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Influence of the leptin and cortisol levels on craving and smoking cessation

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ABSTRACT

Leptin inhibits cortisol release and may increase the craving for cigarettes, hindering the process of smoking cessation. We evaluate the influence of the initial concentration of cortisol and serum leptin on craving and smoking status in individuals after one month of treatment for smoking cessation. The leptin concentration was adjusted by the Initial Body Mass Index (BMI) (leptin/BMI) and the initial percentage of body fat (%BF) (leptin/%BF). The craving was assessed using the Questionnaire of Smoking Urges-Brief (QSU-Brief). The QSU-Brief was assessed about a score of factor 1 (positive reinforcement by tobacco), and factor 2 (negative reinforcement by tobacco). Correlation was found between QSU-Brief (Factor 1 and 2) with the initial concentration of leptin/BF% among those who continued to smoke. There was a negative correlation between cortisol levels and leptin/%BF in individuals who remained smokers after 1 month. There was a positive correlation between leptin/BMI and leptin/%BF with the QSU-Brief (Factor 2) of 1 month in women who remained smokers ($r=0.565$; $p=0.023$) and the QSU-Brief (Factor 2) initial among the abstinent women ($r=0.551$; $p=0.033$). The highest concentrations of leptin were associated with greater craving and difficulty in achieve abstinence.

1. Introduction

According the global estimates of the World Health Organization (WHO) on the burden of smoking-related diseases, it has estimated that 5.1 million deaths worldwide are attributed to the use of cigarettes. Furthermore, about 56.9 million people worldwide have increased by disability-adjusted life years attributed to the same reason. This difference becomes even more pronounced when compared between sexes, because approximately 64% of smoking-related deaths in adults occur among women (World Health Organization (WHO), 2000).

At the time that smokers reduce cigarette smoking or begin the process of withdrawal, may have the craving. According to WHO, the craving can be defined as an intense desire to repeat the experience of the effects afforded by a particular substance. This desire can occur both at the consumption phase as early abstinence or after a long time without the use drugs, and usually are accompanied by changes in mood, behavior and thought (Araújo et al., 2008).

Leptin is an adipocyte-derived signaling molecule, responsible for limiting food intake and promoting increased energy expenditure by interacting with specific receptors located in the central nervous system (CNS) and peripheral tissues (Reseland et al., 2005). It is also responsible for the modulation of the

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hypothalamic–pituitary–adrenocortical (HPA) axis by inhibit cortisol response to stress, presumably acting at the hypothalamic level. By binding to specific receptors located on dopamine neurons of the ventral tegmental area (VTA), leptin also inhibits signaling of dopamine in the nucleus accumbens. The concomitant occurrence of modulation of HPA axis and the inhibition of dopamine transmission by leptin contributes simultaneously to increase the craving (Friedman and Hallas, 1998; Inui, 1999; Palmiter, 2007).

The dysregulation of the stress neuroendocrine system, in particular, HPA axis, has been associated with a variety of psychiatric disorders. Data from clinical and preclinical studies suggest that impairment of HPA axis function and inhibition of cortisol response to stress are associated directly with increased alcohol intake and relapse by tobacco (al'Absi et al., 2011; Roubos et al., 2012).

The most of studies evaluating the effect of serum leptin and craving was conducted with alcoholics (Kiefer et al., 2001; Wurst et al., 2002; Kraus et al., 2004; Toffolo et al., 2012; Aguiar-Nemer et al., 2013). Among smokers, there are only three studies that evaluated a possible effect of serum leptin in the sensation of craving for tobacco (von der Goltz et al., 2009; al' Absi et al., 2011; Potretzke et al., 2014). These studies found a positive association between the intensity of the craving for nicotine and plasma concentrations of leptin. This suggests that the regulation of dopamine transmission by leptin during drug withdrawal alters the intensity of craving committing the maintenance of abstinence.

The maintenance of smoking is associated with a number of metabolic changes and the occurrence of chronic diseases. Thus, the process of smoking abstinence has an important role in health maintenance and improves of the quality of life of recent abstinent individuals beyond to prevention of metabolic disorders (Wilsgaard and Jacobsen, 2007; Rodrigues et al., 2013). Coadjutant to the addiction process, leptin has been associated as an important risk marker for relapse in smokers during critical periods of smoking cessation (Aguiar-Nemer et al., 2013).

Due to the few available studies, there is need for more research to evaluate the action of leptin and cortisol in smoking cessation and its relation with the craving, in order to elucidate the mechanisms involved in the cessation process. Considering that leptin inhibits signaling of dopamine in the nucleus accumbens and the release of cortisol in the HPA axis, the hypothesis of this study is that higher plasma leptin concentrations in the initial period of smoking cessation, provides an increase craving for cigarette and impairs achieve the abstinence. Thus, the aim of the study was evaluate the influence of leptin and cortisol levels in smokers at the beginning of treatment on craving and smoking status after a month of intervention for smoking cessation.

2. Methods

2.1. Delineation, location and study population

The present work is an intervention study conducted with a non-probabilistic sample, who were evaluated smokers attended at the Center Interdisciplinary for Research and Intervention on Tobacco, University Hospital, Federal University of Juiz de Fora (CIPIT/HU-UFJF), for the treatment in intensive approach in the period from September 2011 to February 2014.

The work by CIPIT included prevention activities, treatment and tobacco control, with a multidisciplinary approach based on the guidelines of the National Tobacco Control Program (NTCP) of the National Cancer Institute. Smokers received intensive smoking cessation counseling in structured weekly sessions for one month, followed by two biweekly, then monthly sessions for the duration of 12 months (Instituto Nacional do Câncer (INCA), 2001).

2.2. Inclusion and exclusion criteria

Men and women over age 18 who were diagnosed by physician-administered CIPIT HU/UFJF with smoking by the International Classification of Diseases – 10th edition, were in use tobacco as a drug principal and that accept participate in the research by signature the Free and Clarified Consent Term participated in the study. The following patients were excluded from the study: under 18 years, pregnant women, kidney disease, Acquired Immunodeficiency Syndrome, liver disease, Chronic Obstructive Pulmonary Disease and those who refused to participate. The proposal was approved by the Ethics in Research Committee of the Federal University of Juiz de Fora (CAAE: 0067.0.180.420-11 / no. 081/2011).

2.3. Variables analyzed

Anthropometric assessment was performed at baseline and after one month of the treatment. Nutritional assessment was based on measurements of body weight and height to calculate body mass index (BMI). To measure body weight, Welmy® was used, with a capacity of 150 kg and precision of 0.1 kg, with the participants standing barefoot and wearing light clothing. To measure the height, the portable anthropometric Alturaexata® was used. WHO criteria were used for classification of adults: low weight ($BMI < 18.5\ kg/m^2$); eutrophic ($18.5–24.9\ kg/m^2$); overweight ($25–29.9\ kg/m^2$) and obese ($\geq 30\ kg/m^2$) (World Health Organization (WHO), 2010). For the elderly was adopted the classification of Lipschitz (1994): underweight ($BMI < 22\ kg/m^2$), eutrophic ($22–27\ kg/m^2$), overweight ($> 27\ kg/m^2$). Body fat percentage (%BF) was estimated by prediction equation based on BMI: $\%BF = 1.218x\ (BMI) - 10.13$ (men); $\%BF = 1.48x\ (BMI) - 7$ (women) (Black et al., 1983).

The measurement of abdominal circumference (AC) was performed with use of flexible and inelastic tape in the abdomen at the height of the umbilicus. Waist circumferences (WC) were measured in the mid-point between the lower end of the rib cage and top of the iliac crest in a standing position (World Health Organization (WHO), 2010). For the interpretation of the results was used values ≥ 90 cm and ≥ 80 cm for men and women respectively, indicating accumulation of abdominal fat, being related to a greater risk of developing chronic diseases such as cardiovascular diseases and diabetes mellitus. The hip circumference (HC) was measured with use of flexible and inelastic tape in the region of largest circumference between the waist and the thigh was subsequently used to calculate the waist-hip ratio (WHR), using the values $WHR > 1$ for men and > 0.85 for women (Pouliot et al., 1994).

In the same period of the anthropometric assessment, participants completed a questionnaire assessing craving using the Questionnaire of Smoking Urges-Brief (QSU-Brief)-Brazil Version. The short version is structured with 10 affirmative questions. The QSU-Brief consists in the analysis of two factors. In factor 1 the craving is related with the quality of positive reinforcement by tobacco and refers to the questions of numbers 1, 3, 7 and 10. The Factor 2 relates with the quality of negative reinforcement by tobacco, being composed by the questions 4, 8 and 9. The cutoffs obtained for Factor 1 are: 0–6 points, minimum craving; 7–15 points, light craving; 16–23, moderate craving; and 24 or more points, intense craving. For the Factor 2: 0–2 points, minimum craving; 3–4, light craving; 5–9, moderate craving; and 10 or more points, intense craving (Araújo et al., 2007).

Confirmation of smoking status was performed by measuring carbon monoxide in expired air (COex), in monoximeter piCO+

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Smokerlyzer®, indicating smoking status of smoker for obtained values more than 6 ppm. The scores of the Test of Nicotine Dependence of Fagerstrom, to identify the behavior of smokers were also evaluated. The values when summed indicates one score of the degree of dependence: low (0–4 points), moderate (5 points) or high (5–10 points) (Halty et al., 2002).

2.4. Hormonal analysis: leptin and cortisol

Blood samples for analyses of serum leptin and cortisol were processed by the Laboratory of Clinical Analysis of the HU/UFJF which was collected when participants were still smoking. The collect was performed in the morning after 8 h fasting of individuals. Blood samples were centrifuged and stored at −80 °C until the time of analysis.

The serum leptin concentration was determined by ELISA (Enzyme Linked Immuno Sorbent Assay), using a kit specific for human leptin Milipore®, with detection sensitivity of 0.78–100 ng/mL.

The collect of the blood sample for analysis of cortisol was performed at tube without anticoagulants. For this, 10 mL sample was collected, which was centrifuged after coagulation in ambient temperature at 350 rpm for 5 min. After this process, the serum cortisol was measured in specific kit ARCHITECT Cortisol®. For quantification the equipment ARCHITECT i System® was used. The reference value of serum cortisol adopted by the laboratory was 5.4–25 μg/dL.

2.5. Statistical analysis

For sample characterization, descriptive tables with measures of central tendency and dispersion of variables were used. Quantitative variables that showed symmetrical distribution were described by mean ± standard deviation, and those who showed asymmetric distribution, were described by median (interquartile range).

For assess the normality of the data, the Kolmogorov–Smirnov test was used. The Spearman correlation was used to assess the association between the concentration of leptin and cortisol with a score of QSU-Brief. To compare the differences between means and medians, the T-Student, U-Mann–Whitney and Wilcoxon tests were used. Categorical variables were compared by Chi-square or

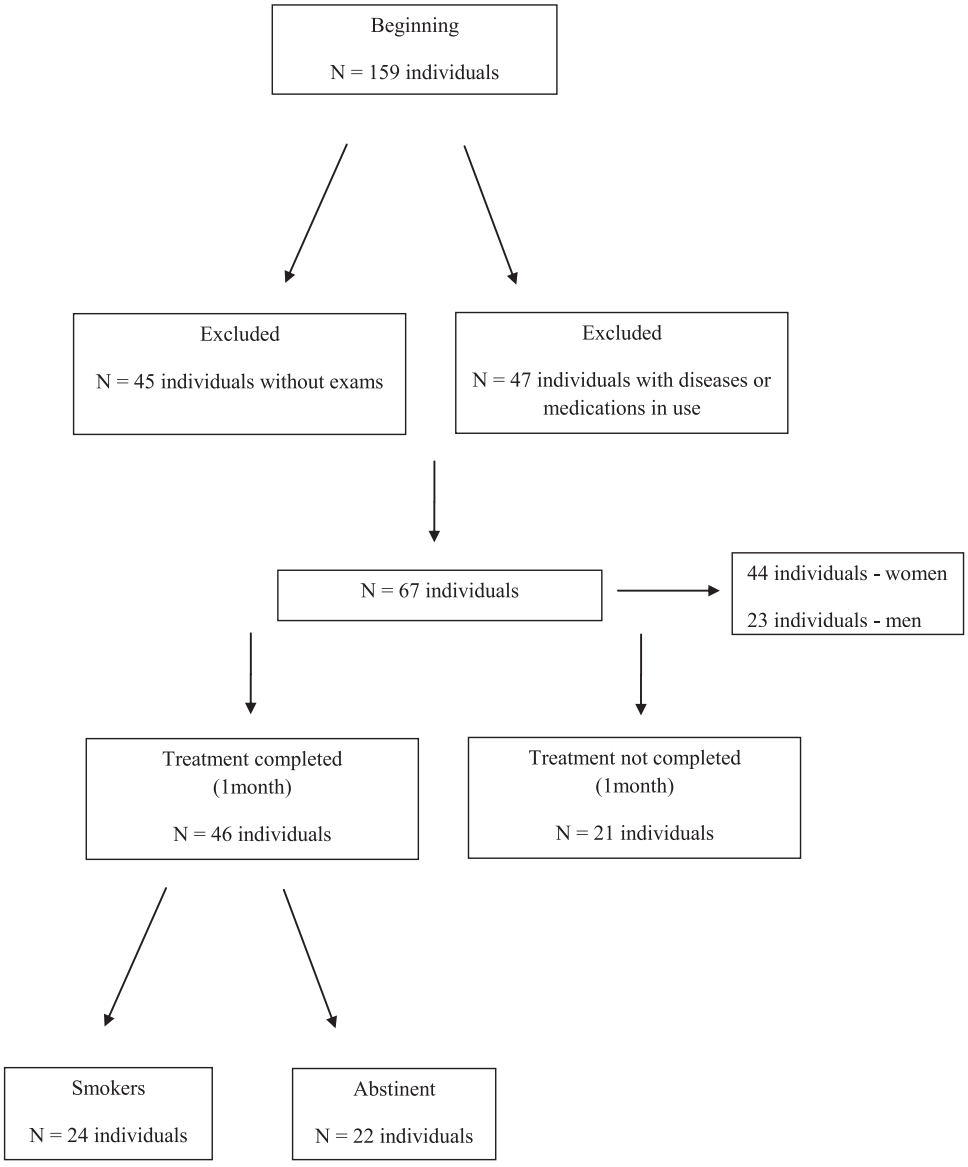

Fig. 1. Study design according to outcome of the treatment.

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Fisher Exact Test. Linear regression was used to adjust the concentration of leptin by BMI and %BF and for this, two adjustment equations were proposed. Formula 1-leptin adjusted for BMI ($y=-14.2+0.953x$ BMI). Formula 2-leptin adjusted for %BF ($y=-8.218+0.665x$ %BF).

The significance of the model was evaluated by the F-test of analysis of variance and the quality of it by the adjusted determination coefficient (adjusted R2). The residues were evaluated according the suppositions of normality, zero mean, constant variance and independence and all the assumptions were followed.

The data were processed and analyzed using PASW 17.0 software and, for effect of interpretation, the limit type I error was up to 5% ($p<0.05$).

3. Results

There were 67 participants included in the study, of which 44 were female and 23 were male. The average age of participants was 52.31 ± 9.72 years. After 1 month, 46 individuals (68.65%) completed treatment for smoking cessation. Fig. 1 describes the study design according to outcome of the treatment.

In Table 1, after 1 month of treatment for smoking cessation, it is observed that there was no difference in levels of leptin, cortisol and others parameters in the study among subjects who completed or not one month of treatment ($p>0.05$).

Table 1
Mean and standard deviation (or median and interquartile range) of anthropometric variables, biochemical, body composition and craving of the participants of the research.

Variables	Completed 1 month ($n=46$)	Not completed 1 month ($n=21$)	p-Value
Cortisol initial (μg/dL)	9.50 (7.90–12.70)	10.40 (9.45–14.00)	0.349
Leptin initial (ng/mL)	11.56 ± 8.60	12.06 ± 6.89	0.800
Leptin/BMI initial	11.63 ± 5.60	12.16 ± 3.30	0.690
Leptin/%BF initial	11.76 ± 6.66	11.67 ± 4.33	0.957
Score fagestrom initial	–	–	–
Low	10.00 (21.70%)	7.00 (33.30%)	0.312
Moderate	36.00 (78.30%)	14.00 (66.70%)	0.312
COex initial (ppm)	10.20 ± 4.82	9.00 ± 5.29	0.446
Number of cigarettes/day initial	20.00 (11.50–21.00)	18.00 (9.00–25.00)	0.484
Score QSU-Brief initial	41.10 ± 17.06	37.04 ± 19.53	0.391
Classification QSU-Brief initial	–	–	–
Light/minimum	46.00 (100%)	21.00 (100%)	–
Moderate/intense	–	–	–
QSU-Brief Factor 1 initial	–	–	–
Light/minimum	14.00 (30.40%)	8.00 (38.10%)	0.536
Moderate/intense	32.00 (69.60%)	13.00 (61.90%)	0.536
QSU-Brief Factor 2 initial	–	–	–
Light/minimum	9.00 (19.60%)	5.00 (23.80%)	0.692
Moderate/intense	37.00 (80.40%)	16.00 (76.20%)	0.692
Weight initial (kg)	69.05 ± 15.13	72.83 ± 12.74	0.324
Body mass index initial (kg/m²)	27.10 ± 5.88	27.66 ± 3.46	0.690
Waist circumference initial (cm)	86.22 ± 12.92	88.60 ± 10.40	0.462
Abdominal circumference initial (cm)	93.30 ± 13.60	94.83 ± 8.99	0.639
Hip circumference initial (cm)	100.20 ± 10.80	100.63 ± 8.24	0.872
Waist-hip ratio initial	0.85 ± 0.08	0.87 ± 0.09	0.241
Body fat percentage initial	30.04 ± 10.02	29.91 ± 6.51	0.957

BMI: body mass index; %BF: body fat percentage; COex: carbon monoxide in expired air; QSU: questionnaire of smoking urges-brief. Mean (standard deviation). Median (interquartile range). $p<0.05$. (T-Student Test, U Mann Whitney or Chi-square).

Table 2
Mean and standard deviation (or median and interquartile range) of anthropometric variables, biochemical, body composition and craving of individuals who completed the follow-up one month.

Variables	Smokers ($n=24$)	Abstinent ($n=22$)	p-Value
Cortisol initial (μg/dL)	8.95 (8.20–19.37)	11.00 (7.40–14.40)	0.695
Leptin initial (ng/mL)	11.77 ± 9.86	11.34 ± 7.21	0.865
Leptin/BMI initial	11.91 ± 5.82	11.32 ± 5.47	0.725
Leptin/%BF initial	12.12 ± 6.89	11.36 ± 6.54	0.703
Score fagestrom initial	–	–	–
Low	4.00 (16.70%)	6.00 (27.30%)	0.384
Moderate	20.00 (83.30%)	16.00 (72.70%)	0.384
COex initial (ppm)	11.70 ± 5.55	9.14 ± 4.11	0.208
COex 1 month (ppm)	8.00 (2.75–15.50)	2.00 (1.00–3.00)	0.006
Number of cigarettes/day initial	20.00 (16.50–25.00)	15.00 (10.00–20.00)	0.161
Number of cigarettes/day 1 month	15.00 (10.00–20.00)	0.00 (0.00–0.00)	0.000
Score QSU-Brief initial	44.33 ± 16.49	37.59 ± 17.35	0.004
Score QSU-Brief 1 month	36.00 (25.00–43.00)	15.00 (10.00–28.50)	0.005
Classification QSU-Brief initial	–	–	–
Light/minimum	24.00 (100%)	22.00 (100%)	–
Moderate/intense	–	–	–
Classification QSU-Brief 1 month	–	–	–
Light/minimum	23.00 (100%)	21.00 (100%)	–
Moderate/intense	–	–	–
QSU-Brief Factor 1 initial	–	–	–
Light/minimum	6.00 (25%)	8.00 (36.40%)	0.403
Moderate/intense	18.00 (75%)	14.00 (63.60%)	0.403
QSU-Brief Factor 2 initial	–	–	–
Light/minimum	3.00 (12.50%)	6.00 (27.30%)	0.207
Moderate/intense	21.00 (87.50%)	16.00 (72.70%)	0.207
QSU-Brief Factor 1–1 month	–	–	–
Light/minimum	12.00 (52.20%)	16.00 (76.20%)	0.098
Moderate/intense	11.00 (47.80%)	5.00 (23.80%)	0.098
QSU-Brief Factor 2–1 month	–	–	–
Light/minimum	5.00 (21.70%)	11.00 (52.40%)	0.035
Moderate/intense	18.00 (78.30%)	10.00 (47.60%)	0.035
Weight initial (kg)	69.73 ± 15.47	68.30 ± 15.08	0.753
Weight final (kg)	70.50 ± 15.37	68.79 ± 15.71	0.711
Weight gain (kg)	0.75 (0.40–1.37)	0.47 (0.16–2.20)	0.758
Body mass index initial (kg/m^2)	27.40 ± 6.11	26.78 ± 5.74	0.725
Body mass index 1 month (kg/m^2)	27.73 ± 6.12	26.91 ± 5.82	0.643
Waist circumference initial (cm)	87.16 ± 12.90	85.20 ± 13.17	0.613
Waist circumference 1 month (cm)	86.77 ± 12.32	85.30 ± 13.04	0.697
Abdominal circumference initial (cm)	94.19 ± 14.08	92.32 ± 13.31	0.648
Abdominal circumference 1 month (cm)	94.45 ± 11.75	92.32 ± 12.44	0.553
Hip circumference initial (cm)	99.84 ± 10.93	100.59 ± 10.90	0.818
Hip circumference 1 month (cm)	100.60 ± 9.51	100.92 ± 10.95	0.918
Waist-hip ratio initial	0.85 ± 0.08	0.84 ± 0.08	0.457
Waist-hip ratio 1 month	0.85 ± 0.08	0.83 ± 0.07	0.411
Body fat percentage initial	30.59 ± 10.36	29.44 ± 9.83	0.703
Body fat percentage 1 month	31.06 ± 10.43	29.59 ± 9.81	0.627

BMI: body mass index; %BF: body fat percentage; COex: carbon monoxide in expired air; QSU: Questionnaire of Smoking Urges-Brief. Mean (standard deviation). Median (interquartile range). $p<0.05$. (T-Student Test, U Mann Whitney or Chi-square).

There was a negative correlation between cortisol levels and leptin/%BF in individuals who completed ($r=-0.398$; $p=0.008$) and did not complete one month of treatment ($r=-0.587$; $p=0.005$). Among those who remained smokers after 1 month, the same correlation ($p=0.031$; $r=-0.442$) was observed. Among abstinent have not this association.

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Of the individuals who completed treatment of 1 month, 52.17% remained smokers and 47.83% become abstinent. In Table 2 we compare individuals who completed treatment and remained smokers with those who have stopped. The abstinent subjects had lower concentration of COex after 1 month [smokers: 8.00 (2.75–15.50)*x* abstinent: 2.00 (1.00–3.00); $p=0.006$] and lower scores of the initial QSU-Brief and after 1 month (smokers-begin: $44.33 \pm 16.49x$ abstinent-begin: 37.59 ± 17.35; $p=0.004$); smokers after 1 month: 36 (25.00–43.00)*x* abstinent after 1 month: 15.00 (10.00–28.50); $p=0.005$. Among the abstinent was also observed differences in the initial COex and after 1 month ($p=0.001$). Regarding the QSU-Brief, there was reduction of in initial score and after 1 month in smokers and abstinent (QSU-Brief smoking: $p=0.004$; abstinent QSU-Brief: $p=0.006$).

Regarding the QSU-Brief (Factor 2) which relates to the quality of the negative reinforcement by substance, the most abstinent individuals (52.4%) showed light/minimal classification, while the most individuals remaining smoking (78.3%) had moderate/heavy classification ($p=0.035$) (Table 2).

About hormonal analysis, no significant differences were observed in the levels of leptin and cortisol, as well as in the initial anthropometric parameters and after 1 month between smokers and abstinent individuals ($p > 0.05$). It was also observed that individuals who had higher concentrations of serum leptin had higher scores of QSU-Brief (Factor 2) initial and after 1 month of treatment ($n=15$–53.6%); $p=0.030$ (Table 2).

Table 3 shows the correlation between the adjusted levels of leptin/BMI and leptin/%BF with QSU-Brief (Factor 1 and 2) initial and after 1 month of accordance with smoking status. Among subjects who continued smoking, a significant positive association was observed between the QSU-Brief (Factor 1 and 2) initial and between QSU-Brief (Factor 2) after 1 month of treatment with leptin/%BF. Among abstinent, there was a significant positive association only between the QSU-Brief (Factor 2) with initial leptin/BMI. No association between leptin/BMI and leptin/%BF and the QSU-Brief (Factor 1 and 2) was found after 1 month between those who remained abstinent. No association was observed between serum cortisol concentrations with the QSU-Brief.

Comparing between genders, there was a positive association between the adjusted levels of leptin/BMI and leptin/%BF with the QSU-Brief (Factor 2) after 1 month in women who continued smoking ($r=0.565$; $p=0.023$). Among abstinent women, there was an association between leptin/BMI and leptin/%BF with the QSU-Brief (Factor 2) initial ($r=0.551$; $p=0.033$). Among men these associations were not found. Furthermore, no differences in the data of male and female smokers and abstinent this study were found. In relation to serum levels of cortisol, there was a negative correlation between the serum levels and the number of cigarettes smoked per day after 1 month only among men who didn't stopped smoking ($r=-0.587$; $p=0.035$). There was no statistically significant correlation between serum cortisol levels and the QSU-Brief scores ($p > 0.05$) (Table 4).

Table 3
Relation between leptin levels adjusted for body fat percentage (BF%) and body mass index (BMI) with QSU-Brief initial and after one month.

Leptin%/BF	QSU-Brief (Factor 1) initial		**Total**	
	Light/minimum	**Moderate/intense**		
	n	***n***	***N***	***p*-Value**
Below mean	9	18	27	0.611
Above mean	5	14	19	
Leptin%/BF	QSU-Brief (Factor 2) initial		**Total**	
	Light/minimum	**Moderate/intense**		
	n	***n***	***N***	***p*-value**
Below mean	7	20	27	0.270
Above mean	2	17	19	
Leptin/BMI	QSU-Brief (Factor 1) initial		**Total**	
	Light/minimum	**Moderate/intense**		
	n	***n***	***N***	***p*-value**
Below mean	11	14	25	0.052
Above mean	3	18	21	
Leptin/BMI	QSU-Brief (Factor 2) initial		**Total**	
	Light/minimum	**Moderate/intense**		
	n	***n***	***N***	***p*-value**
Below mean	7	18	25	0.151
Above mean	2	19	21	
Leptin%/BF	QSU-Brief (Factor 1) 1 month		**Total**	
	Light/minimum	**Moderate/intense**		
	n	***n***	***N***	***p*-value**
Below Mean	17	9	26	0.772
Above Mean	11	7	18	
Leptin%/BF	QSU-Brief (Factor 2) 1 month		**Total**	
	Light/Minimum	**Moderate/Intense**		
	n	***n***	***N***	**p-value**
Below Mean	13	13	26	0.030
Above Mean	3	15	18	
Leptin/BMI	QSU-Brief (Factor 1) 1 month		**Total**	
	Light/Minimum	**Moderate/Intense**		
	n	***n***	***N***	**p-value**
Below mean	17	7	24	0.277
Above mean	11	9	20	
Leptin/BMI	QSU-Brief (Factor 2) 1 month		**Total**	
	Light/minimum	**Moderateintense**		
	n	***n***	***N***	***p*-value**
Below mean	10	14	24	0.423
Above mean	6	14	20	

Mean of leptin: 12 ng/mL/Chi Square/exact Fisher.

Table 4
Correlation between adjusted levels (Leptin/BMI) and (Leptin/%GC) with QSU-Brief initial and after 1 month of treatment according to smoking status.

	Leptin/%BF	Leptin/%BF	Leptin/BMI	Leptin/BMI
	Smokers	Abstinent	Smokers	Abstinent
Initial QSU-Brief (Factor 1)	($r=0.434$*; $p=0.034$)	($r=-0.067$; $p=0.767$)	($r=0.335$; $p=0.110$)	($r=0.258$; $p=0.247$)
QSU-Brief (Factor 2)	($r=0.442$*; $p=0.030$)	($r=0.263$; $p=0.237$)	($r=0.136$; $p=0.525$)	($r=0.489$*; $p=0.021$)
Score QSU-Brief	($r=0.497$*; $p=0.014$)	($r=0.034$; $p=0.881$)	($r=0.288$; $p=0.172$)	($r=0.296$; $p=0.182$)
Final QSU-Brief (Factor 1)	($r=0.304$; $p=0.158$)	($r=-0.028$; $p=0.906$)	($r=0.205$; $p=0.348$)	($r=0.148$; $p=0.522$)
QSU-Brief (Factor 2)	($r=0.595$**; $p=0.003$)	($r=0.246$; $p=0.282$)	($r=0.413$; $p=0.050$)	($r=0.252$; $p=0.271$)
Score QSU-Brief	($r=0.464$*; $p=0.026$)	($r=0.183$; $p=0.427$)	($r=0.390$; $p=0.066$)	($r=0.271$; $p=0.234$)

* $p < 0.005$.

4. Discussion

In this study, we observed an association between higher leptin concentrations in initial of treatment for smoking cessation with the higher score of the QSU-Brief (Factor 2), after 1 month of intervention, indicating a greater influence of negative reinforcement by nicotine on difficulty to smoking cessation. Our results showed that higher serum leptin concentrations among smokers who start treatment may be considered a factor that may be associated with increased craving. Furthermore, the most of individuals who remained smokers after 1 month (78.3%) had moderate and heavy classification of QSU-Brief, indicating

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increased craving for cigarettes and difficulty to achieve abstinence.

It is known that the inhibition of dopamine signaling and release of cortisol in the HPA axis by leptin contributes to the increase of the craving for nicotine in initial period of withdrawal. Nicotine provides an increase in plasma cortisol concentration and may also promote the increase or decrease in leptin concentration, being controversial the postulates regarding this subject. In the first days of abstinence, nicotine withdrawal might lead to reduced cortisol release, which associated with an increase in leptin levels, contribute to the increased intensity of craving (Miyata and Meguid, 2000; al'Absi et al., 2004). Our results showed an inverse association between leptin concentration and levels of cortisol, indicating that higher concentrations of leptin are associated with lower levels of cortisol. This result confirms the interaction between these two hormones, and how leptin contributes directly to the occurrence of craving.

In our study, a negative correlation was found between serum cortisol levels and the number of cigarettes smoked per day after 1 month only among men who did not stop smoking. In the study of (al'Absi et al., 2004), which evaluated the association between changes in cortisol levels and relapse by cigarettes in the early abstinence in men and women, was observed that subjects who relapsed within the first week after cessation, showed a decrease in the concentration of morning cortisol, and greater craving for cigarettes and reduced positive affect (QSU-Brief-factor 1), when compared with abstinent. The increase in cortisol levels among smokers is generally attributed to exposure to nicotine, despite of the comparisons between cortisol levels of smokers and nonsmokers remain inconsistent and cortisol response in smoking cessation unknown (Steptoe and Ussher, 2006).

al' Absi (2006), in a review on the decrease in the concentration of cortisol in the early days of abstinence predicting relapse by cigarettes, noted that hormonal associations with relapse by cigarettes tend to be more consistent in men, while the intensity of withdrawal symptoms tends to be more consistent with relapse by cigarettes in women. The dysregulation of the HPA axis activity during early abstinence exacerbates the symptoms of withdrawal and contributes to rapid relapse observed in the majority of smokers. However more research is needed to investigate the mechanisms of these differences between men and women.

Still is unknown the effect of nicotine on leptin concentrations. It is postulated that the decrease in food intake is associated with an increase in leptin concentration, provided by the constant use of nicotine. However, the acute effects of nicotine on plasma leptin concentrations remain inconsistent. In the studies of (Wei et al., 1997), (Hodge et al., 1997) and (Mantzoros et al., 1998) was found that chronic cigarette smokers showed leptin levels lower than individuals who had never smoked. (Eliasson and Smith, 1999) found that chronic smokers and users of nicotine gums showed higher serum leptin levels than nonsmokers. In contrast, (Donahue et al., 1999) and (Yoshinari et al., 1998) no found correlation between chronic smoking and serum leptin levels (Miyata and Meguid, 2000).

The most studies describe the effects of leptin in the alcohol withdrawal process, and few studies have reported their influence on nicotine dependence. Kiefer et al. (2001) found increased levels of leptin in alcoholic patients in early abstinence compared with healthy controls. (Wrust et al., 2003) no found significant differences between serum leptin levels in alcoholic patients between the first and seventh day of abstinence. Kraus et al. (2004) found a correlation between increased leptin levels with the intensity by craving in alcoholic women. Overall, the results suggest that an increase in leptin levels at the beginning of withdrawal may be considered a factor that influences the increase in drug craving.

Among smokers, until now, only three studies evaluating the influence of leptin on the fissure during smoking cessation. Consistent with our results, (von der Goltz et al., 2009), and (al' Absi et al., 2011) found a positive association between the intensity of the craving for nicotine and plasma leptin concentrations in early abstinence. This suggests that leptin inhibits dopaminergic transmission during drug withdrawal modulating the intensity of the craving. Recently, a work published by (Potretzke et al., 2014) evaluating individuals abstinent for 24 h, found a significant increase of leptin accompanied by acute stress during withdrawal, and association between the levels of this hormone and the craving for cigarettes. In no study there was the adjustment of serum leptin by body adiposity, which may influence the interpretation of results.

In our study, individuals who failed to abstain and continued smoking despite of the intervention for smoking cessation, showed a positive association between leptin/BF% and the QSU-Brief (Factor 1 and 2) initial and QSU-Brief (Factor 2) after 1 month. In individuals who were able to abstain, leptin/BMI also correlated with the QSU-Brief (Factor 2) only at the beginning. In this population, due to the maintenance of abstinence in the period analyzed, there was no association between serum leptin levels adjusted with the QSU-Brief (Factor 2), after 1 month. In women evaluated in this study, an association was also observed between the levels of leptin/%BMI and leptin/%BF with the QSU-Brief (Factor 2) initial those who stopped and the QSU-Brief (Factor 2) after 1 month those who remained smokers. This association constant of the initial concentration of the leptin with QSU Brief (Factor 2) on both smoking status, reinforces the role of leptin in modulating of mesocorticolimbic reward structures and regulation of stress. Furthermore, leptin plays an important role in the neurobiology of the reward system by the drug, contributing to increase of craving and difficulty in smoking cessation.

In work performed by (Toffolo et al., 2012), who analyzed the serum leptin levels in newly abstinent alcoholic women, the authors found that serum leptin levels were higher among newly abstinent women presenting between 1 and 3 months of abstinence. The authors suggested that the increased levels of leptin may be associated to the time of withdrawal. In our study, we considered abstinent those individuals who completed the first month of intensive approach to smoking cessation exempt of tobacco use. This period of abstinence resembles with this study, and in our results, the highest concentrations of initial leptin in women were associated with increased craving for cigarettes.

Our review of the literature did not result in conclusive evidence regarding the relationships between nicotine withdrawal and leptin levels. Perkins and Fonte (2002) suggested that serum leptin concentration after smoking cessation may increase particularly in women. This increase in leptin levels in women may be associated with possible hormonal changes that still remained unresolved and not discussed in the literature. Moreover, Nicklas et al. (1999) reported no significant increase in leptin levels in men after six months of nicotine withdrawal. However leptin levels may be higher in newly abstinent individuals, possibly due to direct or indirect effects of nicotine and can also be affected by the withdrawal process. The mechanisms involved in the changes in leptin levels after smoking cessation remain unknown.

The main limitation of our study refers to the non-probabilistic design, not permitting attribute causality effect between the process of abstinence and changes in leptin levels, beyond of the small sample size due to the high number of people who do not complete treatment for smoking cessation. Furthermore, no analyzes of serum leptin were performed after 1 month of follow-up, but there were no differences in anthropometric parameters and body composition in short term. On the other hand, the adjustments of serum leptin by BMI and %BF to eliminate the effect of adiposity on the results of the analysis of leptin were performed. No hormonal differences between women participants were investigated.

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Beyond of leptin and cortisol, the specifics of each psychotropic drug, the individual characteristics of dependents, as well as differences between the sexes and the period of abstinence may influence craving and relapse by cigarettes, should also be evaluated as determinants of influence in neurobiology of craving.

5. Conclusion

Our results indicated that higher leptin concentrations at the beginning of treatment for smoking cessation was associated with increased craving for cigarettes and difficulty to quit smoking. Difference between the scores of the QSU-Brief between smokers and abstinent was observed. Those who have achieved success to quit smoking remained with lower craving. There was a positive correlation between leptin/BMI and leptin/%BF with negative reinforcement (QSU-Brief-Factor 2) after 1 month, in women who have failed to quit smoking.

Declaration of interests

None declared.

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References

Aguiar-Nemer, A.S., Toffolo, M.C.F., Silva, C.J., Laranjeira, R., Silva-Fonseca, V.A., 2013. Leptin influence in craving relapse of alcoholics and smokers. J. Clin. Med. Resid. 5, 164–167. http://dx.doi.org/10.4021/jocmr1159w.

al'Absi, M., 2006. Hypothalamic–pituitary–adrenocortical responses to psychological stress and risk for smoking relapse. Int. J. Psychophysiol. 59, 218–227. http://dx.doi.org/10.1016/j.ijpsycho.2005.10.010.

al'Absi, M., Hatsukami, D., Davis, G.L., Wittmers, L.E., 2004. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. Drug Alcohol Depend. 73, 267–278. http://dx.doi.org/10.1016/j.drugalcdep.2003.10.014.

al'Absi, M., Hooker, S., Fujiwara, K., Kiefer, F., von der Goltz, C., Cragin, T., Wittmers, L.E., 2011. Circulating leptin levels are associated with increased craving to smoke in abstinent smokers. Pharmacol. Biochem. Behav. 97, 509–513. http://dx.doi.org/10.1016/j.pbb.2010.10.004.

Araújo, R.B., Oliveira, M.S., Pedroso, R.S., Miguel, A.C., Castro, M.G.T., 2008. Craving e dependência química: conceito, avaliação e tratamento. J. Bras. Psiquiatr. 57, 57–63. http://dx.doi.org/10.1590/S0047-20852008000100011.

Araújo, R.B., Oliveira, M.S., Moraes, J.F.D., Pedroso, R.S., Port, F., Castro, M.G.T., 2007. Validação da versão brasileira do Questionnaire of Smoking Urges-Brief. Rev. Psiquiatr. Clín. 34, 166–175. http://dx.doi.org/10.1590/S0101-60832007000400002.

Black, D., James, W.P.T., Besser, G.M., 1983. Obesity: a report of the Royal College of Physicians. J. R. Coll. Phys. 17, 5–65 (accessed 05.12.14).

Donahue, R.P., Zimmet, P., Bean, J.A., et al., 1999. Cigarette smoking, alcohol use, and physical activity in relation to serum leptin levels in a multiethnic population (The Miami Community Health Study). Ann. Epidemiol. 9, 108.

Eliasson, B., Smith, U., 1999. Leptin levels in smokers and long-term users of nicotine gum. Eur. J. Clin. Invest. 29, 145.

Friedman, J.M., Hallas, J.L., 1998. Leptin and the regulation of body weight in mammals. Nature 395, 763–770. http://dx.doi.org/10.1038/27376.

Hodge, A.M., Westerman, R.A., de Courten, M.P., et al., 1997. Is leptin sensitivity the link between smoking cessation and weight gain. Int. J. Obes. Rel. Metab. Disord. 21, 50.

Halty, L.S., Huttner, M.D., Netto, I.C.O., Santos, V.A., Martins, G., 2002. Análise da utilização do Questionário de Tolerância de Fagerstrom (QTF) como instrumento de medida da dependência nicotínica. J. Pneumol. 28, 180–186. http://dx.doi.org/10.1590/S0102-35862002000400002.

Instituto Nacional do Câncer (INCA), 2001. Abordagem e Tratamento do Fumante–Consenso. Retrieved from: ⟨http://www.inca.gov.br/tabagismo/publicacoes/tratamento_consenso.pdf⟩ (accessed 14.03.14).

Inui, A., 1999. Feeding and body-weight regulation by hypothalamic neuropeptides mediation of the actions of leptin. Trends Neurosci. 22, 62–67. http://dx.doi.org/10.1016/S0166-2236(98)01292-2.

Kiefer, F., Jahn, H., Jaschinski, M., Holzbach, R., Wolf, K., Naber, D., Wiedemann, K., 2001. Leptin: a modulator of alcohol craving? Biol. Psychiatry 49, 782–787. http://dx.doi.org/10.1016/S0006-3223(01)01081-2.

Kraus, T., Reulbach, U., Bayerlein, K., Mugele, B., Hillemacher, T., Sperling, W., Kornhuber, L., Bleich, S., 2004. Leptin is associated with craving in females with alcoholism. Addict. Biol. 9, 213–219. http://dx.doi.org/10.1111/j.1369-1600.2004.tb00535.x.

Lipschitz, D.A., 1994. Screening for nutritional status in the elderly. Prim. Care 21, 55–67 (accessed 04.11.14).

Mantzoros, C.S., Liolios, A.D., Tritos, N.A., et al., 1998. Circulating insulin concentrations, smoking, and alcohol intake are important independent. Obes. Res. 6, 179.

Miyata, G., Meguid, M.M., 2000. Is Leptin Involved in the Acute Anorectic Effect of Nicotine? Nutrition 16, 141–142. http://dx.doi.org/10.1016/S0899-9007(99)00223-00223.

Nicklas, B.J., Tomoyasu, J.M., Goldberg, A.P., 1999. Effects of cigarette smoking and its cessation on body weight and plasma leptin levels. Metabolism 48, 804–808. http://dx.doi.org/10.1016/S0026-0495(99)90183-X.

Palmiter, R.D., 2007. Is a dopamine a physiologically relevant median mediator of feeding behavior? Trends Neurosci. 30, 375–381. http://dx.doi.org/10.1016/j.tins.2007.06.004.

Perkins, K.A., Fonte, C., 2002. Effects of smoking status and smoking cessation on leptin levels. Nicot. Tob. Res. 4, 459–466. http://dx.doi.org/10.1080/1462220021000018434.

Potretzke, S., Nakajima, M., Cragin, T., al' Absi, M., 2014. Changes in circulating leptin levels during acute stress and associations with craving in abstinent smokers: a preliminary investigation. Psychoneuroendocrinology 47, 232–240. http://dx.doi.org/10.1016/j.psyneuen.2014.05.008.

Pouliot, M.C., Després, J.P., Lemieux, S., Moorjani, S., Bouchard, C., Tremblay, A., Nadeau, A., Lupien, P.J., 1994. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am. J. Clin. Cardiol. 73, 460–468 (accessed 10.01.14).

Reseland, J.E., Mundal, H.H., Hollung, K., Haugen, F., Zahid, N., Anderssen, S.A., Drevon, C.A., 2005. Cigarette smoking may reduce plasma leptin concentration via catecholamines. Prostaglandins Leukot. Essent. Fat. Acids 73, 43–49. http://dx.doi.org/10.1016/j.plefa.2005.04.006.

Rodrigues, G.R.S., Melquíades, M., Leite, M.A., Louro, M.B., Perches, C., Vargas, A.L.A., Luquetti, S.C.P., Aguiar-Nemer, A.S., 2013. Hormonal, metabolic and nutritional alterations in smokers: emergency for smoking abstinence. J. Brasil. Psiquiatr. 62, 261–267. http://dx.doi.org/10.1590/S0047-20852013000400003.

Roubos, E.W., Dahmen, M., Xu, K.T., 2012. Leptin and the hypothalamo–pituitary–adrenal stress axis. Gen. Comp. Endocrinol. 177, 28–36. http://dx.doi.org/10.1016/j.ygcen.2012.01.009.

Steptoe, A., Ussher, M., 2006. Smoking, cortisol and nicotine. Int. J. Psychophysiol. 59, 228–235. http://dx.doi.org/10.1016/j.ijpsycho.2005.10.011.

Toffolo, M.C.F., Marliére, C.A., Freitas, S.N., Aguiar-Nemer, A.S., 2012. Increasing leptin level in abstaining alcohol-dependent women. Nutr. Hosp. 27, 781–788. http://dx.doi.org/10.3305/nh.2012.27.3.5695.

von der Goltz, C., Koopmann, A., Dinter, C., Richter, A., Rockenback, C., Grosshans, M., Nackovics, H., Wiedemann, K., Mann, K., Winterer, G., Kiefer, F., 2009. Orexin and leptin are associated with nicotine craving: a link between smoking, appetite and reward. Psychoneuroendocrinology 35, 570–577. http://dx.doi.org/10.1016/j.psyneuen.2009.09.005.

Wei, M., Stern, M.P., Haffner, S.M., 1997. Serum leptin levels in Mexican Americans and non-Hispanic whites (association with body mass index and cigarette smoking). Ann. Epidemiol. 7, 81.

Wilsgaard, T., Jacobsen, B.K., 2007. Lifestyle factors and incident metabolic syndrome. The Tromso Study 1979–2001. Diabetes Res. Clin. Pract. 78, 217–224. http://dx.doi.org/10.1016/j.diabres.2007.03.006.

World Health Organization (WHO), 2000. Obesity – preventing and managing the global epidemic. Report of a WHO Consultation on Obesiy. Genebra. Retrieved form: ⟨http://whqlibdoc.who.int/trs/WHO_TRS_894.pdf?ua=1⟩ (accessed 08.05.13).

World Health Organization (WHO), 2010. Global estimate of the burden of disease from second-hand smoke. Geneva. Retrieved form: ⟨http://whqlibdoc.who.int/publications/2010/9789241564076_eng.pdf⟩ (accessed 26.03.14).

Wurst, F.M., Bechtel, G., Forster, S., Wolfersdorf, M., Huber, P., Scholer, A., Pridzun, L., Alt, A., Seidl, S., Dierkes, L., Dammann, G., 2002. Leptin levels of alcohol abstainers and detoxification patients are not different. Alcohol Alcohol. 37, 401–404. http://dx.doi.org/10.1093/alcalc/agg088.

Yoshinari, M., Wakisaka, M., Fujishima, M., 1998. Serum leptin levels in smokers with type 2 diabetes. Diabetes Care. 21, 516.

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