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Short communication

Obesity, metabolic syndrome and Mediterranean diet: Impact on depression outcome

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ABSTRACT

Objective: Obesity, metabolic syndrome (MetS) and low adherence to Mediterranean diet are frequent in major depression patients and have been separately related with prognosis. The aim of this study is to analyse their predictive power on major depression outcome, at 6 and 12 months.
Methods: 273 Major depressive patients completed the Beck Depression Inventory for depressive symptoms and the 14-item Mediterranean diet adherence score. MetS was diagnosed according to the International Diabetes Federation (IDF).
Results: At the baseline Mediterranean diet adherence was inversely associated with depressive symptoms ($p=0.007$). Depression response was more likely in those patients with normal weight ($p=0.006$) and not MetS ($p=0.013$) but it was not associated with Mediterranean diet adherence ($p=0.625$). Those patients with MetS and obesity were less likely to improve symptoms of depression than patients with obesity but not MetS.
Conclusions: Obesity and MetS, but not low adherence to the Mediterranean diet at baseline, predicted a poor outcome of depression at 12 months. Our study suggests that MetS is the key factor that impacts negatively in depression prognosis, rather than obesity or diet. If this finding is confirmed, clinicians should be aware about MetS diagnosis and treatment in overweight depressed patients, especially if outcome is not being satisfactory enough.

1. Introduction

Obesity and depression are growing as health problems in the developed world, with an estimated 350–500 million people are being globally affected with these conditions (Garcia-Toro et al., 2013; Lopresti et al., 2013). One factor that can contribute to explaining it is the population lifestyle changes (Lopresti et al., 2013). In fact, the association between depression and obesity is higher than expected by random effects (Rhee et al., 2014). Bidirectional causality between them is shown in previous studies (Luppino et al., 2010). Metabolic syndrome (MetS) is a combination of risk factors (abdominal or visceral obesity, hypertension, dyslipidemia, and glucose dysregulation) that are predictive diagnostics of coronary artery disease, metabolic diseases and certain cancers (Kahl et al., 2013). In both obesity and depression, MetS is highly prevalent and several studies have suggested that there is a bidirectional relationship between depression and MetS (Marazziti et al., 2014). Diet is a lifestyle key factor that could have influence on the onset of obesity, depression and MetS (Lopresti et al., 2013; Garcia-Toro et al., 2012). Evidence suggests that high adherence to the Mediterranean diet seems to have a favourable effect in preventing and treating depression in both MetS and obesity (Martínez-González et al., 2015; Garcia-Toro et al., 2014).

Diet, obesity and MetS are associated to subsequent incidence of depression (Preiss et al., 2013). A poor diet, obesity and MetS predispose to metabolic changes that interacts with brain function and psychopathology through very complex mechanisms, and probably with individualised effects for each patient (Mansur et al., 2015). Thus, the glucose and insulin homoeostasis, the

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sympathoadrenal and the immune-inflammatory axis, all are key mechanisms that altered involved in oxidative stress and monoamine alterations, leptin and insulin resistance and BDNF and HPA dysregulations (Mansur et al., 2015). Persistence in dysregulation of all these mechanisms has been linked to poor outcome of depression (Yoshimura et al., 2009).

Obesity has been related to treatment resistance in depression (Uher et al., 2009). MetS and a poor-quality diet have been also associated with a worst depression outcome (Jacka et al., 2015). To our knowledge, there is no longitudinal study that examines these three factors simultaneously in depression outcome. This is a very important point given its high interrelation, in order to compare them and clarify their relative contribution.

The purpose of the present study is to analyse the predictive impact of obesity, MetS and Mediterranean diet adherence on major depression outcome, at 6 and 12 months. The hypothesis is that obesity, MetS and low adherence to the Mediterranean diet at baseline will predict a poor outcome of depression at 12 months.

2. Methods

The study was approved by the Ethic and Clinical Research Committees of three Spanish regions (Balearic Islands, Catalonia and Aragon). A detailed research protocol has been registered (ISRCTN73931675) and published elsewhere (Garcia-Toro et al., 2014). Study participants were patients, aged 18 or more, with diagnosis of major depressive disorder as stated by the DSM-IV-TR, mild to moderate depressive symptoms for at least two months of duration who participated in a previous, multi-centre, cluster-randomized controlled trial, aimed to analyse the effectiveness of four structured hygienic-dietary recommendations in depression outcome (Serrano Ripoll et al., 2015). A total of 62 General Practitioners participated in the study and included 273 patients from primary health centres.

2.1. Measurements

Major depression was diagnosed using the Mini International Neuropsychiatric Interview (MINI). Depression severity was measured by the validated Spanish version of the Beck Depression Inventory (BDI-II). This instrument is widely used as it allows patients to self-score for depressive symptoms, avoiding evaluation bias, and determines a cut-off for mild or moderate depression. More than a 50% decrement for basal BDI and 12 month BDI was considered depression response.

Mediterranean diet was measured by a 14-item Mediterranean diet adherence score (MEDAS). The total score was categorized in two groups: <7 points (low adherence) and ≥ 7 points (high/medium adherence). Metabolic syndrome was diagnosed using the IDF criteria (Garcia-Toro et al., 2014).

All outcome variables were assessed 3 times: prior to the start of the study (baseline), after 6 and 12 months after inclusion (first and second follow-up respectively) in individual and face-to-face data collection.

3. Statistical analyses

Analyses were performed using SPSS version 21.0. Participants were categorized by sex to illustrate any difference between these groups, using Chi-square and *t*-Student tests, as appropriate. The main analysis examined the associations between MetS and BMI as categorical variables and BDI at 12-month as a continuous variable using general linear models.

4. Results

4.1. Descriptive

82% of the patients sampled were women, with an average of 51 years, one-third of patient were obese (BMI > 30). Seventy seven (28.3%) of the patients meet criteria for MetS.

At baseline MEDAS score was inverse and significantly associated with BDI score. Patients who were consuming less than 3 portions of fruits, one or more portions of butter, or soda drinks a day were significantly associated with higher basal BDI score. However, consuming more poultry meats than red meats was inversely associated with basal BDI score (Table 1).

4.2. Bivariate associations between depression response, diet, obesity and MetS

Response to depression was more likely in those patients with normal weight and not MetS but it was not associated with MEDAS score (Table 1). Although those patients were consuming nuts, at least once a week generating a tendency of response relatively ($p=0.063$) higher.

4.3. General linear models

We fit three stages of general linear model to the data to examine the contribution of obesity and MetS and potentially confounding variables to depression recovery measured at 12 month of follow-up. Models 1 and 2 showed a positive association between obesity, MetS and 12-month BDI differences adjusted by sex and age. Notably, when we introduced both terms in model 3, overweight adjusted by MetS change the direction of the association from positive to negative.

In order to further explore the potentially combined effect of obesity and MetS in depression recovery, patients were categorized in three groups: (1) no obesity and no MetS; (2) obesity and no MetS; (3) obesity and MetS. Those patients with MetS and obesity were less likely to improve symptoms of depression at 6 and 12 month of follow-up (Fig. 1).

5. Discussion

Our results indicated that both obesity and MetS predict a worst outcome of depression. Patients with comorbid obesity and MetS at baseline are clearly the most associated to a poorer depression prognosis one year later. Depression outcome of obesity without MetS patients is no different than no obesity and no MetS patients. Low adherence to the Mediterranean diet does not worsen depression prognosis at one year follow-up.

Obesity and depression are growing major public health concern and MetS could be a key mediator factor (Mansur et al., 2015). MetS has been linked to inflammatory processes and organism oxidative stress. These processes have been also described in depression (Maes et al., 2009). Moreover, the persistence of oxidative and inflammatory dysregulation has been linked to the risk of chronic depression (Yoshimura et al., 2009). Therefore, for depression improvement is important to ameliorate inflammatory and oxidative dysregulation (Lopresti et al., 2013). This leads to argue that, in addition to prescribing the most complete and energetic antidepressant treatment, it could be helpful to detect and treat MetS cases to improve depression prognosis. For instance, one option could be through interventions that would improve the quality of diets facilitating weight loss. Up to now, these programs were considered unviable because the interventions were potentially stressful in depressed patients (Serrano Ripoll et al., 2015);

Table 1
Cross-sectional and longitudinal associations between Mediterranean diet, BMI, MetS and basal BDI, 12 months BDI and 12 months BDI change. *N*=166.

	Basal BDI mean (SD)	*p*-Value	12 months BDI mean (SD)	*p*-Value	BDI difference mean (SD)	*p*-Value
BMI		0.169		0.012		**0.006**
Normal weight	23.6 (6.9)		13.6 (8.7)		−10.0 (8.0)	
Overweight	22.2 (7.4)		15.8 (10.5)		−6.1 (6.7)	
Obesity	24.8 (7.8)		19.6 (11.3)		−5.3 (9.5)	
Metabolic syndrome		0.473		0.01		**0.013**
No	23.8 (8.0)		15.5 (10.1)		−8.3 (8.1)	
Yes	24.7 (7.6)		19.68 (10.8)		−5.0 (8.5)	
Mediterranean diet		**0.007**		0.136		0.625
Low adherence	24.9 (8.1)		17.6 (10.6)		−7.0 (8.5)	
Moderate/high	22.1 (6.7)		15.1 (9.9)		−7.6 (7.8)	
Med. diet components						
Olive oil main culinary fat		0.541		0.459		0.098
No	25.2 (8.6)		14.9 (11.8)		−10.8 (8.8)	
Yes	24.0 (7.8)		17.1 (10.4)		−6.9 (8.2)	
Olive oil ≥ 4 tablespoons/d		0.973		0.963		0.463
No	24.1 (7.6)		16.9 (10.0)		−7.9 (7.1)	
Yes	24.1 (7.9)		16.9 (10.1)		−6.9 (8.8)	
Vegs ≥ 2 serv./d		0.137		0.396		0.421
No	24.7 (8.4)		17.5 (10.9)		−7.6 (8.9)	
Yes	23.3 (7.0)		16.2 (9.9)		−6.6 (7.6)	
Fruits ≥ 3 serv./d		**0.070**		0.697		0.570
No	24.7 (8.1)		17.1 (10.6)		−7.4 (8.99)	
Yes	22.9 (7.2)		16.5 (10.2)		−6.7 (7.2)	
Red meats < 1/d		0.131		0.095		0.220
No	24,9 (8.4)		18.2 (10.7)		−6.4 (8.5)	
Yes	23,4 (7.2)		10.1 (15.7)		−7.9 (8.1)	
Butter, marg, cream < 1/d		**0.015**		0.083		0.825
No	25.0 (7.7)		17.9 (10.4)		−7.3 (8.3)	
Yes	22.5 (7.8)		17.15 (10.3)		−6.9 (8.5)	
Soda drinks < 1/d		**0.009**		**0.008**		0.514
No	25.0 (8.1)		18.4 (10.7)		−6.9 (8.7)	
Yes	22.4 (7.3)		14.2 (9.4)		−7.7 (7.6)	
Wine ≥ 3 glasses/wk		0.677		0.771		0.534
No	24.2 (7.9)		17.0 (10.6)		−7.0 (8.6)	
Yes	23.6(7.2)		16.4 (9.7)		−8.0 (6.9)	
Legumes ≥ 3/wk		0.799		0.865		0.824
No	24.0 (7.8)		17.0 (10.6)		−7.1 (8.5)	
Yes	24.4 (7.9)		16.6 (9.7)		−7.4 (7.6)	
Fish and seafood ≥ 3/wk		0.488		0.149		0.675
No	23.8 (7.9)		16.1 (10.89)		−7.3 (9.0)	
Yes	24.6 (7.6)		18.4 (9.7)		−6.8 (7.0)	
Cakes, sweets < 3/wk		0.951		0.361		0.535
No	24.1 (8.1)		16.4 (10.7)		−7.4 (8.7)	
Yes	24.0 (7.4)		17.9 (10.1)		−6.6 (7.7)	
Nuts ≥ 1/wk		0.716		0.507		**0.063**
No	23.9 (7.7)		17.3 (10.5)		−6.3 (8.4)	
Yes	24.3(8.0)		16.3 (10.4)		−8.6 (8.0)	
Poultry > red meats		**0.007**		0.331		0.124
No	21.9 (6.5)		15.7 (10.2)		−5.5 (8.2)	
Yes	24.8 (8.1)		17.3 (10.5)		−7.7 (8.3)	
Vegetables styr-fry		0.257		0.881		0.662
No	24.8 (8.0)		17.0 (10.0)		−7.4 (8.3)	
Yes	23. 7 (7.7)		16.8 (10.89)		−6.9 (8.4)	

*ANOVA and Chi-square tests. SD=standard deviation, MetS=metabolic syndrome, BDI=Beck Depression Inventory.

however, recent studies have shown opposite evidences (Katon et al., 2012).

Interestingly, in our study obese patients without MetS do not have a worst depression prognosis. In other words, MetS but not obesity *per se*, seems to be the key predisposing factor to depression initiation and maintenance, as previously suggested previously (Mansur et al., 2015). Certainly it is not a conclusive finding, especially for the scarce study sample, that preclude us to study patients with MetS and no Obesity. However, this is consistent with a growing medical literature that indicates that "metabolically healthy obese" (*fat fit*) are not predisposed towards health problems of obese but not fit people (*fat not fit*) (Barry et al., 2014). Mediating this circumstance could be the MetS presence or absence, which probably imply greater degree of inflammation and oxidative stress in obese patients, and therefore a greater neurobiological connection with depression (Maes et al., 2009). Certain psychosocial factors associated with obesity as important mediators of depressive risk (onset and maintenance) has been identified: lower self-esteem, worsen self-image, functional limitations, social rejection, employment discrimination, etc. (Luppino et al., 2010). Our data indicate that at least these factors do not have the most important role explaining the obesity–depression comorbidity. However, some studies with bipolar patients have found that obesity, but not MetS, negatively affects outcome (McElroy et al., 2015). We need more studies to clarify whether this discrepancy is due to methodology or disorder differences.

Regarding the Mediterranean diet adherence we have not found an influence on the evolution of patients, despite the correlation between the MEDAS score and some items (consumption of sodas, butter and white meat preference for red) with the

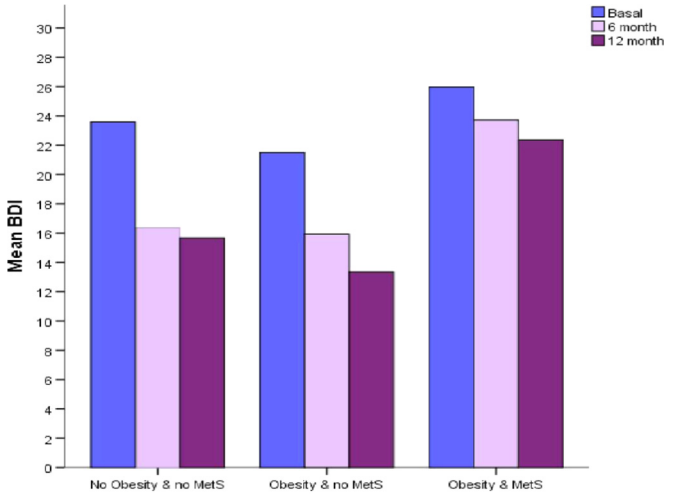

Fig. 1. Association between obesity, MetS and BDI change. * $p=0.002$ for the comparison of 6 month BDI between groups, $p=0.002$ for the comparison of 12 month BDI between the 3 groups and ** $p=0.037$ for the comparison of the difference between 12 month BDI and basal BDI between the 3 groups. $p=0.721$ for the comparison of basal BDI between the 3 groups (none, only obesity, obesity and MetS). ANOVA test was used. MetS=metabolic syndrome, BDI=Beck Depression Inventory.

severity of depression at baseline. Surprisingly, more red meat consumption is associated with lower baseline depression score. These findings were unexpected as the Mediterranean diet discourages frequent red meat consumption and suggests white meat replacement. Nevertheless, previous studies have already reported this controversial finding linking depression and red meat intake (Opie et al., 2014).

The present study has some weaknesses that need to be acknowledged for further interpretation. Sample is not big enough to make analysis such as a comparative study of patients with MetS but not obesity. This sample of patients display obesity-related disorders, with a potential worst depression outcome, however our data cannot confirm it (Mansur et al., 2015). This study was designed to evaluate the impact of lifestyle recommendations on depressive patients, offering them different diet suggestions (Uher et al., 2009). Nevertheless, we have already mentioned that this fact did not have any effect in the outcome of depression, but in any case it has been taken into account in the statistical analysis (Serrano Ripoll et al., 2015). Adherence to Mediterranean diet is only assessed through the self reported MEDAS scale. The trial was made with a clinical sample of three Spanish regions, and this may limit the generalisability of the findings. The core strength of this study is the prospective of a simultaneous evaluation of MetS, obesity and Mediterranean diet in major depression patient's outcome.

This study has a direct clinical implication as it suggests that obesity with MetS could be a key risk factor for bad depression prognosis. There is an extensive literature on the risk factors for Chronic Major Depression Disorder. Some of the most often demonstrated are early stages of onset, with factors such as family history of mood disorders, lower socioeconomic status, co-occurrence of other mental disorders, low quality of life, delaying first treatment-seeking for depression, and other greater number of stressful life events (Garcia-Toro et al., 2013). Obesity with comorbid MetS could be another poor response factor for depression, however can be reversible. It is important to consider MetS in obese patients and, if confirmed, intervene with clear recommendations. We are learning that depressive patients are able to change their diets and physical activity levels, but need tailored support and information throughout the process (Serrano Ripoll et al., 2015). This study suggests that MetS could be an important mediator factor between obesity and depression, but prior studies point to obesity itself (Luppino et al., 2010). Further research on the relationship between obesity and MetS relationship will help to define the importance in depression prognosis.

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