



Depressive symptoms in obesity: Relative contribution of low-grade inflammation and metabolic health

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ARTICLE INFO

Keywords:

Depression
Obesity
Inflammation
C-reactive protein
Metabolic health
Metabolically unhealthy obesity

ABSTRACT

Background: Recent reports suggest that the risk of depressive symptoms in obesity is potentiated in subjects presenting a metabolically unhealthy phenotype. Inflammation is often considered a defining criteria of metabolic health. However, this factor may drive the association of metabolic health with depressive symptoms given its well-known role in the pathophysiology of depression. This study aimed at determining the relative contribution of inflammation and metabolic abnormalities to depressive symptoms in obesity.

Methods: One-hundred severely obese adults (BMI ≥ 35 –40 kg/m²) and 25 non-obese control individuals (BMI < 30 kg/m²) were recruited. Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and Mini-International Neuropsychiatric Interview (MINI). Serum high-sensitive C-reactive protein (hs-CRP) was measured as a marker of systemic inflammation. Metabolically unhealthy obesity was defined as obesity associated with two or more metabolic alterations, including low high-density lipoprotein cholesterol, hypertriglyceridemia, high fasting glucose and hypertension.

Results: Total MADRS scores were significantly higher in obese subjects with significant inflammation (hs-CRP ≥ 5 mg/L) compared to those with low inflammation (hs-CRP < 5 mg/L) and non-obese controls. Interestingly, hs-CRP levels significantly predicted MADRS scores in the whole population under study and in the group of obese subjects. Overall, no association was found between MADRS scores and individual metabolic alterations or the composite measure of metabolically unhealthy obesity. Similarly, the association of hs-CRP with MADRS scores in obese patients was not modulated by metabolic health factors.

Conclusions: These results indicate that systemic inflammation represents a stronger contributor of obesity-related depressive symptoms than metabolic health *per se*. This supports the notion that inclusion of inflammation in the definition of metabolically unhealthy obesity drives the association found between poor metabolic health and depressive symptoms.

1. Introduction

Depression is a complex mental health disorder with an estimated global prevalence of 320 million people worldwide (World Health Organization, 2017). Representing the leading cause of disability in the world, depression is associated with substantial medical and economical costs and its burden is still on the rise. Factors contributing to the increasing rate and burden of depression include the poor clinical response to conventional antidepressant treatments in at least one third of

cases, the growth and aging of the population, as well as the growing prevalence of chronic medical conditions that are associated with an increased vulnerability to depression (Capuron et al., 2017; Miller and Raison, 2016). Obesity, which is considered the pandemic of the 21st century, represents one of these chronic conditions at greater risk for depression. Consistent with this notion, the prevalence of depression is significantly higher in obese subjects compared to the general population (Evans et al., 2005; Lasselin and Capuron, 2014), and there are multiple reports of the association between body mass index (BMI) and/

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or waist circumference, the reference measures of obesity, and depressive symptoms in epidemiological and clinical studies (Geoffroy et al., 2014; Zhao et al., 2011). Moreover, recent data also suggest a role for adiposity/obesity in treatment-resistant depression (Kloiber et al., 2007; Oskooilar et al., 2009; Raison et al., 2013). In this context, significant efforts to understand the relationship between obesity and depression and to elucidate the biological factors and physiological processes linking these two conditions are timely.

While the mechanisms underlying the increased depressive morbidity in obese subjects are likely to be multidimensional, recent literature points to metabolic health as a key determinant. In particular, it has been proposed – based on results from multiple longitudinal studies – that metabolically unhealthy obesity substantially increases the risk of depression (Hamer et al., 2012; Phillips and Perry, 2015). Accordingly, in a recent pooled analysis of eight studies, metabolically healthy obesity was found to be associated with a slightly increased risk of depressive symptoms compared to non-obesity but this risk was significantly exacerbated in subjects with metabolically unhealthy obesity, defined as being associated with two or more metabolic alterations including high blood pressure, high triglycerides, low high-density lipoprotein cholesterol (HDL-C), high C-reactive protein (CRP) and high glycated hemoglobin (Jokela et al., 2014). Interestingly, in this report, the risk of depressive symptoms increased almost linearly with the number of metabolic abnormalities, suggesting a specific and quasi-direct link between metabolic health and depressive symptomatology.

Albeit the characterization of metabolically healthy obesity tends to be homogenous across studies (Stefan et al., 2013), there is no universal definition of metabolically unhealthy obesity. Not only the number of metabolic abnormalities may vary across studies (> 1 or > 2), but also the nature and characteristics of the metabolic alterations considered for the definition of this condition appear sometimes inconsistent or questionable. For instance, in most of the studies, including those cited above, inflammation, reflected by increased levels of CRP, represents one defining criteria of metabolically unhealthy obesity. However, given the well-known role of inflammation in depression (Raison et al., 2006), the inclusion of this factor in the definition of metabolically unhealthy obesity raises concerns as it may substantially drive by itself the associations found between depressive symptoms and metabolic health. Chronic low-grade inflammation is a fundamental characteristic of obesity, which is now considered not only as a metabolic disorder but also as an inflammatory condition affecting both the innate and adaptive immune systems (Kanneganti and Dixit, 2012; Shoelson et al., 2007). Originating primarily from the adipose tissue in which immune cells accumulate and secrete inflammatory factors (Castanon et al., 2014; Wellen and Hotamisligil, 2003), systemic inflammation in obesity may lead to increased neuroinflammatory processes and subsequently drive behavioral alterations (Capuron et al., 2017; Castanon et al., 2015). In parallel, a large database substantiates the involvement of inflammatory processes in the pathophysiology of depression (Anisman et al., 2005; Capuron and Miller, 2011; Dantzer et al., 2008; Miller and Raison, 2016; Raison et al., 2006). Support to this finding comes from clinical data indicating that: i) chronic inflammatory cytokine treatment in the medically ill patients induces depression in 30–50% of cases (Capuron et al., 2002; Musselman et al., 2001; Raison et al., 2006), ii) anti-cytokine therapies improve depressive status in patients with inflammatory conditions and comorbid depression (Tyring et al., 2006) as well as in patients with treatment-resistant depression (Raison et al., 2013), iii) samples of depressed patients exhibit higher levels of inflammatory markers (Dahl et al., 2014; Goldsmith et al., 2016; Haroon et al., 2012; Maes et al., 1991), and iv) individuals with systemic signs of inflammation are at greater risk for depression (Matcham et al., 2013; Miller et al., 2008). Relevant to obesity, mounting clinical findings show that depressive symptoms are associated with increased concentrations of inflammatory markers, including CRP and interleukin (IL)-6, in obese subjects or in patients afflicted with the metabolic syndrome (Capuron et al., 2008; Dixon et al., 2008). Moreover, in a

longitudinal cohort study of older adults, CRP at baseline was found to explain approximately 20% of the obesity-related increase in depression scores over 4 years of follow-up (Daly, 2013). Interestingly, in other studies, reductions in inflammatory markers following weight loss were found to correlate with significant improvement in the emotional status and depression scores of severely obese individuals (Capuron et al., 2011a; Emery et al., 2007).

Altogether, these data provide strong support to the possibility that inflammation, when considered for the definition of metabolically unhealthy obesity, may represent one major determining and mediating factor of the relationship between obesity, metabolic health and depression. The aim of this study was to test this hypothesis by determining the relative contribution of chronic low-grade inflammation and metabolic abnormalities to depressive symptoms in severely obese subjects.

2. Methods

2.1. Participants

2.1.1. Obese subjects

One hundred adult subjects with severe or morbid obesity ($\text{BMI} \geq 35\text{--}40 \text{ kg/m}^2$) meeting eligibility criteria for bariatric surgery were recruited. They were enrolled from the services of digestive and bariatric surgery of two private clinics (Tivoli and Jean-Villar) from Bordeaux area, France.

2.1.2. Control subjects

A group of twenty-five non-obese individuals ($\text{BMI} < 30 \text{ kg/m}^2$) with no acute or chronic immune/inflammatory condition were included as control participants. These subjects were either non-obese patients with non-inflammatory conditions enrolled from the same clinics as obese participants or healthy volunteers recruited through advertisements.

In the two groups, exclusion criteria were: age > 65 years old; acute or chronic inflammatory conditions (other than obesity or obesity-related pathologies); current treatment with antidepressants or any other psychotropic drug; current diagnosis of psychiatric disease (except for major depression); and/or severe medical illness. All participants provided written informed consent after reading a complete description of the study. The study was approved by the local Committee for the Protection of Persons (CPP) of Bordeaux.

2.2. Measurements

2.2.1. Neuropsychiatric assessments

Depressive symptoms were assessed using the 10-item, clinician administered, Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). DSM criteria for the diagnosis of current major depression were determined using the Mini-International Neuropsychiatric Interview (MINI) administered during a semi-structured interview by trained raters (Sheehan et al., 1998).

2.2.2. Inflammatory profile

Fasting blood samples were collected in all study participants for the measurement of serum concentration of high sensitivity (hs)-CRP, a stable marker of systemic inflammation. After 30–45 min at room temperature, samples were centrifuged (3200 rpm, 10 min at 4°C), and sera were stored at -80°C , until the assays. Hs-CRP concentrations were determined by enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's specifications (CYT298, Millipore, Billerica, Massachusetts). The assay sensitivity and intra-/inter-assay variability were respectively 0.20 ng/mL , $\pm 4.6\%$ and $\pm 6.0\%$.

2.2.3. Clinical and metabolic characteristics of obese participants

General clinical characteristics, such as demographic and

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