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Artigo Original

The Impact of Abstinence on Serum Leptin Levels and on the Nutritional Profile of Alcoholics

O Impacto da Abstinência nos Níveis Séricos de Leptina e no Perfil Nutricional de Alcoolistas

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ABSTRACT

Introduction: Alcohol use disorder (AUD) is associated with changes in metabolism and in the nutritional profile. Food-seeking behaviors and psychoactive substances share common biological pathways that activate the reward system and leptin is a modulator of this system. **Objective:** To measure serum leptin levels and nutritional status of individuals with before their detoxification and then 15 days later. **Material and Methods:** In total, 38 men diagnosed with AUD and admitted to a detoxification unit were analyzed. Serum leptin levels, Body Mass Index (BMI), Waist Circumference (WC) and body composition were assessed by Bioelectrical Impedance Analysis (BIA) within the first 48 hours of hospital admission and again 15 days after the first assessment. **Results:** Weight, BMI and WC increased significantly during detoxing (p<0.001), but body fat and leptin levels percentages remained similar. At admission, leptin levels were positively correlated with body fat (0.607), WC

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(0.696), and BMI (0.357). After 15 days, only leptin and BMI were significantly correlated (0.462). **Conclusion:** Our results reinforce the relationship between leptin and nutritional parameters related to body weight. It is essential to educate about nutrition and to encourage healthy eating behaviors so individuals with AUD can reduce weight gain during the recovery period.

Keywords: Alcohol Use Disorder; Body Composition; Nutritional Status; Body Mass Index; Leptin.

RESUMO

Introdução: O transtorno por uso de álcool (TUA) está associado a alterações metabólicas e perfil nutricional. Comportamento de busca de alimentos e substâncias psicoativas compartilham vias biológicas comuns ativando o sistema de recompensa e a leptina modula esse sistema. **Objetivo:** Avaliar níveis séricos de leptina e estado nutricional de indivíduos antes e 15 dias após a desintoxicação. **Materiais e M**étodos: Foram analisados 38 homens com diagnóstico de TUA internados em unidade de desintoxicação. Níveis séricos de leptina, Índice de Massa Corporal (IMC), Circunferência da Cintura (CC) e composição corporal foram avaliados por Bioimpedância Elétrica (BIA) nas primeiras 48 horas de internação e 15 dias após a primeira avaliação. **Resultados:** Peso, IMC e CC aumentaram significativamente durante a desintoxicação (p<0,001), mas os percentuais de gordura corporal e níveis de leptina permaneceram semelhantes. Na admissão, os níveis de leptina foram positivamente correlacionados com a gordura corporal (0,607), CC (0,696) e IMC (0,357). Após 15 dias, apenas leptina e IMC foram significativamente correlacionados (0,462). **Conclusão:** Os resultados reforçam a relação entre leptina e parâmetros nutricionais relacionados ao peso corporal. A educação nutricional e o incentivo ao comportamento alimentar saudável são essenciais para que indivíduos com TUA reduzam o ganho de peso na desintoxicação.

Palavras-chave: Transtorno do Abuso de Álcool; Composição Corporal; Estado Nutricional; Índice de Massa Corporal; Leptina.

INTRODUCTION

Alcohol use disorder (AUD), a major public health problem, affects about 2.3 million people aged 12 to 65 in Brazil[1]. It is a multifactorial and chronic condition that causes many legal, social, and occupational problems[2], and affects central nervous, digestive, and cardiovascular systems[3,4]. AUD results in physical and psychiatric diseases and increases global morbidity and mortality rates[3,5]. Excessive alcohol use causes 5.1% of all deaths worldwide (about 3 million) and 5.3% of diseases and injuries in general (DALY – Disability-Adjusted Life Year). In fact, mortality from alcohol use is more common than death from diseases such as tuberculosis, HIV/AIDS, and diabetes[3].

Chronic alcohol use can affect nutritional status and eating habits[6,7]. There are changes in digestion, absorption and metabolism of nutrients, which can lead to malnutrition, overweight or obesity, metabolic disorders, dysbiosis[8–10] and affect body composition, hormones, appetite, and satiety mechanism[6,7,11,12].

Especially during abstinence, the nutritional profile of substance users is characterized by overweight[13–15]. In the first six months of abstinence, users reported binge eating and use of food to satisfy cravings for psychoactive substances[12,16]. Evidence indicates that alcoholism and food-seeking behaviors share common biological pathways[17,18]. Hyper-palatable foods, rich in fat[19] and sugar[20], affect the brain's reward system similarly to psychoactive substances (PAS)[18,21], promoting excessive food intake and associating encouragement with reward[17]. Thus, it is suggested that alcohol abuse is replaced by the intake of high-caloric foods with low nutritional value to keep the reward system active along with the pleasure associated with it[22]. Therefore, alcohol users are increasingly at risk of obesity and other health-related disorders[13,23].

Considering evidences, there seems to be a neurochemical overlap between the reward system and the system that regulates energy balance. Among the neuropeptides with significant roles in both pathways, leptin stands out[24]. Leptin is a hormone that acts on receptors in the hypothalamus and plays a key role in regulating energy intake and expenditure, including appetite and metabolism. It modulates reward-driven behavior, especially by attenuating dopaminergic activity[25,26]. Studies on individuals with substance use disorder found a positive correlation between leptin and body mass index (BMI)[6,27]. As described by Escobar et al.[14], high leptin levels were associated with increased BMI and severe addiction in crack and cocaine users. Individuals with AUD had higher leptin levels compared to the controls, regardless of BMI[28]. However, some studies described controversial results about leptin levels, especially during alcohol abstinence. Some studies reported an increase in leptin levels during abstinence[29,30], while others found no change[31] or even a decrease in serum levels[24].

It is important to identify the nutritional profile and body composition of abstinent alcoholics and to assess their serum leptin levels, associated with anthropometric parameters, in order to support better treatments with nutritional interventions. Studies about leptin levels and nutritional status in individuals with AUD, who lack of a specific nutritional support are conflicting. Therefore, this study aims to verify the variation in the serum leptin levels of alcoholics at the beginning of abstinence and its association with nutritional status and body composition, assessed by anthropometry and bioelectrical impedance.

MATERIAL AND METHODS

This is a 15-day longitudinal study carried out at the Addiction Psychiatric Unit of a teaching hospital in southern Brazil. This study was approved by the Research Ethics Committee of the Hospital (CAAE 80099317.6.0000.5327) and all participants signed an informed consent form. Furthermore, all researchers signed the data confidentiality term, guaranteeing anonymity and confidentiality of the participants' data, according to the Guidelines and Norms for Research Involving Human Beings, Resolution 466/2012 of the National Health Council (CNS, 466 /2012).

Participants and procedure

This study followed the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) to evaluate 38 men diagnosed with AUD, aged from 18 to 60 years, without the associated use of psychoactive substances other than tobacco (65.8%). Patients with cardiac, endocrine, renal, or liver disease who stayed at the hospital for less than 15 days were excluded. All patients admitted to the Addiction Psychiatric Unit who met our inclusion and exclusion criteria were invited to participate in the study. Data was collected from December 2018 to August 2019 at hospital admission and after 15 days of hospitalization.

Sociodemographic and alcohol consumption data, including clinical and psychiatric information, were extracted from the patient's hospital records. The type of alcoholic beverage was converted into grams of ethanol based on the amount of pure ethanol (about 14g) in a standard drink, equivalent to 40ml of distilled beverage, 340ml of beer or 140ml of table wine[32].

Anthropometric and body composition assessment

Anthropometric and body composition data obtained in the first 48 hours after hospital admission and 15 days after the first evaluation. Trained professionals conducted all procedures, hospital nutritionists (LB and JVF) collected the anthropometric measurements, and the equipment was calibrated following the manufacturer's recommendation.

BMI was calculated with weight divided by height in squared meters (kg/m^2). The BMI classification followed the cutoff points of the World Health Organization[33] as follow: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m²), overweight (25–30 kg/m²), and obese (> 30 kg/m²). Weight was measured with a fixed electronic anthropometric scale from Lider® (Araçatuba, SP). Subjects were barefoot, wearing as little clothing as possible, placed at the center of the scale. Height was measured using an anthropometric ruler fixed to the scale while the patient was in the Frankfurt position[34].

Waist circumference (WC) was obtained using a non-elastic metal measuring tape from Cescorf®. Patients stood erect with no upper clothes, a relaxed abdomen and arms extended along the body. The midpoint between the last costal arch and the iliac crest was used as a reference in an orthostatic position during exhalation[34]. Men who have waist circumference greater than 94 cm are considered to be at increased risk for cardiometabolic disease[23].

Bioelectrical impedance analysis (Byodinamics®, model 450) was used to assess body composition while the patient laid down with legs and arms parallel to the body and away from the trunk. Electrodes were placed in recommended locations, according to the manufacturer's guidelines and established international protocols[35].

Biological and laboratory markers

Blood samples used to assess lipid and liver markers were collected at admission, as part of the hospital protocol. The biochemistry department of the hospital performed the analyses, using the colorimetric method for Gamma-Glutamyl Transferase (GGT) and the enzymatic method for the other tests, following local routine protocols.

For the analysis of leptin levels, peripheral venous blood samples were collected at two different times: on the 1st day after hospital admission and after 15 days of hospitalization. All blood samples were collected after a 12h fasting, between 7:30 and 08:00 AM. Samples were collected in tubes without anticoagulants and centrifuged for 15 min at 4°C and 1500 rpm within 30 minutes after collection. Serum was separated, aliquoted into 1.5 mL microtubes and stored at −80°C for further analysis. Serum leptin levels were analyzed by the Multiplex Bead Immunoassay, using the Human Magnetic Custom Luminex Kit by Luminex System 200 (Invitrogen from Life Technologies, MD, USA). All analyses were performed in duplicate, using commercial kits and in accordance with the manufacturer's specifications.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 18.0. The distribution of variables was analyzed using the Kolmogorov-Smirnov test for normality. Continuous variables were described as mean ± SD or median and interquartile range [25–75]. Categorical variables were described as absolute and relative frequencies. Longitudinal analyses were conducted with the Wilcoxon tests to compare serum leptin levels, weight, BMI, body fat and WC at hospital admission and 15 days later. Spearman correlation analyses were used to assess the relationship between these variables and the influence of alcohol use (e.g., age at first use, years of use, quantity, and recent use) on leptin levels and anthropometric features.

RESULTS

Our sample is composed mostly of white men (n=32, 84.2%), with median age of 51.5 years (IQR 45.7–56.0), low schooling level (< 8 years of study = 60.5%), single or living without a partner (68.4%), and employed (71.1%). Table 1 shows the anthropometric and body composition characteristics, and the concentrations of laboratory markers of individuals with AUD. Regarding nutritional status, many patients were overweight or obese at admission (55.3%) and after 15 days of hospital treatment (60.6%). Body weight (72.7–75.1 kg), BMI (25.92–26.86 kg/m²) and WC (94.25–96.05 cm) increased significantly in the same period. However, no difference was observed regarding the percentage of body fat (p>0.05). Moreover, serum leptin concentrations were similar between the 1st day of hospitalization and after 15 days of abstinence from alcohol (p=0.654).

Table 1. Demographic and clinical data

Variable	At admission – 1st day	15 days after admission	*p*-value
Weight (kg)	72.70 [61.9–81.2]	75.1 [65.4–83.7]	<0.001
Body fat (kg)	20.25 [16.4–23.6]	20.7 [17.4–23.2]	0.980
Body fat index	26.50 [24.2–29.7]	26.30 [23.7–29.3]	0.264
BMI (kg/m^2)	25.92 [21.6–28.2]	26.86 [23.5–28.8]	<0.001
BMI (category)			
Underweight	1 (2.6)	-	
Normal weight	16 (42.1)	15 (39.5)	
Overweight	18 (47.4)	18 (47.4)	
Obese	3 (7.9)	5 (13.2)	
Waist circumference (cm)	94.25 [87.9–100.0]	96.05 [89.6–102.0]	<0.001
Laboratory markers			
Gamma-glutamyl transferase	71.00 [37.0–175.0]	-	
Aspartate aminotransferase	37.00 [20.0–90.0]	-	
Alanine aminotransferase	25.00 [19.0–61.0]	-	
Triglycerides	136.00 [82.5–230.0]	-	
Cholesterol	190.00 [165.0–216.0]	-	
HDL cholesterol	69.00 [42.0–83.0]	-	
Leptin (ng/mL)	1.638 [1.230–2.095]	1.869 [1.332–2.443]	0.654

Data is shown as median and interquartile range [25–75] or as N (%). BMI: Body mass index

Positive correlations, from moderate to strong, between BMI on the 1st and 15th days were observed in relation to body fat (1st and 15th days) and WC (1st and 15th days) (p<0.05) (Table 2). Liver profile and lipid profile markers were not correlated with BMI, except for aspartate aminotransferase (r=−0.325, p=0.050). Leptin levels at admission were positively correlated with body fat (1st and 15th days), WC (1st and 15th days), and BMI (1st and 15th days). After 15 days, only leptin and BMI had a significant relationship (1st and 15th days) (Table 3). No correlation between liver and lipid markers and leptin levels was observed.

Table 2. Spearman correlations between BMI and clinical variables and laboratory markers

Variable	BMI – 1st day	BMI – 15th day
Age	−0.174/p=0.29	−0.148 / p=0.377
Body fat (1st day)	0.833 / p<0.001	0.797 / p<0.001
Body fat (15th day)	0.872 / p<0.001	0.833 / p<0.001
Body fat index (1st day)	0.391 / p=0.048	0.403 / p=0.041
Body fat index (15th day)	0.583 / p=0.002	0.572 / p=0.002
Waist circumference (1st day)	0.884 / p<0.001	0.889 / p<0.001
Waist circumference (15th day)	0.878 / p<0.001	0.895 / p<0.001

Values show the Spearman correlation coefficient.

Table 3. Spearman correlations between leptin levels and clinical variables and laboratory markers

Variable	Leptin – 1st day	Leptin – 15th day
Age	−0.022 / p=0.903	0.018 / p=0.921
Body fat (1st day)	0.607 / p=0.005	0.222 / p=0.347
Body fat (15th day)	0.652 / p=0.002	0.330 / p=0.156
Body fat index (1st day)	0.234 / p=0.321	0.263 / p=0.262
Body fat index (15th day)	0.411 / p=0.072	0.362 / p=0.116
Waist circumference (1st day)	0.696 / p=0.001	0.303 / p=0.194
Waist circumference (15 day)	0.695 / p=0.001	0.209 / p=0.376
BMI – 1st day	0.357 / p=0.045	0.475 / p=0.006
BMI – 15 days	0.389 / p=0.028	0.462 / p=0.008

Values show the Spearman correlation coefficient.

Characteristics related to alcohol consumption are described in Table 4. Among the most consumed alcoholic beverages, liquor stands out (81.5%, cachaça and vodka), followed by beer (7.9%). Most patients consumed alcohol daily (86.6%), consuming 350g of ethanol per day. Analyses were controlled for age of onset of alcohol use, years of use. The amount and frequency of alcohol ingestion were related to anthropometric variables and leptin levels. However, no influence was observed.

Table 4. Drug use characteristics

Variable	Median (interquartile range)
Age at first alcohol use	16 [13 – 18.7]
Years of alcohol use	28 [20 – 33.5]
Alcohol use (g/day)	350 [204 – 525]
Frequency of alcohol use	
Daily	33 (86.8)
Three times or more (per week)	5 (13.2)
Alcohol use in the last 30 days	30 [15 – 30]
Alcohol source (type)	
Liquor	31 (81.5)
Beer	3 (7.9)
Both types	4 (10.5)

Data is shown as median and interquartile range [25–75]

DISCUSSION

Scientific literature has provided little attention to nutritional parameters of individuals undergoing treatment for AUD. In this study, relationships between leptin, anthropometric data, and BMI were examined. We found that this group of patients showed significant weight gain during detoxification and, although we did not find any significant difference in leptin levels between the 1st and 15th day of abstinence, their levels were positively correlated with BMI and WC at both times. These results are relevant to clinical practice.

From a nutritional point of view, alcohol is the only psychoactive substance that can provide calories to the body (about 7.1 kcal per gram of metabolized ethanol), although it is not a source of essential nutrients[36]. Overall, excessive weight gain is commonly reported during the withdrawal from several substances [7, 13, 37]. In addition, alcoholics were binge eating[16] and eating more hyper-palatable foods during the early stages of detoxification, configuring a temporary protective factor against relapse [38,39]. This occurs because food with added sucrose provides the same immediate reward as alcohol, and the individual craving for sucrose or any sweet taste is comparable to the degree of craving and reward produced by some drugs [40,41].

The biopsychological processes behind substance abuse are similar to eating processes. Both share the brain circuitry related to reward, relevance, and motivation and are strongly influenced by emotional states[21,42]. Furthermore, they are related to personality traits[43], impulsiveness[44], and tolerance to stress and frustration[45]. Therefore, both addiction and obesity reflect imbalances in brain responses to gratifying stimuli from the environment[17,46].

Recent evidence has shown how appetite-regulating peptides, especially leptin, affect AUD. Leptin also affects the neurobiology of alcohol craving[25,47] and may be a potential biomarker for degree of dependence[48]. Chronic ethanol consumption can affect serum leptin levels via different mechanisms, including: body fat reduction, hormonal change, pro-inflammatory cytokines increase, and dysregulation of the hypothalamic-pituitary-adrenocortical axis[31]. We observed no significant changes in serum leptin levels during withdrawal, corroborating the observational study (longitudinal on day 1 and day 15 of admission) by Santolaria et al.[31], where they found no increased leptin levels in alcohol use disorders. Our findings also support the results of previous human clinical studies, conducted by Wurst et al.[49], who compared the plasma leptin concentrations of healthy individuals and abstinent alcoholics on day one and day seven of hospitalization. They found no significant differences between groups and no changes in leptin levels over time could be detected. On the other hand, Mehta et al.[47] found a significant decrease of leptin levels from day 1 to day 7 and from day 7 to day 21. Kim and colleagues[50] did an observational study that showed a reduction of leptin concentration in all groups over 30 days of abstinence, indicating that the levels of this peptide may be affected by detoxification.

We also observed a positive correlation between leptin and BMI and leptin and WC levels, similar to some previous findings in the literature that analyzed men[24,48] and women[51]. Studies with other psychoactive substances also show a positive correlation between BMI and leptin levels, including cocaine[27] and crack[14].

Characteristics of the participants must also be considered. Several factors influence serum leptin levels, including age, amount of ethanol consumed, smoking habits, serum levels of testosterone and estradiol, growth factors such as IGF-1 and CRP, and cytokines such as IL-6.Butthey are mostly affected by body fat[31]. This confirms our correlation analyses. In this sense, overweight and obesity are associated with higher levels of leptin, which can be influenced by a so-called resistance to leptin, a multifactorial and dynamic process with various changes, from hormonal imbalance to receptor traffic and brain signaling alterations. Despite new information about this peptide, the molecular and cellular bases of selective resistance to leptin remain undefined[52,53].

Our study highlights the high alcohol consumption of the participants (median: 350g) showing a profile of heavy consumers. Alcohol use seems to damage health proportionally to the amount ingested over a long period of time. Excessive chronic consumption (300g per week in men, similar to that found in our sample) worsens the damage[54,55]. Furthermore, weight gain in individuals who consume more than 350g of alcohol per week increases the risk of cirrhosis, hepatitis, and steatosis from two to three times[54–56]. Individuals in our sample reported a greater consumption of distilled beverages, corroborating worldwide data which shows that 44.8% of the total alcohol is consumed as liquors. The second most consumed type of beverage is beer (34.3%), followed by wine (11.7%)[3] . Most users are also daily consumers, which highlights the severity of their illness and addiction.

This study has some limitations. Sample size may have influenced the results and prevented us from detecting smaller effect size associations. However, voluntary hospitalization favors early treatment abandonment, making it difficult to collect data at the two proposed dates. Hospital beds are scarce in an addiction unit and filled with individuals who are undergoing treatment to recover from various psychoactive substances, which limits alcohol users from getting specialized treatment. Moreover, our sample is composed only of men undergoing detoxification. Thus, our results should be viewed with caution if applied to women and may not represent male alcoholics in general. Although some patients received specific medication for diseases, all of them underwent the same structured medication protocol for the treatment of alcohol withdrawal. We also did not measure food intake before and during hospitalization, which could be analyzed together with serum leptin levels.

CONCLUSIONS

Individuals with AUD had a significant increase in weight, BMI, and WC after 15 days of hospitalization, but serum leptin levels were stable during detoxification. It is still essential to investigate how leptin and other neurobiological aspects of appetite regulation affect alcohol dependence, since it may lead to significant clinical advances and better comprehension of the causes for weight gain during withdrawal, allowing patients to get adequate treatment.

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Author Contribution

LB: contributed substantially to the conception and design of the research, data collection, analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

JBS: contributed substantially to the data collection, analysis, and interpretation of data.

DNSSF: contributed substantially to the data collection, analysis, and interpretation of data.

ME: contributed substantially to the conception and the design of the research, analysis, interpretation of data, and revised the manuscript with an important intellectual contribution.

JVF: contributed substantially to the data collection, analysis, interpretation of data, and revised the manuscript with an important intellectual contribution.

GCF: contributed substantially to the analysis, interpretation of data, and drafted the manuscript with an important intellectual contribution.

LVD: contributed substantially to the analysis, interpretation of data, and revised the manuscript with an important intellectual contribution.

AOS - contributed substantially to the analysis, interpretation of data, and revised the manuscript with an important intellectual contribution.

MEKH: coordinated the study; contributed substantially to the conception and the design of the research, analysis, interpretation of data, and revised the manuscript with an important intellectual contribution.

All the authors read, commented on, and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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