Journal of Psychiatric Research 111 (2019) 24–29

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Increased levels of serum leptin in the early stages of psychosis

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ARTICLE INFO

Keywords:
Leptin
At-risk mental state
First-episode psychosis
Sex
Food intake
Stress

ABSTRACT

Background: Studies evaluating leptin levels in patients with first-episode psychoses (FEP) have been inconclusive, and apparently, the high levels of leptin reported in patients with schizophrenia may be associated with weight gain. The aim of this study was to evaluate leptin levels at the early stages of the disease and the relationship between leptin and lifestyle habits, stress-related variables and metabolic parameters.

Methods: In total, 14 at-risk mental state (ARMS) patients, 39 FEP patients, 32 psychotic patients in the critical period (CP) and 21 healthy controls (HCs) were assessed. Anthropometric and biochemical parameters, as well as dietary intake, physical activity, stress-related variables and symptomatology, were collected.

Results: Leptin levels were higher in the ARMS, FEP and CP patients than in the HCs. After controlling for age, sex, BMI, physical exercise, tobacco use and dietary intake, the highest differences in leptin levels were observed between the ARMS patients and HCs ($p = 0.025$). In the whole sample, leptin levels were positively correlated with BMI ($p < 0.001$), waist circumference ($p < 0.001$), insulin levels ($p = 0.020$), levels of the inflammatory marker IL-6 ($p = 0.007$) and energy intake ($p = 0.043$) and negatively correlated with HDL cholesterol ($p = 0.018$). Interestingly, energy intake and food craving scores were positively correlated with levels of leptin only in females ($p = 0.022$ and $p = 0.036$, respectively).

Discussion: The present study detected increased leptin levels in the early stages of psychosis and significant correlations between leptin levels and anthropometric, lipid, hormone, and cytokine parameters. We found higher leptin levels in women, and we identified dietary intake habits associated with leptin exclusively in females that advocate considering sex in future studies.

1. Introduction

Leptin is a 16-kDa peptide hormone and a cytokine-like molecule encoded by the *LEP* gene that is mainly secreted into circulating blood from white adipocytes, although lower amounts are produced in other tissues and organs (Margetic et al., 2002). Leptin mainly serves as a feedback signal from fat cells to the central nervous system in the regulation of feeding, energy balance and body adiposity. However, leptin has other functions, including regulation of thermogenesis, regulation of cardiovascular functions via the autonomic nervous system, glucose homeostasis, immune and inflammatory responses, reproduction, bone formation, locomotor activity, neuroplasticity, development and other brain functions (Ramos-Lobo and Donato, 2017). Circulating leptin binds to leptin receptors, which are known to stimulate gene transcription and have ubiquitous expression. In the brain, and specifically in the hypothalamus, leptin modulates the neuroendocrine axes, including the hypothalamic-pituitary-adrenal (HPA) axis (Maniam and Morris, 2012). Furthermore, leptin has neurotrophic effects, such as stimulating brain-derived neurotrophic factor (*BDNF*) gene translation, and regulates neuron excitability by enhancing NMDA receptor functions. All of these mechanisms are involved in psychological functions such as cognition, motivated behavior and responsiveness to stress (Stieg et al., 2015).

Leptin has been hypothesized to have a role in schizophrenia, mainly because of its relationship with weight gain and obesity (Henderson et al., 2015). Increased leptin levels in patients with a mean illness duration of 9.3 years have been identified in a meta-analysis including 1674 patients and 2033 controls (Stubbs et al., 2016).

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https://doi.org/10.1016/j.jpsychires.2019.01.006
Received 24 September 2018; Received in revised form 9 December 2018; Accepted 7 January 2019

Table 1
Characteristics of the subjects in each study group.

	HC n = 21	ARMS n = 14	FEP n = 39	CP n = 32	p-value
Females, N (%)	14 (67)	4 (29)	11 (28)	16 (50)	**0.017**
Age (years)	29 ± 3	22 ± 3	23 ± 4	25 ± 5	< **0.001**
Caucasian, N (%)	21 (100)	11 (79)	32 (82)	24 (75)	0.113
BMI (kg/m^2)	22 ± 3	23 ± 3	24 ± 4	25 ± 4	**0.010**
Waist circumference (cm)	77 ± 9	82 ± 10	87 ± 9	90 ± 11	< **0.001**
Physical activity (MET-min/w)	2803 ± 2505	1666 ± 1463	2151 ± 1545	2130 ± 1605	0.149
Lipids					
HDLc (mg/dL)					
females	66.9 ± 3.6	49.3 ± 4.2	56.4 ± 5.1	52.9 ± 2.9	**0.032**
males	61.1 ± 3.3	41.7 ± 2.2	47.7 ± 2.4	44.8 ± 1.9	**0.003**
Triglycerides (mg/dL)	60 ± 22	90 ± 43	106 ± 69	108 ± 68	**0.001**
Triglycerides/HDLc ratio					
females	1.0 ± 0.1	2.3 ± 1.0	1.6 ± 0.2	1.9 ± 0.3	**0.012**
males	1.0 ± 0.2	2.1 ± 0.3	2.6 ± 0.4	3.0 ± 0.6	**0.016**
Hormones					
Insulin (μIU/L)	1.2 ± 2.0	2.6 ± 3.0	7.6 ± 18.5	4.5 ± 3.1	**0.001**
Cortisol (ng/mL)	19 ± 6	19 ± 6	18 ± 5	21 ± 4	0.124
Leptin (ng/mL)					
females	19 ± 21	44 ± 29	38 ± 30	45 ± 36	**0.005**
males	5 ± 6	8 ± 7	8 ± 10	11 ± 14	0.560
Inflammatory markers					
IL-6 (pg/mL)	0.29 ± 0.36	0.75 ± 0.67	0.52 ± 0.58	0.65 ± 0.50	**0.010**
Fibrinogen (mg/L)	267 ± 47	246 ± 58	260 ± 64	258 ± 63	0.518
CRP (mg/L)	0.9 ± 1	1.1 ± 1.3	2.0 ± 3.8	2.7 ± 2.8	**0.012**
NTL ratio	1.5 ± 0.6	1.6 ± 0.6	1.8 ± 0.8	1.8 ± 0.8	0.610
Dietary intake					
Total energy (kcal/day)					
females	1575 ± 129	2134 ± 339	2226 ± 124	2124 ± 158	**0.008**
males	2242 ± 148	2438 ± 291	2611 ± 138	2575 ± 132	0.492
Stress scores					
PSS	15 ± 8	30 ± 12	26 ± 10	21 ± 7	< **0.001**
HRS	87 ± 81	145 ± 88	194 ± 93	185 ± 129	**0.003**
FCQ	26 ± 9	32 ± 16	33 ± 15	29 ± 13	0.325
Substance use					
Daily smokers	3 (14)	6 (43)	31 (80)	22 (69)	**0.002**
Daily cannabis	0 (0)	2 (14)	19 (49)	3 (9)	**0.001**
Pharmacological treatment					
Antipsychotics	–	5 (36)	36 (92)	27 (84)	< **0.001**
Antidepressants	–	8 (57)	8 (21)	3 (9)	**0.002**
Mood stabilizers	–	3 (21)	8 (21)	2 (6)	0.197
Psychopathology					
Total PANSS score	–	58.9 ± 15.9	59.8 ± 16.6	49.2 ± 15.2	**0.019**
Total HDS score	–	12.7 ± 4.1	9.3 ± 7.8	5.2 ± 5.4	**0.003**

Abbreviations: HC: healthy control; ARMS: at-risk mental state; FEP: first-episode psychosis; CP: critical period; BMI: body mass index; MET: multiples of the resting metabolic rate measured with the International Physical Activity Questionnaire (IPAQ)/week; HDLc: high-density lipoprotein cholesterol; IL-6: interleukin 6; CRP: c-reactive protein; NTL: neutrophil to lymphocyte ratio; PSS: perceived stress scale; HRS: Holmes-Rahe social readjustment scale; FCQ: food craving questionnaire; PANSS: positive and negative syndrome scale; HDS: Hamilton depression scale.
Data are shown as the mean ± standard deviation or number of subjects, N, and percentage (%). The Kruskal-Wallis test was used to compare diagnostic groups. Data are shown separately for males and females if they showed statistically significant differences by the Mann-Whitney *U* test.

Although, conflicting results have been obtained in early psychosis, where increases, decreases or nondifferences in leptin levels between early psychotic patients and control individuals have been reported (Balõtšev et al., 2017; Bocchio-Chiavetto et al., 2018; Chouinard et al., 2018; Pillinger et al., 2017; Stubbs et al., 2016). This study aimed to examine leptin levels in the early stages of psychosis by comparing at-risk mental state (ARMS) subjects, patients with recent-onset psychosis and healthy control (HC) subjects. Additionally, we assessed whether lifestyle habits, stress-related variables and metabolic parameters were associated with leptin levels when controlling for sex.

2. Methods

2.1. Subjects

We conducted a cross-sectional study with a selection of 85 unrelated patients, 54 males and 31 females, attending our Early Psychosis Program (Hospital Universitari Institut Pere Mata, Reus, Spain) and 21 HC individuals, 7 males and 14 females (Table 1). With the aim of differentiating the stage of the illness in patients with a recent-onset psychosis, we divided patients with an established psychotic disorder into two groups: first episode psychosis (FEP) and critical period (CP). All FEP patients had a duration of illness < 1 year. The CP group included patients with two or more psychotic episodes in the first 5 years of illness or with one psychotic episode and a duration of illness between 1 and 5 years. Therefore, we considered 3 clinical groups: ARMS (N = 14), FEP (N = 39) and CP (N = 32). The DSM-IV diagnoses in the FEP patients were as follows: schizophreniform disorder (n = 7), schizoaffective disorder (n = 2) and psychotic disorder not otherwise specified (n = 30). Diagnoses in the CP patients were schizophreniform disorder (n = 2), schizophrenia (n = 7), bipolar disorder (n = 4) and psychotic disorder not otherwise specified (n = 19). HC subjects were patient's friends, nongenetic relatives and university students directly interviewed by an experienced psychiatrist to exclude subjects with a past or current history of psychiatric disorders. The exclusion criteria to participate in the study were as follows: pregnancy, substance-induced psychosis, intellectual disability, neurological disorder, severe head injury, active glucocorticoid treatment, oral contraceptive pill use, type

1 diabetes mellitus and active substance dependence other than tobacco or cannabis. Finally, no participant had a history of type 2 diabetes, dyslipidemia, coronary artery disease, hypothyroidism or hypertension.

Approval was obtained from the local ethics committee, and all of the participants provided written informed consent after complete description of the study. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Clinical measurements

All patients were assessed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Vazquez-Barquero et al., 1994) by a trained psychiatrist, and diagnoses were obtained with OPCRIT 4 for Windows. ARMS subjects fulfilled the criteria for any of the three ultrahigh-risk groups when assessed with the Comprehensive Assessments of ARMS (Yung and McGorry, 2007). Positive, negative and general symptoms were assessed with the positive and negative syndrome scale (PANSS) (Kay et al., 1987). HCs scored lower than 7 on the general health questionnaire (GHQ-28) (Lobo et al., 1986).

Biometric and biochemical parameters, dietary intake, stress scores and current substance use were obtained from patients and HCs. Weight, height and waist circumference were obtained by physical examination, and BMI was expressed as weight (kg)/height (m^2). The International Physical Questionnaire-short form (IPAQ-SF) (Craig et al., 2003) was used to assess the physical activity of participants and expressed as metabolic equivalents of task (MET)-minutes/week, which considers the number of vigorous, moderate and walking activities performed during the last week. We evaluated two stress measures: the number of stressful life events in the past six months, assessed using the Holmes-Rahe social readjustment scale (HRS) (Holmes and Rahe, 1967) and the psychological perception of stress, assessed using the perceived stress scale (PSS) (Cohen et al., 1983). Dietary habits were assessed by means of a clinical interview conducted by a nutritionist. Food intake was registered using 24-h recall, and CESNID software (Centre d'Ensenyament Superior de Nutrició i Dietètica, University of Barcelona, Santa Coloma de Gramenet, Barcelona, Spain) was used to calculate the daily calorie and nutrient intake, as previously described (Gattere et al., 2018; Manzanares et al., 2014). Dietary recall was obtained for working days to avoid potential changes in dietary habits during the weekend. To assess the craving for foods, namely, the desire or urge for food consumption, we used the food craving questionnaire (FCQ) (Moreno et al., 2008).

2.3. Laboratory analysis

A fasting morning (8:00–10:00 a.m.) blood sample was obtained from all participants and transported to the biobank in less than 1 h for quick processing and storage at a temperature of −80 °C that lasted less than one year. Frozen aliquots were sent to specific laboratories to measure hormones, lipids and inflammatory markers. Leptin was measured with an enzyme-linked immunosorbent assay (RayBiotech, Inc., GA, USA). The sensitivity of the assay was 2 pg/mL. Intra-assay and interassay coefficients of variation (CV) were < 10% and < 12%, respectively. Total cortisol and insulin were measured using the Maglumi 2000 Analyzer chemiluminescence immunoassay system (SNIBE Co, Ltd, Guandong, China) with intra-assay CV < 5% and interassay CV < 9% for both assays. Sensitivity was 2.5 ng/mL for cortisol and 3.0 μIU/ml for insulin. Lipid parameters were measured by spectrophotometry. C-reactive protein (CRP), fibrinogen and interleukin 6 (IL-6) were measured as previously described (Stojanovic et al., 2014).

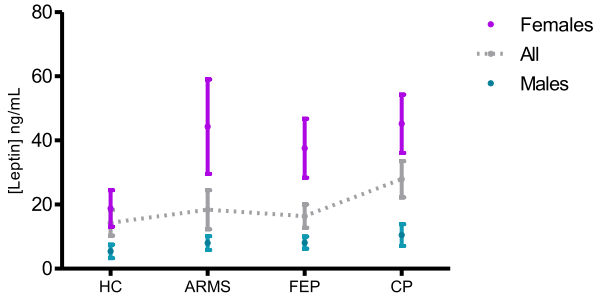
2.4. Statistical analysis

Data processing and statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The Shapiro-Wilk test indicated that most of the variables were not normally distributed, and the Mann-Whitney *U* test showed that some variables were significantly different between males and females. In these cases, characteristics of the sample were reported stratified by sex. Study groups were examined using the Kruskal-Wallis nonparametric test to identify whether they were significantly different. The general linear model (GLM) was used to identify whether leptin levels differed among the four groups using age, sex, BMI, physical activity, tobacco use and dietary intake as covariates. To evaluate the relationship between leptin and age, BMI, waist circumference, physical activity, lipid and hormonal variables, inflammatory markers, diet intake and stress measures, we used partial correlation analysis controlling for sex across the whole dataset and Spearman's correlations in the sample stratified by sex. In addition, in the patient sample (ARMS, FEP and CP), psychopathology and equivalent doses of chlorpromazine were also investigated for their putative association with leptin levels using Spearman's correlations. Finally, the GLM was used to identify whether leptin levels differed among subjects under the three grouped pharmacological treatments (risperidone/paliperidone, olanzapine/clozapine and aripiprazole) considering BMI and sex as covariates. All tests were 2-tailed, and $p < 0.05$ was considered statistically significant. We did not correct for multiple comparisons because the analyses were exploratory in nature.

3. Results

Preliminary analyses of raw data showed that females exhibited higher levels of leptin ($U = 411$, $p < 0.001$), higher levels of HDL cholesterol ($U = 713$, $p < 0.001$) and lower daily caloric intake ($U = 719$, $p < 0.001$) than males. We also identified higher leptin levels in the ARMS, FEP and CP patients than in the HCs (Fig. 1). After controlling for age, sex, BMI, physical exercise, tobacco use and dietary intake, the highest estimated marginal means were observed in the ARMS subjects (Fig. 1). As can be observed in the figure, the main differences were observed in females. We also explored whether leptin

A



B

	EMM ± SE	95% Confidence Interval	
		Lower bound	Upper bound
HC	8.7 ± 4.8	-0.8	18.2
ARMS	25.4 ± 5.0	15.4	35.3
FEP	21.6 ± 3.2	15.3	28.0
CP	20.4 ± 3.1	14.4	26.6

EMM: estimated marginal means; SE: standard error; HC: healthy control; ARMS: at-risk mental state; FEP: first-episode psychosis; CP: critical period.

General linear model adjusted for age, sex, body mass index, physical activity, number of cigarettes smoked/day and daily dietary intake: F=12.634; p<0.001; adjusted R squared =0.53

Group comparisons:
HC vs. ARMS: p=0.025; HC vs. FEP: p=0.043; HC vs. CP: p=0.052

Fig. 1. Leptin levels in the study groups. A. Observed means; B. Estimated marginal means.

levels differed between the three main pharmacological treatments prescribed in the sample considering BMI and sex as covariates. Higher levels of leptin were observed in patients on aripiprazole treatment (28 ± 5 ng/mL; N = 16) compared to risperidone/paliperidone (14 ± 4 ng/mL; N = 29) (p = 0.027). Leptin levels in patients on olanzapine/clozapine (24 ± 4 ng/mL; N = 23) were not different from those on risperidone (p = 0.535) or aripiprazole (p = 0.285) and were very similar to the leptin levels in patients who were not taking antipsychotics (24 ± 5 ng/mL; N = 17). Leptin levels in patients undergoing antidepressant treatment (N = 19) were 28 ± 5 ng/mL compared to 20 ± 2 ng/mL in patients who were not taking antidepressants (N = 66) (p = 0.133). Likewise, leptin levels in patients who were taking mood stabilizers (N = 13) were 19 ± 5 ng/mL compared with 22 ± 2 ng/mL in patients who were not taking mood stabilizers (N = 72) (p = 0.552).

Leptin levels positively correlated with BMI, waist circumference and insulin in both male (ρ = 0.717, p < 0.001; ρ = 0.698, p < 0.001 and ρ = 0.314, p < 0.015, respectively) and female (ρ = 0.646, p < 0.001; ρ = 0.579, p < 0.001 and ρ = 0.382, p < 0.010, respectively) subjects and in the whole sample controlling for sex (ρ = 0.623, p < 0.001; ρ = 0.563, p < 0.001 and ρ = 0.229, p < 0.026, respectively) (Table 2). In addition, leptin levels were negatively correlated with high-density lipoprotein (HDL) cholesterol (ρ = −0.233, p = 0.018) and positively correlated with IL-6 (ρ = 0.262, p = 0.007) and the triglyceride/HDL cholesterol ratio (ρ = 0.232, p = 0.019) in the total sample but not in the stratified analyses. No relationship was observed between leptin levels and the neutrophil to lymphocyte (NTL) ratio (ρ = 0.167, p = 0.091). Total daily energy ingested positively correlated with leptin levels in the whole sample (ρ = 0.201, p = 0.043) and in females (ρ = 0.349, p = 0.022) but not in males (ρ = 0.004, p = 0.978). Remarkably, total energy intake and the food craving score positively correlated with levels of leptin in females (ρ = 0.349, p = 0.022 and ρ = 0.317, p = 0.036, respectively) but not in males (ρ = 0.004, p = 0.978 and ρ = −0.148, p = 0.272). As expected, the food craving score positively correlated with total energy ingested in females (ρ = 0.385, p = 0.011) and in male individuals (ρ = 0.293, p = 0.031).

Stress parameters, either HRS or PSS scores, were not associated with leptin levels (Table 2), although marginal significance was observed regarding the total score of the HRS in females (ρ = 0.297, p = 0.051). Additionally, in females, HRS positively correlated with the food craving score (ρ = 0.382, p = 0.011) and perceived stress (ρ = 0.318, p = 0.038).

Finally, psychotic symptoms measured with the PANSS did not show any association with leptin levels, and the antipsychotic doses converted into chlorpromazine equivalents (mg/day) were not correlated with the leptin levels (Supplementary Table 1).

Table 2
Spearman's ρ correlation coefficients between leptin and study variables stratified by sex and partial correlation coefficient in the whole sample controlling for sex.

	Males (N = 62)	Females (N = 44)	All (N = 106)
Age (years)	- 0.124	- 0.085	- 0.012
BMI (kg/m^2)	0.717***	0.646***	0.623***
Waist circumference (cm)	0.698***	0.579***	0.563***
Physical activity (MET-min/w)	- 0.297*	- 0.196	- 0.115
HDLc (mg/dL)	- 0.034	- 0.231	- 0.233*
Triglycerides (mg/dL)	0.189	0.259	0.186
Triglycerides/HDLc ratio	0.183	0.257	0.232*
Insulin (μIU/L)	0.314*	0.382*	0.229*
Cortisol (nmol/L)	- 0.062	- 0.089	- 0.086
IL-6 (pg/mL)	0.184	0.261	0.262**
Fibrinogen (mg/L)	- 0.083	0.041	0.063
CRP (mg/L)	0.292*	0.107	0.119
NTL ratio	- 0.060	0.221	0.167
Total energy (Kcal/day)	0.004	0.349*	0.201*
PSS score	0.130	- 0.047	0.000
HRS score	- 0.007	0.297	0.109
FCQ score	- 0.148	0.317*	0.102

*, **, ***: p-values < 0.05, 0.01, 0.001.
HDLc: high-density lipoprotein cholesterol; IL-6: interleukin 6; CRP: c-reactive protein; NTL: neutrophil to lymphocyte ratio; PSS: perceived stress scale; HRS: Holmes-Rahe social readjustment scale; FCQ: food craving questionnaire.

4. Discussion

Central nervous system (CNS) and non-CNS endocrinological alterations have been reported in FEP patients who may eventually contribute to the premature mortality associated with schizophrenia (Pillinger et al., 2018). Therefore, the identification of biomarkers involved in metabolic alterations related to disease onset and progression are of great interest. Nonetheless, studies investigating endocrinological markers should take into account the specific contribution of interactions with many other factors such as unhealthy lifestyle habits (including poor diet and lack of physical activity) and the very relevant secondary effects of pharmacological treatment.

The present study focused on the analysis of leptin in the early stages of psychosis because increased leptin levels have been implicated in metabolic syndrome, diabetes mellitus, hypertension and multiple cardiovascular diseases (Dong and Ren, 2014), medical conditions that are comorbid with schizophrenia (Mitchell et al., 2013). Moreover, although it has been demonstrated that leptin levels were higher in schizophrenia patients compared to control individuals (Stubbs et al., 2016), studies in FEP patients have been inconclusive (Balõtšev et al., 2017; Bocchio-Chiavetto et al., 2018; Chouinard et al., 2018; Pillinger et al., 2017; Stubbs et al., 2016). We showed that leptin levels were increased in ARMS, FEP or CP patients compared to HCs. Interestingly, the highest leptin levels were observed in people at risk of psychosis (ARMS) and mostly in women. Recent studies in FEP patients have reported lower leptin levels when compared to HCs (Balõtšev et al., 2017) that increased over the first months of treatment (Balõtšev et al., 2017), which was thought to be associated with weight gain (Perez-Iglesias et al., 2008). In another recent study, significantly increased leptin levels were reported in non-affective, nonschizophrenia FEP patients compared to a HC group, although no differences were identified when the control group was compared to schizophrenia or affective FEP patients (Bocchio-Chiavetto et al., 2018). Likewise, leptin levels were not increased in FEP patients who exhibited abnormalities in the insulin signaling pathway (Chouinard et al., 2018). It is worth mentioning that leptin levels have been demonstrated to be significantly higher in women than in male subjects (Stubbs et al., 2016) and, thus, sex should be included in all the analyses or samples should be stratified by sex, which has not been done in most studies. This is a limitation because we could not discuss our results in the context of previous studies, as they did not report leptin levels stratified by sex.

In our sample of patients in the early stages of the psychotic illness, we showed that leptin levels were positively correlated with BMI, waist circumference and insulin levels, similar to previous results in schizophrenia (Chen et al., 2018). Our study also showed that increased leptin levels are present in people with prodromal psychotic symptoms, especially females. It is worth mentioning that most of the subjects in the ARMS group were not on antipsychotic treatment or received lower antipsychotic doses and had a lower BMI than the FEP and CP groups, suggesting that leptin abnormalities are present before starting antipsychotic treatment and at least partially independent of weight gain. The observed association between leptin levels and lipid and inflammatory markers reinforces the hypothesis that metabolic alterations are present at early stages of the psychotic illness, before the chronic establishment of disease. In line with this result, previous studies in drug-naïve FEP patients have shown more insulin resistance (Fernandez-Egea et al., 2009; Ryan et al., 2003) and higher levels of

visceral fat (Ryan et al., 2004) than HCs. Interestingly, we observed that the triglyceride/HDL cholesterol ratio, a potential marker of insulin resistance, was higher in patients compared to HCs and positively correlated with leptin levels. There is also an increased pro-inflammatory state in people at risk for psychosis (Stojanovic et al., 2014) or with an FEP (Miller et al., 2011); however, we could not identify any relationship between the NTL ratio, a subclinical marker of inflammation, and leptin levels, as has been reported in non-affective psychotic adolescent inpatients (Bustan et al., 2018).

We have showed that patients on aripiprazole antipsychotic treatment showed higher levels of leptin compared to those who were on risperidone or olanzapine. These results are in line with a previous study comparing leptin levels in FEP patients undergoing treatment with aripiprazole, quetiapine or ziprasidone that reported higher leptin levels in women treated with aripiprazole compared to those treated with ziprasidone or quetiapine (Pérez-Iglesias et al., 2014). In that study, aripiprazole treatment was associated with the highest level of weight increase, and similarly, our study identified that patients taking this antipsychotic treatment showed the highest BMI. However, our study was not randomized as was Pérez-Iglesias et al. (2014). Thus, there may be a prescription bias on the part of psychiatrists. It could be, for instance, that overweight patients are more often treated with aripiprazole than other antipsychotics that induce more weight gain (e.g., olanzapine) (Leucht et al., 2013). Moreover, it could be that some patients in the CP have been switched from other antipsychotics to aripiprazole because of weight gain, and thus, the correlation found between aripiprazole and leptin might be confounded by these issues. In this sense, we need to be cautious when drawing conclusions about antipsychotic treatments due to the cross-sectional and nonrandomized design of our study. However, it is worth mentioning that no female ARMS patient was taking aripiprazole, suggesting that the high leptin levels in this group were not influenced by this pharmacological treatment.

In a previous study, we showed that perceived stress was associated with craving in early psychosis (Gattere et al., 2018). However, neither stress parameters nor food craving were associated with leptin levels in the whole dataset. Interestingly, food craving and total energy intake correlated with leptin levels in females but not in males. Studies in this field are scarce; nonetheless, leptin has been related to food craving in women, although craving also depends on the menstrual cycle and estradiol levels (Krishnan et al., 2016). Likewise, it has been found that the plasma concentration of leptin fluctuates with psychological measures throughout the day, including food craving (Licinio et al., 2014). In the present study, total dietary intake in the ARMS, FEP and CP patients was increased compared to HCs and correlated with leptin levels; however, appetite is not suppressed by leptin in the hypothalamus, at least in women, as food intake and food craving positively correlate with leptin levels, suggesting that there might be sex differences in leptin signaling. Animal studies have also reported sex-related differences in brain sensitivity to leptin and insulin (Clegg et al., 2003). Several hypotheses have been advanced to explain the poor response of the hypothalamus to suppress appetite in obese individuals. Recently, a disruption in a protein complex involved in oxide transport under conditions of overnutrition has been noted as a potential target explaining appetite-suppressing defects in obesity (Fruhwürth et al., 2018). Both insulin and leptin require binding to this protein complex, and alterations in both hormones have been implicated in early psychosis (Balõtšev et al., 2017; Bocchio-Chiavetto et al., 2018; Chouinard et al., 2018; Perez-Iglesias et al., 2008).

Our findings related to the ARMS subgroup, which showed high leptin levels despite being the leaner group of patients and those treated for a shorter duration, suggest the importance of the stage of the illness. As discussed in a recent review on the role of stress-related biomarkers in the pathogenesis of psychotic disorders (Labad, 2019), different stages of psychotic illness might reflect different cumulative stress and allostatic load effects, although drawing conclusions when comparing ARMS and psychotic patients is difficult due to the potential existence of important confounders (treatment differences, severity of symptoms and/or metabolic comorbidities). It can be speculated that people at risk for psychosis may show biologically adaptive responses before the psychotic onset (lower allostatic load stage) that are later lost when the psychosis is established (higher allostatic load stage), thus revealing maladaptive responses. In line with this view, the previous study from our group (Manzanares et al., 2014) reported different behavioral changes in dietary habits related to stressful life events between ARMS patients and those with psychotic disorders: life stress was associated with a reduction in refined sugar intake in ARMS patients but with an increased intake in patients with a psychotic disorder. In our current study, craving was associated with leptin levels in females, and the result that leptin levels were higher in ARMS patients suggests the potential role of the stage of the illness when exploring biomarkers that are influenced by stress, as is the case for leptin.

Leptin levels have been positively correlated with positive, general and total PANSS scores, suggesting that they may be associated with symptomatology (Nurjono et al., 2014), although higher leptin levels have also been inversely correlated with positive symptoms in a previous study (Takayanagi et al., 2013), leading to inconclusive results. We could not confirm previous associations between PANSS scores and leptin levels.

Future research is needed during this very early phase of psychotic disease to decipher the psychoneuroendocrinological mechanisms involved in disease onset, as preventive actions to avoid metabolic alterations should also be implemented in these very early phases. Meanwhile, our study supports the conclusion that ARMS individuals, mainly female individuals, could benefit from early interventions targeting nutrition, physical activity and appropriate antipsychotic prescriptions, as has been noted in FEP patients (Pillinger et al., 2017). This early intervention should be emphasized in females because of the extremely high levels of leptin we observed and the association with total energy intake and food craving that we exclusively observed in women. Finally, we identified relationships between leptin levels and the abovementioned variables that may guide future studies exploring the mechanisms involved in weight gain in early psychosis. These studies need to take into account the effect of medication, including both antipsychotic and antidepressant treatment.

Some limitations of this study include the small sample size and heterogeneity in both psychopharmacological medication and type of antipsychotic treatment. However, we explored the relationship between leptin and several other variables, such as stress, lipid profile, inflammatory markers, dietary and physical exercise habits, and, most importantly, sex.

In conclusion, the present study identified increased leptin levels in patients in the early stages of psychoses as well as a correlation between leptin and lipid and inflammatory markers, insulin and daily energy intake. Future studies should consider sex since, in addition to the fact that leptin levels are higher in women; there are some specific relationships between leptin levels and diet, as well as food craving, that may be related exclusively in women.

Role of funding source

None of the funders had a role in study design, in the collection and analysis of data, in the interpretation of results, in the writing of the manuscript, or in the decision to submit the article for publication.

Conflicts of interest

None.

Author contributions

Study conceptualization: Martorell, Labad and Vilella. Data

collection: Ortega, Moreno, Montalvo, Monseny, Sánchez-Gistau and Labad. Data analysis: Muntané, Martorell and Porta-López. Manuscript drafting: Martorell, Muntané, Porta-López and Labad. All authors have reviewed and approved the final version of the manuscript.

Acknowledgment

Funding for this study was provided by Fundació la Marató de TV3 (grants numbers 092230, 092231) and from the Instituto de Salud Carlos III (grant number PI10/01607). GM was the recipient of a BP-DGR scholarship from the Generalitat de Catalunya. LO and JL have received a personal grant to support their research activity (SLT002/16/0125 and SLT006/17/00012, respectively). The Health Department of the Generalitat de Catalunya also supported this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.006.

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