observed in other chronic non-communicable diseases such as diabetes or heart disease. In addition, depression has also been associated with increased national absenteeism and health care costs (8,9). The World Health Organization (WHO) has stated that depression, followed by cardiovascular disease, will continue to be the leading cause of disability worldwide in the coming years (10).

Obesity is another disease of global proportions that mainly affects industrialized countries and has been affecting an increasing number of individuals (11). According to the WHO, by 2016, there were 1.9 billion overweight adults in the world, of whom some 650 million were obese, noting that these conditions were once problems of the first world. Still, these disorders are now increasing in low- and middle-income countries, particularly in urban settings (12).

On the other hand, it has been estimated that six of every ten adults in Latin America had obesity by 2016, and approximately 40% of children and adolescents are overweight (13). Similarly, in Ecuador, according to the 2012 national health and nutrition survey (ENSANUT), 62.8% of the participants had weight-related problems, of which 40.6% were overweight and 22.2% obese, with a lower obesity prevalence in rural settings like the Sierra (14.9%), Coast (20.5%) and Amazon (16.1%) respectively (14).

In this regard, obesity has been linked to a wide range of comorbidities, including hypertension, atrial flutter, atherosclerosis, type 2 diabetes, non-alcoholic fatty liver disease and steatohepatitis, musculoskeletal system disorders, cancer, and psychiatric disorders associated with functional impairment, cognitive dysfunction, anxiety, depression and reduced quality of life (15,16). Obesity is also associated with higher healthcare costs, increased medication use, high absenteeism rates, disability, early retirement, and loss of productivity (17,18).

Based on the high prevalence of obesity and depression, a possible link between the two diseases has been presumed and consequently studied in recent years. Many epidemiological studies and meta-analyses have demonstrated a positive and statistically significant association between obesity and depression, positioning them as commonly comorbid chronic conditions (19–23). In this regard, it has been shown that obesity increases the risk of developing depression. In the same vein, depression, specifically in its atypical forms, can lead to obesity, establishing a bidirectional relationship (24). A meta-analysis of longitudinal studies found that obese people have a 55% risk of developing depression, while depressed people exhibited a higher risk of developing obesity (58%) (21). Factors like gender, age, ethnicity, and socioeconomic status probably were confounding variables in this relationship (25).

The molecular mechanisms involved in developing these entities have been extensively studied. They could originate in the hypothalamic-pituitary-adrenal (HPA) axis dysregulation,
low-grade inflammation, endocrine disorders, and oxidative stress genetic factors (26,27). Depression and obesity share critical immune features like adipose and central nervous system inflammation. This is especially true in the adipose tissue where monocytes experience polarization to M1 macrophages during hypertrophic expansion since leptin, IL-1, and IL-6 change the proteomic program in the sick adipocytes. It is essential to highlight that insulin and leptin resistance and increased cortisol blood levels may cause dysregulation of the HPA axis in obese people via increased inflammation induction (27,28).

Since the pathophysiological processes linking obesity and depression are not fully understood yet, this narrative review provides an in-depth view of the epidemiological and molecular evidence supporting the bidirectional link between these exciting conditions.

**Obesity and depression: epidemiological evidence of a bidirectional association**

There is epidemiological evidence demonstrating the link and interaction between obesity and depression. Furthermore, several cross-sectional and longitudinal studies meta-analyses have confirmed the positive association between both pathologies, highlighting the bidirectional nature of the association as the main feature of this phenomenon (Table 1) (21,23,29-41). For this reason, some authors have focused their attention on whether obesity increases the risk of depression or whether depression increases the obesity risk. A systematic review including 25 population-based studies found that 10 of these reported that significant weight gain or body mass index (BMI) represented good predictors for the onset and severity of depression. Whereas, of the remaining 15 studies assessing the depression related to obesity, only half reported that depression was a significant predictor of weight gain and BMI over time (39).

Furthermore, variability in weight gain according to depression subtype has been reported in people with the highest BMI levels, specifically in individuals with atypical depression than those with melancholic depression (32). Similarly, evidence shows that the onset of obesity in late adolescence increases the likelihood of developing depression in adulthood. In contrast, the development of depression in early adolescence increased the risk of obesity in late adolescence (35,41).

Another peculiarity of this pair of diseases is that their association seems stronger among women (21,29,30) and morbidly obese individuals. At the same time, it becomes weaker or even non-significant when the patient is male or when the BMI is between 25-30 kg/m² (21,29). In this regard, Byrne et al. proposed that the increased risk of developing depression in women may be due to the increase in sex hormones during adolescence, which may increase the risk of obesity (40).

On the other hand, this relationship is stronger when abdominal circumference is employed as a diagnostic criterion for obesity rather than BMI. This behavior could be explained because visceral fat accumulation is associated with more metabolic disturbances and a higher low-grade inflammation process. Moreover, obese individuals with hypertension, insulin resistance, dyslipidemia, elevated C-reactive protein (CRP), and other disorders had a higher risk of depression than obese subjects with a healthier metabolic profile (36,38).

Another relevant factor to consider is antidepressant medication because there is a common belief that these drugs can increase patients’ weight. In this regard, a meta-analysis including 116 studies assessing the influence of antidepressant administration on body weight found that, in the short term, these drugs do not significantly impact patients’ anthropometric variables. However, when assessing its long-term effect (up to 4 years), only mirtazapine was associated with obesity (42). Similarly, another meta-analysis, including 70 clinical studies, reported that normal or overweight patients with depression had better remission rates with antidepressant treatment than obese patients (43). Likewise, a longitudinal study in patients with depression under pharmacological treatment revealed that depression status was a better predictor of weight gain than antidepressant treatment (44). These findings suggest that the relationship between obesity and depression has a common pathophysiological origin beyond the use of the antidepressant.
## Table 1

Epidemiological evidence of the association between obesity and depression

| Authors (year)       | Journal                          | Methodology                  | Results                                                                 | Conclusions                                                                 |
|----------------------|----------------------------------|------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Luppino y col. (2010) (21) | Archives of general psychiatry (Q1) | SR and Meta-analysis: 15 longitudinal studies (N=58745). | Obe -> Dep: OR= 1.55; 95% CI= 1.22–1.98; p<0.001. | Obesity increases the risk of depression and depression predicts the development of obesity. |
| de Wit y col. (2009) (23) | Psychiatry Research (Q1) | SR and Meta-analysis: 17 Cross-sectional studies (N= 204507). | Obe -> Dep: OR= 1.26; 95% CI= 1.17–1.36; p<0.001. | There is a significant positive association between depression and obesity, which appeared to be more marked among women. |
| Jung y col. (2017) (29) | The British journal of psychiatry (Q2) | SR and Meta-analysis: 183 clinical studies, cross-sectional and longitudinal studies (N= 6788834) | Obe -> Dep: - BMI 25-29.9 kg/m²: OR= 1.02; 95% CI= 0.84-1.23; p<0.05. Men: OR= 0.84; 95% CI= 0.72-0.97; p>0.05. Women: OR= 1.16; 95% CI= 1.07-1.25; p<0.05. | Obesity increases the risk of depression. The association between obesity and depression differs by gender. Morbid obesity increases the risk of depression more than non-morbid obesity. |
| Abou Abbas y col. (2015) (30) | Clinical obesity (Q3) | SR and Meta-analysis: 8 Cross-sectional studies and case-control studies (N= 12641) | Obe -> Dep: OR= 1.27; 95% CI= 1.11–1.44; p=0.003. | There is evidence of a positive association between obesity and depression among adult populations in Middle Eastern countries, which appears to be more marked among women. |
| Mannan y col. (2016) (31) | Asian Journal of Psychiatry (Q2) | SR and Meta-analysis: 21 Longitudinal studies (N= 226063) | Dep -> Obe: RR= 1.37; 95% CI = 1.17-1.48; p<0.05. | This study suggests a bidirectional link between obesity and depression. However, the direction in which depression leads to obesity appears stronger. |
| Silva y col. (2019) (32) | Obesity Reviews (Q1) | SR and Meta-analysis: 22 Observational studies (N= 14757) | Atypical depression vs Melancholic: DMP = 2.55; 95% CI = 1.32 -3.70; p < 0.001. | Atypical depression was significantly associated with elevated BMI compared to melancholic depression. |
| Quek y col. (2017) (33) | Obesity Reviews (Q1) | SR and Meta-analysis: 18 Cross-sectional studies (N= 51272) | Children and adolescents Obe -> Dep: OR= 1.34; 95% CI = 1.10–1.64; p = 0.005. | Obese children and adolescents are more likely to suffer from depression and depressive symptoms. |

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The previously demonstrated bidirectional relationship between depression and obesity can be explained based on behavioral, psychological, and biological factors shared by both pathologies, or that some of these factors present in one of them lead to the development of the other, the purpose of this section is to delve into the biological aspects common to both pathologies. Thus, it is plausible that the biological bases of obesity and depression may have a common genetic component, which leads to alterations in the systems that maintain energy balance and the brain circuits that regulate mood and homeostatic responses. It is therefore not uncommon to observe that hyperactivation of the HPA axis, the autonomic nervous system (ANS), the systemic inflammatory response, neuroinflammation, and energy metabolism are some of the most studied biological determinants that molecularly link obesity and depression and that may act as common mechanisms or as mediating mechanisms in the causal relationships between them (Figure 1).
According to recent evidence, the link between depression and obesity (from a phenotypic point of view) may originate in partially overlapping genetic factors. In fact, these factors are equally involved during the development of these pathologies, with an additive genetic effect accounting for 40% of these conditions’ heritability (45,46). Genome-wide association studies conducted in patients and animal models of depression have identified at least half a hundred genetic loci associated with depression phenotypes (47-49). Some of these factors overlap or were relatively close to genes previously linked to BMI and severe early-onset obesity (50,51). These include the ras kinase suppressor gene 2 (KSR2), olfactomedin 4 (OLFM4), and neuronal growth regulator gene 1 (NEGR1), the latter responsible for modulating synaptic plasticity in the cortex, hypothalamus, and hippocampus, and thus, interfering with appetite and mood regulation and playing a crucial role in the possible shared mechanisms between obesity and depression (52-54).

Genome-wide association studies for obesity have recognized >200 loci related to BMI, obesity status, and measures of fat distribution (50). In addition, genes close to loci associated with BMI are also highly expressed in the hypothalamus and pituitary gland and the hippocampus and limbic system, structures involved in appetite and energy homeostasis and mood regulation, respectively (46). These findings suggest a genetic overlap of brain regions involved in mood regulation with specific brain regions involved in the body mass and energy homeostasis, a fact reaffirmed by studies showing partial overlap of the polygenic architecture of depression on obesity-related traits (55).

**HPA axis hyperactivity**

Within the neurobiology of psychiatric disorders, one of the most consistent findings is hypercortisolism caused by hyperactivation of the HPA axis, leading to a non-adaptive or physiological secretion of cortisol (56). HPA axis hyperactivation represents an important and latent...
mechanism connecting depression and obesity. Indeed, chronic exposure to elevated cortisol levels induces neurotoxicity in stress-susceptible limbic regions associated with depression, such as the amygdala and hippocampus (57-59). The influence of chronic hypercortisolism on mood is well-illustrated in Cushing’s syndrome, where 50%-80% of patients with active disease have depressive symptoms or major depressive disorder. This entity improves with an appropriate hypercortisolism treatment, demonstrating the role of cortisol in depression (60).

Prolonged hyperactivation of the HPA axis is common in at least 50% of adult obese patients. Similarly, it has also been found that hypercortisolism can substantially increase the risk of developing obesity in children (61-62). In addition, a decreased rate of brown fat thermogenesis due to low energy expenditure, increased appetite for hypercaloric foods, adipogenesis induction, and visceral adipose tissue hypertrophy are some of the mechanisms triggered by high cortisol levels in obesity (63).

A finding of interest in the HPA axis during chronic inflammation secondary to obesity is glucocorticoid receptor (GR) activity dysregulation, which influences the axis inhibition indirectly, as this receptor is responsible for the negative feedback of cortisol suppression. In this respect, proinflammatory adipokines activate components of the intracellular signaling cascade that repress the nuclear translocation of the GR or are involved in the interaction between this receptor and gene promoter response elements (64). Likewise, altered 5α-reductase activity and dysregulation of 11-β-hydroxysteroid dehydrogenase (11-βHSD) isoenzymes 2 and 1 are other alterations in cortisol metabolism related to obesity and depression interplay (65,66).

### Inflammation activation

People with depression exhibit all the inflammation features, including inflammatory cytokines elevation, plasma and cerebrospinal fluid upregulation of soluble cytokine receptors and acute phase proteins increment, chemokines adhesion molecules, and inflammatory mediators such as prostaglandins elevations in plasma. Of these, the Tumor Necrosis Factor-alpha (TNFα) and interleukin-6 (IL-6) appear to be the most reliable peripheral biomarkers of major depression (28,77).

In obesity, macrophages and other immune cells’ infiltration into adipose tissue drive the production of proinflammatory cytokines, contributing to a low-grade inflammatory state, one of the obesity hallmarks (78). Peripheral immune activation induced by the sick adipose tissue leads to neuroinflammation through humoral and neuronal pathways expressed as an increased cytokine expression in the hippocampus and cortex in animal models of obesity (79,80). In this vein, neuronal pathways are activated to counteract this peripheral inflammation that seeks to inhibit cytokine production through efferent signaling, such as inflammatory activation of the afferent and efferent vagal pathways (81).
When these regulatory pathways are altered, non-resolved inflammation contributes to obesity development.

It has also been described that central inflammation also affects monoaminergic neurotransmission, one of the main pathophysiological processes seen in depression (82). In this sense, stress and immuno-inflammatory activation stimulate depressive symptoms development and onset, with a correlation of IL-6, C-reactive protein (CRP), and cortisol levels with depression severity (24). In addition, systemic inflammation promotes neuroinflammation, a pathological process resulting in microglial proliferation and a decrease in the astrocytes population, favoring kynurenine pathway activity, which ultimately reduces tryptophan bioavailability for serotonin synthesis. In this respect, studies have shown that high gamma interferon (IFN-γ) and IL-6 levels induce indoleamine 2,3-dioxygenase expression, which reduces tryptophan bioavailability by promoting its degradation to quinolinic acid. This neurotoxic end product causes neuronal damage in the hippocampus, increasing excitotoxicity and decreasing neurotrophic factors (such as BDNF) synthesis, affecting hippocampal neurogenesis (24,83). Thus, the prolonged involvement of the central nervous system (CNS) in systemic inflammatory activation is another pathophysiological process in obesity and depression. Its importance relies on the chronic inflammation effect on other neuroendocrine systems alteration such as the HPA axis and those involved in energy homeostasis.

Neuroendocrine disruption of energy metabolism

The hypothalamus is the regulatory center of hunger, appetite, satiety, and energy balance. It is well-known that the specific neurons involved in the control of food intake are located in specific regions of this structure, which are highly sensitive to hormones such as leptin, insulin, and ghrelin (90). Among the components responsible for energy metabolism homeostasis, leptin and insulin-mediated regulation play a central role in the link between obesity and depression. Leptin is a peptide hormone produced in white adipose tissue with critical regulatory functions in energy homeostasis. By acting on specific neurons in the hypothalamus, leptin enables the integration of physiological and behavioral pathways that promote energy expenditure and inhibit food intake (91). Leptin resistance represents a state commonly associated with obesity, where the anorexigenic effect is diminished despite its high circulating concentrations. Plausible explanations for this phenomenon may be due to defective intracellular signal transduction, problems at the leptin receptor level, or alterations in the transport of this hormone across the blood-brain barrier (92). In this regard, the inflammation associated with obesity (elevated CRP levels) and neuroinflammation (activation of inhibitory signals from negative feedback loops) trigger responses that affect the binding of leptin to its hypothalamic receptor (92,93).

Leptin and leptin resistance also play an important role in mood regulation, as evidenced at the preclinical level, where peripheral and central administration of leptin have antidepressant effects (94), which can be explained through its ability to enhance neurogenesis and neuroplasticity in the cortex and hippocampus, through its direct action on neurons in the hippocampus and amygdala, and modulation the immune system and the HPA axis (95,96). In addition, several researchers have hypothesized that leptin resistance represents a phenotype that increases the risk of depression. Thus, elevated levels of circulating leptin are significantly associated with neuro-vegetative depression symptoms, such as hyperphagia and weight gain (97,98).

Obesity is frequently associated with insulin resistance, a state with a low peripheral response
to insulin despite high circulating levels, which is promoted by increased concentrations of proinflammatory adipokines that interfere with intracellular insulin signaling and insulin receptor response (99,100). This dysregulation in glucose metabolism due to insulin resistance in specific brain regions, specifically in the medial prefrontal cortex and the hippocampus, is related to the impairment of executive functions, memory, and neuronal damage. Thus, it has been proposed that central insulin dysregulation plays a role in psychiatric illnesses developing such as depression and dementia (101,102).

Saturated or trans-fat-rich foods consumption may increase the likelihood of depression through increased general and abdominal adiposity, whereas diets containing mainly unsaturated fats reduce the likelihood of depression and decrease depressive symptoms. Furthermore, saturated fatty acids may alter the leptin and insulin signaling pathway at the hypothalamic level, with one study finding that elevated serum saturated fatty acid levels correlate with the severity of depression (90).

**Ca\(^{2+}\) signaling pathways Dysregulation**

Some authors have hypothesized that intracellular Ca\(^{2+}\) dysregulation is also part of the pathophysiological processes of depression and obesity. Preclinical studies have demonstrated Ca\(^{2+}\)-mediated signaling involvement in neurons, which plays a key role in cell death and neurotransmitter release mechanisms (103,104). Thus, these researchers have found that Ca\(^{2+}\) dysregulation, abnormal neuronal death, and decreased neurotransmitter release were linked to the progression of obesity and clinical symptoms of depression. Some of the Ca\(^{2+}\) alterations associated with obesity and depression include increased inositol triphosphate-sensitive calcium stores, increased ryanodine-mediated Ca\(^{2+}\) release, and increased Ca\(^{2+}\) entry through voltage-gated channels, leading to increased intracellular calcium concentration, altering its physiological functioning (103,104). Based on the above, it is believed that calcium-blocking drugs could improve depressive symptoms and reduce the progression of obesity by reducing high intracellular Ca\(^{2+}\) concentrations (103,105). Likewise, the relationship between the Ca\(^{2+}/\)cAMP signaling pathway and the interaction between obesity and depression has been studied, showing that increases in cAMP concentration induce a more significant release of calcium from the endoplasmic reticulum; however, the true role of this pathway in obesity and depression needs to be further investigated (106).

**Hypothalamic and insular alterations**

The aforementioned pathophysiological processes mediate regulatory and homeostatic mechanisms of appetite at the CNS level, promoting obesogenic and depressive behaviors. In this sense, peripheral biological signals of inflammation, metabolic dysregulation, and stress, among others, activate central structures such as the insula and hypothalamus related to interoceptive and homeostatic perception. In this sense, clinical and preclinical evidence shows that obesity and depression are linked to alterations in the hypothalamic response to metabolic signals, such as occurs in leptin resistance, where the hypothalamus does not correctly respond to anorexigenic leptin signals, just as elevated cortisol levels are associated with altered hypothalamic function, promoting the development of obesity or depressive symptoms (97,98,107,108).

The insula and its vagal afferents are another structure that receives peripheral body information (with visceral interoception function), which is involved in the interaction between obesity and depression (109,110). Studies have shown that the insula receives anorexigenic signals from biomarkers related to energy homeostasis, such as glucose, ghrelin, and insulin (111-113), thus decreasing its physiological activity (114,115). However, in obese patients, it has been observed that sensitivity to internal satiety signals is diminished due to altered response in the insula activity (116). Similarly, studies have shown that depression results partly from interoceptive body misperception (117,118). In fact, neuroimaging studies highlight altered insula activity in patients with depression, which could explain the somatic symptoms and altered body awareness in this disorder (119,120).
CONCLUSIONS

There is overwhelming evidence of a bidirectional association between obesity and depression, a link that appears to be stronger in females than in males. Furthermore, evidence suggests that obese individuals have an increased depression risk than their overweight counterparts, mainly when BMI ≥ 40 kg/m², while atypical depression is most strongly associated with obesity.

From a molecular point of view, even though obesity and depression share a critical genetic component; in reality, HPA axis hyperactivation with hypercortisolemia, sympathetic hyperactivation, immunoinflammatory activation, and neuroendocrine alterations, leading to low-grade systemic inflammation and neuroinflammation, which ultimately induces neurotoxicity and adiposopathy promoting obesogenic and depressive behaviors.

These findings have practical and clinical relevance, already representing the basis for the design and promotion of therapeutic strategies to treat depressive symptoms in obese patients, weight gain in patients with depression, or promote their treatment as comorbid diseases.

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