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Highlights

- MetS was more prevalent among subjects with depression and anhedonia
- Subjects with depression and anhedonia have a worse metabolic profile
- Anhedonia may contribute to development of MetS

Metabolic syndrome, depression and anhedonia among young adults

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Abstract

The aim of this study was to assess the association between anhedonia and metabolic syndrome in a well-characterized community sample of individuals with a current depressive episode. This is a cross-sectional study with young adults aged 24 to 30 years old. Depressive episode and the presence of anhedonia was assessed using the Mini

International Neuropsychiatric Interview – Plus version (MINI Plus). The MetS was assessed using the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III). The sample included 931 subjects, being 22 had depression without anhedonia, whereas 55 had depression with anhedonia. MetS was more prevalent among subjects with depression and anhedonia (43.6%) when compared to individuals without anhedonia and population control group. Moreover, subjects with depression and anhedonia have a significant increase of levels of glucose, triglycerides, total-cholesterol and LDL-cholesterol, as well as significant decreased in the HDL-cholesterol level. The present study showed that individuals with depression and anhedonia present higher prevalence of MetS. Our study suggests that the use of the concept of anhedonia may contribute to a better understanding of the complex relationship between depression and metabolic syndrome.

Keywords: depression; anhedonia; metabolic syndrome

1. Introduction

Anhedonia is defined by DSM-V as the diminished ability to obtain pleasure from otherwise positive stimuli and as a keystone symptom of various neuropsychiatric disorders, such as major depressive disorder (MDD) (American Psychiatric Association, 2013). It is one of the main symptoms of depression and recent studies indicate that approximately 40% of individuals diagnosed with depression experience significant anhedonia (Pelizza and Ferrari, 2009; Romer Thomsen et al., 2015; Spijker et al., 2001). Emerging evidence consistently documents that depression is an important risk factor for Metabolic Syndrome (MetS) (Pan et al., 2012; Vancampfort et al., 2014). A recent meta-analysis found that individuals with depression showed 1.5 times higher of developing MetS compared with general population controls (Vancampfort et al., 2014). It's considered the influence of anhedonia on unhealthy lifestyles such as poor dietary habits, lack of physical exercise, smoking and excessive alcohol consumption. Psychotropic drugs are also established risk factors that contribute to the MetS (Ho et al., 2014). Lifestyle may be impaired in the presence of anhedonia due to the lack of motivation to develop and/or maintain a healthy lifestyle including physical activity and eating habits (Ghanei Gheshlagh et al., 2016; Lehto et al., 2008; Pan et al., 2012).

MetS is a clustering of cardiovascular and metabolic risk factors that include impaired glucose metabolism, dyslipidemia, abdominal obesity and hypertension (Eckel et al., 2005). Approximately one-third of the adult population fulfills the diagnostic criteria for MetS, increased to 42% in individuals with depression (Eckel et al., 2005; Pan et al., 2012). This high co-occurrence between depression and MetS suggests a possible pathophysiological overlap (Pan et al., 2012). High cortisol secretion due to hyperactivity the hypothalamic-pituitary-adrenal (HPA) axis, insulin resistance and unhealthy lifestyle habits are some factors that may mediate the association between depression and MetS (Martinac et al., 2014). In this sense, epidemiologic studies evaluating the association

between depressive disorders/symptoms and MeS suggest that a bidirectional relationship exists between these conditions. Depression occurs at a higher rate in individuals with components of MeS (and vice versa). While there are numerous accounts on the association between depression and MetS fewer studies looked specifically at the relationship between metabolic changes and anhedonia (Ghanei Gheshlagh et al., 2016; Lehto et al., 2008; Pan et al., 2012). Thus, our hypothesis is that individuals with depression suffering from anhedonia, would present a higher prevalence of metabolic syndrome than those not suffering from anhedonia. The aim of this study was to assess the association between anhedonia and metabolic syndrome in a well-characterized community sample of individuals with a current depressive episode.

2. Methods

2.1. Study design and sample

This is a cross-sectional report corresponding to the second wave of a population-based cohort study of 1560 young adults aged 18-24 years. Sample selection was performed using clusters, considering the census division of the city (Pelotas-Brazil) in 2010 (IBGE – *Instituto Brasileiro de Geografia e Estatística*; <http://www.ibge.gov.br>). In order to assure the necessary sample size, 89 census-based sectors were randomly selected. The home selection in the sectors was performed using a systematic sampling. Further details of the study are available elsewhere (Cardoso Tde et al., 2015; Duarte Faria et al., 2015; Jansen et al., 2011). The second wave took place between 2012-2014, approximately five years after the first phase. All young adults who participated in the first phase were invited to participate in the second phase.

The participation rate in the second phase was 80.70% from the first cohort sample, for a total of 1260 young adults. Among these, 237 individuals declined blood collection, resulting in a total of 1023 subjects eligible for this study. All participants agreed to

participate in the study by providing their free, informed consent. This study was approved by the Research Ethics Committee of the *Universidade Católica de Pelotas* (UCPel) under protocol number 2008/118. The youngsters who presented any psychiatric disorders and/or drug abuse were directed to psychiatry outpatient care.

2.2. Instruments

2.2.1. Sample characteristics

The socioeconomic evaluation of the participants was assessed using the *Brazilian Association of Research Companies* (ABEP, 2008). This classification is based on the total of material goods and the householder's schooling: "A" refers to the highest socioeconomic level, and "E" being the lowest. Substance abuse or dependence was assessed with the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), and a cut-off of 4 points for substance abuse/dependence (Henrique et al., 2004; Humeniuk et al., 2008). In addition, the individuals were asked about any psychotropic drug use.

2.2.2. Assessment of depression and anhedonia

The Mini International Neuropsychiatric Interview – PLUS (MINI-PLUS) was administered to all participants by master's and PhD level trained psychologists. It was used for the diagnoses of current depression and anhedonia (Amorim et al., 1998). For the populational control group, we excluded individuals with only anhedonic without depression (13), individuals with bipolar disorder in episode (n=40) and euthymic (n=39), totaling 944. The MINI-PLUS is a semi-structured clinical interview based on DSM-IV criteria.

2.2.3. Assessment of Metabolic Syndrome

The diagnosis of metabolic syndrome was defined using the National Cholesterol Education Program – Treatment Adult Panel III (NCEP/ATPIII) modified criteria (Grundy et al., 2005). When a subject has three of the five listed criteria, a diagnosis of the metabolic syndrome can be made. The criteria listed include: 1) glucose intolerance presenting higher fasting glucose or equal to 100 mg/dL; 2) increased waist circumference or abdominal

obesity (≥ 102 cm for men and ≥ 88 cm for women); 3) raised triglyceride levels ≥ 150 mg/dL; 4) reduced HDL-C ≤ 40 mg/dL for men and ≤ 50 mg/dL for women; and 5) elevated blood pressure (systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg). Consequently, we computed Castelli risk index 1, i.e. total/HDL cholesterol, and Castelli risk index 2, i.e. LDL/HDL cholesterol.

Anthropometric measurements were taken for the evaluation of metabolic syndrome. Waist circumference (WC) was assessed to the nearest 0.1 cm using an inelastic measuring tape midway between the lower ribs margin and the iliac crest in the horizontal plane. Height was measured without shoes to the nearest 0.1 cm. Weight was measured in kilograms to the nearest 0.1 Kg. Body Mass Index (or BMI) was calculated as the weight (in kilograms) and height (in meters), according to the formula: Kg/m² (WHO, 2008). Systolic and diastolic blood pressures were measured using a sphygmomanometer. Individuals remained seated for 5 minutes prior to obtaining the measurements. At least two blood pressure measurements were performed, spaced 1-2 min apart, and additional measurements if the first two were discordant. The average blood pressure was then recorded (Mansia et al., 2007).

Ten milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at $3.500\times g$ for 15 min, and serum was kept frozen at -80 °C until analysis. Techniques for measurements of serum levels of glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were used in accordance with guidelines of the manufacturers of commercial Kits, Katal Biotecnologica® (MG, Brazil). Serum levels of glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were expressed in mg/dL.

2.2.4. Data analysis

Descriptive data are expressed as means and standard deviations (SD). Demographic and clinical characteristics were analyzed using chi-square test and one-way ANOVA where applicable. Comparisons between metabolic parameters in subjects with depression, with and without anhedonia, and control group were made by ANOVA, followed by the Bonferroni post-hoc test. We used multiple linear regression to control for possible confounding factors, based on a conceptual model with three hierarchical levels: the first, composed of demographic variables (gender, ethnicity, and age); the second level, the socioeconomic index; and third, by morbidities and lifestyle habits (abuse / dependence alcohol, abuse / dependence on tobacco, psychoactive drugs, and medication), staying in the model the variables with $p < 0.20$. Results with p values < 0.05 were considered statistically significant.

3. Results

The sociodemographic status and clinical characteristics of the subjects are shown in Table 1 according to the depression diagnosis (populational controls, depression with anhedonia, depression without anhedonia). Seventy-seven individuals were diagnosed with depression. Of these, twenty-two (28.6%) had depression without anhedonia, whereas 55 (71.4%) had depression with anhedonia. Differences in the three groups were found in gender ($p < 0.001$), ethnicity ($p = 0.003$), socioeconomic classification ($p < 0.001$) and use of psychiatric medication ($p < 0.001$).

MetS was more prevalent in people with depression and anhedonia (43.6%) when compared to individuals without anhedonia and populational controls ($p < 0.001$). Similarly, those with depression and anhedonia had significantly higher glucose ($p < 0.001$), triglycerides ($p < 0.001$), total-cholesterol ($p < 0.001$) and LDL-cholesterol ($p < 0.001$) levels, as well as significant decreased HDL-cholesterol level ($p < 0.001$) when compared to without anhedonia and populational controls. Bonferroni post hoc test for multiple comparisons

showed differences between individuals with and without anhedonia on levels of glucose ($p<0.001$), triglycerides ($p<0.001$), total-cholesterol ($p=0.003$) and LDL-cholesterol ($p=0.003$), such as castelli risk index 1 and 2 ($p<0.001$) (Table 2).

After adjustments for demographic variables (gender, ethnicity and age), socioeconomic index, morbidities and lifestyle habits (abuse/dependence alcohol, abuse/dependence on tobacco and medication), these differences remained statistically significant (Glucose: $p<0.001$; $B=0.282$; triglycerides: $p<0.001$; $B=0.160$; total-cholesterol: $p<0.001$; $B=0.199$; HDL-cholesterol: $p<0.001$; $B=-0.179$; LDL-cholesterol: $p<0.001$; $B=0.147$; Castelli risk index 1: $p<0.001$; $B=0.480$; Castelli risk index 2: $p=0.038$; $B=0.238$).

4. Discussion

People in this population-based sample who had anhedonia had a higher prevalence of metabolic syndrome than those depressed, but not anhedonic. Higher levels of glucose, total-cholesterol, triglycerides, LDL-cholesterol, and lower HDL-cholesterol levels were also observed in people with anhedonia.

The results of the present study are in line with evidence suggesting that anhedonia has important clinical consequences in depression (Lally et al., 2015; Pelizza and Ferrari, 2009). Moreover, literature shows that prevalence and morbidity risk of depressive disorder are higher in women than in men (Leach et al., 2008). Our study has a higher prevalence of anhedonic among women with depression, reaching almost 90%. A large cross-national study encompassing 23 European countries confirms that women report higher level of depressive symptoms than men, however the authors did not show what symptoms was association (Van de Velde et al., 2010). We believed that there are distinct neuroendocrine adaptations between men and women, which may interfere with the symptomatology of anhedonia (Shimamoto et al., 2015) and consequently to metabolic syndrome.

Previous studies showed that anhedonia is independently associated with major adverse clinical events and all-cause mortality (Davidson et al., 2010; Nefs et al., 2016). A recent longitudinal study involving 1465 subjects with type 2 diabetes showed that anhedonia predicted a two-fold increase in mortality. This study followed patients along 5.5 years, suggesting that anhedonia predicted a shorter survival time, mainly due to cardiovascular risk (Nefs et al., 2016). Our study found that individuals with anhedonia have higher Castelli risk indexes 1 and 2, which are associated with increased cardiovascular risk and may increase mortality. These findings suggest that assessing the presence of anhedonia in those with major depression may provide new insights on mechanisms underlying increased risk of cardiac events.

Our results demonstrate higher levels of glucose, total-cholesterol, triglycerides, LDL-cholesterol, and lower HDL-cholesterol levels in individuals with depression and anhedonia. While depression has been associated with increased glycemia and cholesterolemia, symptoms of anhedonia were not systematically assessed (Moreira et al., 2016; Vancampfort et al., 2015). Nefs, et al. (2016), found that changes in serum levels of cholesterol, glucose and blood pressure can be mediator for higher mortality in subjects with symptoms of anhedonia (Nefs et al., 2016). Keranen et al., (2010 and 2009), found that the presence of anhedonia, regardless mood disorder diagnosis, was associated with an increased food intake, binge eating and obesity (Keranen et al., 2010; Komulainen et al., 2011).

However, in our study we did not find an association between anhedonia and obesity. The lack of association in our sample might be explained by the fact of our sample be composed of young adults with mean age of 25.8 years old, while Keranen's studies the mean of age was 49 years old. In a longitudinal study with healthy adult subjects, anhedonia was associated with weight gain at one year follow-up, while subjects without anhedonia were able to lose weight within a one-year follow-up (Ibrahim et al., 2016).

In view of the metabolic and endocrine disturbances that are characteristic of MetS, as well as how these changes may impact the central nervous system, a possible role of metabolic changes in the causality of depression has been suggested (Der-Avakian and Markou, 2012; Hyman and Fenton, 2003). Anhedonia has been recently conceived that regulates emotional responses linked to reward. Recent neuroimaging studies in depressed patients showed reduced activation of the reward circuitry in depression, specifically the nucleus accumbens and anterior cingulate cortex (Satterthwaite et al., 2015). It is possible that individuals with anhedonia seek reward through palatable and high-calorie food. These foods are usually high in refined sugars and saturated fats, leading to hyperphagia, which associated with a sedentary lifestyle, may contribute significantly to obesity and, consequently, can lead to metabolic syndrome (de Oliveira et al., 2014; Ibrahim et al., 2016; Kanoski and Davidson, 2011). Brinkmann et al., 2009, assessed blood pressure reactivity in individuals submitted to reward and punishment tests. The authors found that subjects with depression showed less reactivity in systolic blood pressure suggesting anhedonic behavior (Brinkmann et al., 2009). Moreover, it is known that leptin-related metabolic routes are important in appetite regulation and may be disrupted in patients with depression (Dillon et al., 2014). Similarly, hormone released in response to physiologic stress, can lead into weight gain through appetite stimulation (Epel et al., 2001). However, in the present study we were not able to assess levels of these hormones. Further studies are needed to assess the relationship between anhedonia and the appetite hormones.

To the best of our knowledge, this study is the first investigating the anhedonia as a particularly prominent risk factor for metabolic syndrome among individuals with a current depressive episode. Moreover, it is a population-based study in which participants were systematically recruited according to the clusters of census data of the city, which greatly enhances the validity of these findings. The study has some limitations. Because of the cross-sectional design, we cannot make causal inferences between MetS and anhedonia. We

did not assess behavioral factors such as sedentary lifestyle and eating habits. The subgroup of subjects with and without anhedonia is relatively small, with wide confidence intervals resulting. We did not assess anhedonia in the control subgroup. The young age of our sample makes the generalization of this study limited. Our sample was recruited from just one specific city in the south of Brazil, and it certainly would be of interest to have replications from diverse samples confirming these findings. All participants were recruited from an urban area, and the absence of people from rural areas could limit extrapolation to these populations.

5. Conclusion

In conclusion, the present study showed that individuals with depression and anhedonia present higher prevalence of MetS. Our study suggests that the use of the concept of anhedonia may contribute to a better understanding of the complex relationship between depression and metabolic syndrome. Future studies are needed to investigate the impact of anhedonia on health outcomes among patients with mood disorders.

Conflict of interest

All authors declare they have no conflicts of interest.

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Table 1. Demographic and clinical Characteristics according to depression diagnosis.

	Total	Populational	Current depression		<i>p value</i>
	Sample	Controls	Anhedonia	No anhedonia	
Gender, female ^a	545 (57.7)	481 (55.5)	46 (83.6)	18 (81.8)	<0.001
Ethnicy, Caucasian ^a	654 (69.3)	613 (93.7)	27 (49.1)	14 (63.6)	0.003
Age ^b	25.81 ± 2.17	25.79 ± 2.18	26.56 ± 2.15	25.27 ± 2.05	0.318
ABEP ^a					<0.001
Upper	561 (59.4)	537 (61.9)	12 (21.8)	12 (54.5)	
Middle or lower	425 (41.5)	383 (38.1)	43 (78.2)	10 (45.5)	
Alcohol ^a	202 (21.4)	180 (20.8)	16 (27.3)	6 (29.1)	0.272
Smoking ^a	216 (22.9)	193 (22.3)	16 (29.1)	7 (31.8)	0.303
Psychoactive drugs ^a	86 (10.3)	81 (10.6)	2 (3.9)	3 (18.8)	0.171
Psychotropic medication ^a	214 (22.7)	163 (18.8)	36 (65.5)	15 (68.2)	<0.001
Age of onset ^c	23.20 (18.00 – 25.00)	-	18.00 (15.75-23.00)	20.50 (18.00-24.25)	0.260
TOTAL	944	867 (91.8)	55 (5.8)	22 (2.3)	

^a chi- squared test, represented by n (%); ^b ANOVA, represented by mean ± SD; ^c Kruskal-wallis, represented by median (interquartile range). ABEP: *Associação Brasileira de Empresas de Pesquisa*

Table 2. Metabolics characteristics according to depression diagnosis.

Variables	Total sample	Populational control	Current Depression		<i>p</i> va betw grou
			Anhedonia	No anhedonia	
Metabolic Syndrome^a	217 (23.0)	189 (21.8)	20 (43.6)	8 (36.4)	0.00
Metabolic characteristics					
Abdominal circumference (cm) ^b	84.93±14.41	84.83 ± 14.49	89.00 ± 14.71	83.17 ± 13.26	0.32
BMI (Kg/m ²) ^b	26.34 ± 5.42	26.28 ± 5.39	27.43 ± 5.52	26.21 ± 5.48	0.14
Blood pressure (mmHg) ^b					
Systolic	126.47±19.11	126.63±19.21	130.27±17.85	123.05±18.18	0.06
Diastolic	78.06±12.78	78.05±12.74	80.58±13.24	77.17±13.15	0.22
Glicose (mg/dL) ^b	87.39±21.11	85.41±16.01	125.74±48.93	85.35±9.24	< 0.0
Triglycerides (mg/dL) ^b	132.22 ± 72.00	127.77 ± 62.12	226.49±139.82	122.59±36.28	< 0.0
Total cholesterol (mg/dL) ^b	199.79±53.21	195.93±51.78	247.71±61.62	201.84±59.08	< 0.0
HDL cholesterol (mg/dL) ^b	44.49±16.06	45.30 ± 16.19	32.63 ± 6.95	38.92 ± 4.85	< 0.0
LDL cholesterol (mg/dL) ^b	127.06±49.46	125.23±49.03	169.45±47.79	123.87±51.79	< 0.0
Castelli risk index 1 ^b	4.87±1.91	4.71±1.75	7.76±2.39	5.34±1.37	< 0.0
Castelli risk index 2 ^b	3.21 ± 1.67	3.08±1.57	7.76±2.39	3.36±1.39	< 0.0
TOTAL	944	867 (91.8)	55 (5.8)	22 (2.3)	

^a chi- squared test, represented by *n* (%); ^b ANOVA, followed by Bonferroni post-hoc test, represented by mean ± SD; BMI: body mass index; HDL-cholesterol: High density lipoprotein cholesterol; LDL-cholesterol: Low density lipoprotein cholesterol; Castelli risk index 1 = total/HDL cholesterol; Castelli risk index 2: LDL/HDL cholesterol.

1 – Depression with anhedonia group versus populational control group

2- Depression without anhedonia group versus populational control group

3- Depression with anhedonia group versus depression without anhedonia group.