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BRIEF COMMUNICATION

Gender differences of cannabis smoking on serum leptin levels: population-based study

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Objective: To evaluate the serum leptin levels in cannabis smokers.
Methods: This was a cross-sectional population-based study of participants between the ages of 18 and 35 years. The data were collected through a self-administered questionnaire covering socio-demographic data and the use of psychoactive substances. Leptin levels were measured using a commercial ELISA kit.
Results: Of the 911 participants, 6.7% were identified as cannabis smokers and had significantly lower leptin levels ($p = 0.008$). When stratified by gender, there was a significant decrease in leptin levels among male smokers ($p = 0.039$).
Conclusion: Cannabis smoking was linked to leptin levels in men, suggesting that the response to biological signals may be different between men and women.

Keywords: *Cannabis sativa*; leptin; young adults; gender

Introduction

Cannabis is the world's most widely used illicit drug, with high prevalence rates in Latin America.[1] It has been documented in the literature that cannabis stimulates the appetite, which appears to be linked to Δ-9-tetrahidrocanabinol (THC) and cannabidiol (CBD), its main active substance, through the activation of CB1 receptor (CB1R).[2,3] CB1R is widely expressed in the hypothalamus, which is the key region involved in the regulation of appetite and includes appetite hormones, such as leptin.[4] Leptin is a hormone released primarily from adipocytes. It reaches the brain through the bloodstream, binding to specific receptors. This hormone is considered one of the major regulators of food intake and metabolic rate, since it is associated with energy balance. It acts on the hypothalamus and activates the anorexigenic mechanisms, regulating food intake.[5]

Previous studies have shown that there are neurons sensitive to leptin, including endocannabinoids. CB1R is blocked by the THC and CBD inhaled from cannabis smoke. CB1R, which also controls leptin, causes it not to activate, since the cannabinoid system is under the negative control of leptin.[4,6] However, contradictory results have been observed about the interaction between cannabis and appetite hormones. Wagner et al. found that oral administration of a CB1R antagonist reduced plasma leptin levels in obese individuals. A study conducted by Di Marzo et al. revealed that a single intravenous leptin injection in rats decreased the hypothalamic levels of the endocannabinoids, anandamide and 2-arachidonyl-glycerol (2-AG) in the hypothalamus.[2,7] However, Riggs et al. found significant changes in leptin levels after cannabis smoking, but not in placebo.[4]

Other studies, moreover, have suggested that gender impacts the effects of cannabis use. Men consume cannabis in greater amounts and at higher rates than women.[1] On the other hand, Monteleone et al. demonstrated an inverse relationship between endogenous cannabinoid and circulating leptin in women.[8] To the best of our knowledge, no prior studies have examined the effects of cannabis use on leptin in population-based samples. Thus, the aim of this present study was to evaluate the serum leptin levels of cannabis users from a population-based sample between the ages of 18 and 35 years.

Methods

This was a cross-sectional study nested in a population-based study of 18- to 35-year-old residents of Pelotas (Brazil). Sample selection was performed by multistage clusters,

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considering the census division of the city (Pelotas) in 2010, which includes a population of 97,000 individuals in the specified age range within its 495 sectors (Instituto Brasileiro de Geografia e Estatística [IBGE]; http://www.ibge.gov.br). In order to guarantee a wide and representative sample, 83 census-based sectors were systematically and randomly selected with a skip of six sectors. Home selection in the designated sectors was performed according to a systematic sampling procedure: the first selected house was at the corner pre-established by the IBGE as the beginning of the sector, with the next four houses skipped; thus, every fifth residence was selected. After initial contact and presentation of the study, residents of the specified age range were invited to participate and signed the informed consent form. Individuals unable to understand and/or respond to the instruments due to physical or cognitive issues were excluded from the study. This study was approved by the research ethics committee of the Universidade Católica de Pelotas (UCPel) (protocol no. 15/2010).

Socioeconomic evaluation was carried out using the National Economic Indicator (Indicador Econômico Nacional – IEN).[9] Sociodemographic data, which included tobacco and/or psychoactive substance use (cocaine, crack, and *Cannabis sativa*), were collected through a self-administered questionnaire. The CAGE questionnaire was used to evaluate alcohol use problems.[10] Individuals diagnosed with mood disorder according to the Mini International Neuropsychiatric Interview (MINI) and those who reported using crack and/or cocaine were excluded from the present study.[11] A blood sample was taken between 8:00 a.m. and 11:00 a.m. The serum leptin levels were measured using a commercially available immunoassay kit (DuoSet, R&D Systems, Minneapolis, MN, USA).

The statistical analysis was conducted using GraphPad Prism 6.0 and SPSS version 21.0 for Windows. The chi-square test was used for the statistical inference analysis to describe the total sample and to determine the association between *Cannabis sativa* users and the sociodemographic characteristics. The serum leptin levels had a non-Gaussian distribution. The nonparametric tests (Mann-Whitney, the Kruskal-Wallis and the Spearman's correlation) were used to compare data. Serum leptin levels were presented as median and interquartile range (IQR). A linear regression analysis was applied to control for possible confounding factors, with $p \leqslant 0.2$ in the bivariate analysis. Results with $p < 0.05$ were considered statistically significant.

Results

Of the 911 analyzed subjects, 6.7% were identified as cannabis smokers, and 72.1% were men. Table 1 shows the sociodemographic and the clinical characteristics of the sample according to the *Cannabis sativa* smokers and the serum leptin levels. Cannabis smokers had a lower BMI (24.67 ± 4.26 kg/m^2) and waist circumference (81.99 ± 12.18 cm) than nonsmokers (BMI: 26.13 ± 5.49 kg/m^2; p = 0.041; waist circumference: 86.17 ± 13.03 cm; p = 0.020). When stratified by gender, the mean BMI (p = 0.037) and waist circumference ($p \leqslant 0.001$) of male cannabis smokers remained significantly lower than male nonsmokers. No difference was found between female cannabis smokers and nonsmokers regarding BMI and waist circumference. Serum leptin levels correlated positively with BMI in the total sample (r = 0.268; $p \leqslant 0.001$) in men (r = 0.533; $p \leqslant 0.001$) and women (r = 0.166; $p \leqslant 0.001$). Moreover, they correlated with waist circumference in the total sample (r = 0.106; p = 0.024) in men (r = 0.270; $p \leqslant 0.001$) and women (r = 0.160; p = 0.010) (data not shown). Cannabis smokers had significantly decreased serum leptin levels (p = 0.008). When stratified by gender, however, there was a significant difference only among men (p = 0.039) (Figure 1).

A linear regression was carried out to check the sample's statistical power. No statistically significant differences were found in women (p = 0.505; β = -0.031; 95% confidence interval [95%CI] -0.430 to 0.168). Statistically significant differences were found in men (p = 0.039; β = -0.155; 95%CI -0.382 to -0.090). To check the influence of possible confounding factors, we performed an adjusted analysis for BMI, waist circumference and alcohol use, and the results remained significant for the total sample (B = -0.324; $p \leqslant 0.001$), women (B = -0.041; p = 0.380), and men (B = -0.185; p = 0.049) (data not shown).

Discussion

The present study evaluated serum leptin levels in young cannabis smokers. Cannabis is the world's most widely used illicit substance, especially among young males.[1] Users of other illicit drugs, such as cocaine and crack, were excluded from the present study, since their use can modulate certain hormones, including leptin.[12]

Commonly known effects of cannabinoid consumption are increased food cravings and intake. Kirkham systematically reviewed the ''wanting'' and ''liking'' aspects in relation to endocannabinoids and concluded that they may be essential for reward anticipation and the initiation of eating and that endocannabinoid activity contributes to the pleasure associated with food. However, there is an urgent need to define the psychological consequences of cannabis smoking in human studies,[13] and the influence of cannabis smoking on appetite hormones has been little studied.

In our study, we found lower leptin levels in cannabis smokers than in nonsmokers. Leptin is an important appetite hormone and is mainly produced from adipocytes, which modulate central-peripheral communication to maintain energy balance via hypothalamic receptors.[4,5] Previous studies have suggested that leptin interferes in the of endogenous cannabinoids levels, which are mediated by CB1R downregulation.[2] However, few studies have investigated the association between leptin levels and cannabis smoking. Muniyappa et al. observed no difference in serum leptin levels between smokers and a control group,[3] while Riggs et al. showed significantly increased leptin levels in cannabis smokers.[4] Previous studies have described low leptin levels with increased appetite,[2,4] and that cannabis smokers had a 20% higher calorie intake than nonsmokers.[3,14] However, these studies

Table 1 Sociodemographic and clinical characteristics of the sample according to *Cannabis sativa* smokers and serum leptin levels

Characteristics	Sample distribution	*Cannabis sativa* smokers	p-value	Leptin levels in total sample	p-value	Leptin levels in *Cannabis sativa* smokers	p-value
Gender*†			⩽ 0.001		⩽ 0.001		0.006
Female	515 (56.5)	17 (27.9)		13.64 (5.55-47.53)		11.91 (5.09-35.84)	
Male	396 (43.5)	44 (72.1)		3.55 (1.50-11.53)		1.93 (0.79-26.45)	
Ethnicity*†			0.561		0.533		0.297
Caucasian	630 (75.4)	44 (72.1)			9.71 (3.41-27.25)	4.94 (1.41-15.76)	
Non-Caucasian	205 (24.6)	17 (27.9)			7.16 (2.37-25.18)	2.31 (0.78-6.41)	
Age (years)‡§	26.0±5.14	24.13±4.59	0.016	r = 0.041	0.216	r = 0.197	0.346
National Economic Indicator (IEN)*‖			0.956		0.836		0.552
1 (lowest)	304 (33.4)	24 (39.3)		8.16 (2.82-25.85)		4.94 (1.11-14.87)	
2 (middle)	303 (33.3)	13 (21.3)		7.80 (2.67-28.34)		2.10 (0.86-18.10)	
3 (highest)	302 (33.2)	24 (39.3)		9.29 (3.61-23.47)		2.38 (1.57-13.19)	
Years of schooling‡§	11.22±3.51	10.92±3.29	0.471	r = -0.042	0.210	r = 0.066	0.630
BMI‡§	26.04±5.42	24.67±4.26	0.041	r = 0.268	⩽ 0.001	r = 0.369	0.006
Abdominal circumference‡§	85.78±12.84	81.99±12.18	0.020	r = 0.136	0.060	r = 0.129	0.012
Tobacco use*†			0.638		0.230		0.308
No	683 (75.6)	28 (46.7)		9.20 (3.28-25.72)		3.45 (1.72-11.90)	
Yes	221 (24.4)	32 (53.3)		7.60 (2.40-27.41)		4.94 (0.74-22.41)	
Alcohol use*†			0.002		0.006		0.048
No	811 (89.2)	45 (73.8)		9.15 (3.44-25.72)		4.11 (1.49-11.90)	
Yes	100 (10.8)	16 (26.2)		3.49 (1.31-22.15)		2.33 (0.81-13.69)	
Total	911	61 (6.7)		8.83 (3.01-25.72)			

BMI = body mass index; IEN = Indicador Econômico Nacional.
Leptin serum levels expressed by ng/mL.
* χ^2 test, presented as n (%);
† Mann-Whitney test;
‡ Student's *t*-test, presented as mean ± standard deviation;
§ Spearman's or Pearson's correlation test;
‖ Kruskal-Wallis, both presented as median and interquartile range.

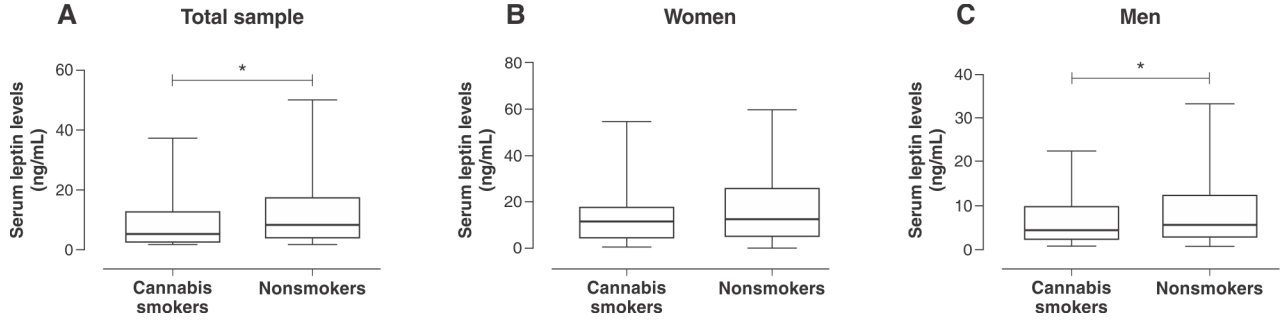

Figure 1 A) Serum leptin levels in the total sample. Serum leptin levels were significantly lower between cannabis smokers (3.01 [0.79-12.19] ng/mL) than nonsmokers (9.68 [3.35-25.81] ng/mL; p = 0.008). B) Serum leptin levels in women. No difference was found between cannabis smokers (11.92 [5.25-45.87] ng/mL) and nonsmokers (13.90 [5.55-48.29] ng/mL; p = 0.332). C) Serum leptin levels in men. Serum leptin levels were lower in cannabis smokers (1.74 [0.64-8.28] ng/mL) than nonsmokers (3.74 [1.59-12.04] ng/mL; p = 0.039). Values are presented as box-plots with median and interquartile range. * p ⩽ 0.05 is considered statistically significant.

did not evaluate the differences between genders. We believe that the low leptin levels of cannabis smokers may be associated with the exogenous stimulation of cannabinoids that, together with the production of endogenous cannabinoids, can lead to a decrease in leptin levels, since they are negatively regulated. Moreover, our results suggest that the mechanisms involving leptin and endocannabinoids may be different between genders.

Regarding the anthropometric variables, the literature reports that the abdominal obesity rate and mean BMI are lower in cannabis smokers than nonsmokers, which corroborates our findings. Moreover, we also found that the abdominal obesity rate and mean BMI, as well as leptin levels, are lower in male cannabis smokers. Le Strat et al. found that obesity was significantly lower in cannabis users than in nonusers (16.1% vs. 22.0%).[15] The same research group has proposed a seemingly paradoxical hypothesis that THC may produce weight loss and may be a useful for treating obesity and its complications. This led to the development of a therapeutic approach using

CB1 cannabinoid receptor blockers, such as Rimonabant, to produce weight loss and improve metabolic profile.[16] However, the authors pointed out that smoking cannabis does increase the risk of depression and anxiety, and therefore, its use should be further investigated.

One possible explanation for our results is that the number of women who reported smoking cannabis was low, which may have caused the lack of significance in leptin levels. Another possible explanation is that the composition of the endogenous cannabinoid system is distinct in women, with dynamic changes due to fluctuations in gonadal sex hormones, as has been suggested in preclinical studies.[5] Unfortunately, in the present study, we did not evaluate the influence of sex hormones or the frequency or amount of cannabis smoked. Moreover, we did not evaluate dietary habits. However, our study was able to evaluate young subjects in a population-based study.

In the present study, we sought to evaluate the relationship between cannabis use and changes in leptin levels. Our results showed that cannabis smoking affects leptin production, a hormone that inhibits hunger, as well as that the response to biological signals can differ between genders. Further studies are needed to investigate the effects of THC on the endocannabinoid system and on appetite hormones between genders.

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Disclosure

The authors report no conflicts of interest.

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