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FULL-LENGTH REPORT

# Plasma concentration of leptin is related to food addiction in gambling disorder: Clinical and neuropsychological implications

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**ABSTRACT**

*Background:* Data implicate overlaps in neurobiological pathways involved in appetite regulation and addictive disorders. Despite different neuroendocrine measures having been associated with both

gambling disorder (GD) and food addiction (FA), how appetite-regulating hormones may relate to the co-occurrence of both entities remain incompletely understood. *Aims:* To compare plasma concentrations of ghrelin, leptin, adiponectin, and liver-expressed antimicrobial peptide 2 (LEAP-2) between patients with GD, with and without FA, and to explore the association between circulating hormonal concentrations and neuropsychological and clinical features in individuals with GD and FA. *Methods:* The sample included 297 patients diagnosed with GD (93.6% males). None of the patients with GD had lifetime diagnosis of an eating disorder. FA was evaluated with the Yale Food Addiction Scale 2.0. All patients were assessed through a semi-structured clinical interview and a psychometric battery including neuropsychological tasks. Blood samples to measure hormonal variables and anthropometric variables were also collected. *Results:* From the total sample, FA was observed in 23 participants (FA+) (7.7% of the sample, 87% males). When compared participants with and without FA, those with FA+ presented both higher body mass index (BMI) ($p < 0.001$) and leptin concentrations, after adjusting for BMI ($p = 0.013$). In patients with FA, leptin concentrations positively correlated with impulsivity, poorer cognitive flexibility, and poorer inhibitory control. Other endocrine measures did not differ between groups. *Discussion and conclusions:* The present study implicates leptin in co-occurring GD and FA. Among these patients, leptin concentration has been associated with clinical and neuropsychological features, such as impulsivity and cognitive performance in certain domains.

**KEYWORDS**

gambling disorder, food addiction, leptin, impulsivity, addictive behaviors

## INTRODUCTION

Gambling disorder (GD) is classified as a behavioral addiction in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013). It is characterized by a recurrent and maladaptive gambling behavior, impaired control and increasing priority given to gambling, as well as continuation or escalation of gambling despite the occurrence of negative consequences in different domains of patients' daily lives (Potenza et al., 2019). GD shares clinical and etiological aspects with substance use disorders (SUDs), including neurobiological features (Griffiths, 2017; Linnet, 2020; Solé-Morata et al., 2022).

Although food addiction (FA) is not currently recognized as a formal diagnostic entity, the concept has been supported through clinical and biological studies (Gearhardt, Davis, Kuschner, & Brownell, 2011). This construct may in part explain high and rising rates of obesity in contemporary society that might relate to addictive properties of food promoting the consumption of densely caloric, hyperpalatable, inexpensive, processed foods (Gearhardt, Grilo, Dileone, Brownell, & Potenza, 2011). However, there is a lack of consensus regarding some aspects of this construct, such as the most appropriate conceptual framework to explain FA (Gearhardt & Hebebrand, 2021; Treasure, Leslie, Chami, & Fernández-Aranda, 2018). There are authors who define FA as addictive-like eating (Hebebranda et al., 2014), while others propose a substance-based addiction model (Fernandez-Aranda, Karwautz, & Treasure, 2018; Schulte, Avena, & Gearhardt, 2015). The latter model suggests that some foods, especially palatable ones with large amounts of processed sugars and fats, may lead to overeating and addictive-like behaviors by activating brain reward pathways, in a similar way to what occurs in SUDs (Gearhardt, Phil, & Corbin, 2011; Schulte et al., 2015). Moreover, many clinical and neurobiological similarities have been identified between FA and addictive disorders, such as an excessive preoccupation and desire for rewarding consumption, the development of tolerance and abstinence, and difficulties decreasing consumption despite negative consequences (Fletcher & Kenny, 2018; Gearhardt, Phil, & Corbin, 2011; Pursey, Contreras-Rodriguez, Collins, Stanwell, & Burrows, 2019; Volkow, Wang, Fowler, Tomasi, & Baler, 2012). Some authors have raised concerns regarding the diagnostic overlap between binge eating disorder (BED), an eating disorder (ED) characterized by recurrent episodes of bingeing in the absence of compensatory behaviors and FA, although recent studies provide evidence supporting that they are separate entities, which reflect different clinical situations (di Giacomo et al., 2022).

Along these lines, previous work has suggested a potential association between FA and GD (Etxandi et al., 2021; Jiménez-Murcia et al., 2017). The prevalence of FA in patients with GD has been estimated at around 7.8% (Granero et al., 2018), and co-occurrence between GD and FA has been related to specific clinical features in individuals with GD, such as higher body mass index (BMI), more psychopathology, and elevated harm avoidance (Etxandi et al., 2021). Moreover, some works hypothesized that the comorbidity with FA could be associated with gambling patterns indicative of more protracted or severe GD, which makes its study of special interest to identify possible preventive and early detection strategies (Etxandi et al., 2021).

Interestingly, one area of recent attention when studying the neurobiology of addictive disorders involves neurohormonal systems implicated in appetite regulation, with such systems linked to brain reward pathways (Etxandi et al., 2022; Iovino et al., 2022). Among endocrine factors involved in the reward circuit, ghrelin (an appetite stimulating hormone) has been shown to be a neural reinforcer for both natural (e.g., food) and non-natural (e.g., money) rewards, which influences dopamine signaling in brain areas related to reward processing (e.g., mesolimbic regions) (Farokhnia et al., 2018; Vengeliene, 2013). The liver-expressed antimicrobial peptide 2 (LEAP-2) is a recently described endocrine factor involved in appetite regulation that antagonizes the effects of ghrelin (Ge et al., 2018; Lugilde et al., 2022). Although there is currently less evidence of its involvement in addictive disorders, it has been related to impulsivity (Voigt et al., 2021), which has been linked to addictions including GD (Brewer & Potenza, 2008). Other endocrine factors such as adipocytokines (i.e., leptin and adiponectin) produced by adipose tissue have also been studied in relation to addictive disorders (Escobar et al., 2018; Housová et al., 2005; Novelle & Diéguez, 2018). Leptin is an important

peripheral signal regulating food intake, with appetite-suppressing functions and circulating concentrations related to BMI (Hellström et al., 2004). Both leptin and adiponectin have also been linked to impulsivity (Sutin et al., 2013) and craving in SUDs (Hillemacher et al., 2009; Martinotti et al., 2017). Noticeably, these endocrine factors linked to SUDs have prompted investigations in behavioral addictions such as GD (Geisel, Hellweg, Wiedemann, & Müller, 2018). A recent case-control study described an increase in ghrelin concentrations, but a decrease in LEAP-2 and adiponectin in individuals with versus without GD, after adjusting for BMI (Etxandi et al., 2022).

Regarding neurobiological correlates of FA, prior efforts have explored possible endocrine alterations (Leigh & Morris, 2018). Both ghrelin and leptin may play a significant role in FA (Piccinni et al., 2021). On the one hand, ghrelin signaling has been suggested as a key regulator of obesity, and higher concentrations have been associated with increased food craving and consumption (Lopez-Aguilar, Ibarra-Reynoso, & Malacara, 2018). It has also been hypothesized that higher fasting leptin concentrations may underlie excessive food intake (Miller et al., 2014). FA has been associated with lower leptin concentrations in adolescents with normal weight whereas with higher leptin concentrations in individuals with overweight (Peters et al., 2018). The authors hypothesized that the negative association between leptin concentrations and FA under normal-weight conditions could be explained by a stronger sense of hunger and a greater propensity for overeating in these individuals, which could have led to greater FA severity. In individuals with overweight, high circulating leptin concentrations may reflect leptin resistance, in which the failure of leptin-level-induced feeding suppression may lead to the development of FA (Peters et al., 2018; Yu, Fernandez, Meng, Zhao, & Groth, 2021).

To the best of our knowledge, no previous studies have investigated hormonal factors in the co-occurrence of FA and a behavioral addiction such as GD. The main aim of the present study was to explore whether there were differences in plasma concentrations of hormones involved in appetite regulation (namely ghrelin, LEAP-2, adiponectin, and leptin) in a sample of patients diagnosed with GD, with and without FA. Moreover, we aimed to explore correlates between concentrations of any implicated hormones and clinical and neuropsychological variables in the subgroup with FA. These included measures of cognitive domains described as core features in well-known neuroscientific models of addiction and especially related to impulse control, that we hypothesized to co-occur in GD and FA, such as prefrontally mediated executive functions (i.e., cognitive flexibility, inhibitory control, decision making, working memory, attention, and set-shifting) (Bechara & Van Der Linden, 2005; Blaszczynski & Nower, 2002; Mallorquí-Bagué et al., 2018; van Timmeren, Daams, van Holst, & Goudriaan, 2018). We hypothesized that circulating concentrations of appetite-regulating hormones would differ between GD patients with and without FA, with levels of implicated hormones correlating with impulsivity measures in the FA subgroup.

# METHODS

## Participants

The sample consisted of $n = 297$ seeking-treatment outpatient adults with GD. Participants were mostly male ($n = 278$, 93.6%) and with a mean age of 39.58 years ($SD = 14.16$). They were voluntarily recruited from April 2018 to September 2021 at the Behavioral Addictions Unit within the Clinical Psychology Unit of Bellvitge University Hospital (Barcelona, Spain). All patients had a diagnosis of GD according to DSM-5 criteria (APA, 2013). None of them presented a lifetime ED, which constituted an exclusion criteria together with the presence of an organic mental disorder, an intellectual disability, a neurodegenerative disorder (such as Parkinson's disease), or an active psychotic disorder.

## Measures

***Hormonal assays.*** Peripheral blood samples were collected by venous aspiration with ethylenediamine tetraacetic acid (EDTA) (25 mM final concentration), obtained at 9 am after at least 8 h of overnight fasting. Blood was centrifuged at 1,700 g in a refrigerated (4°C) centrifuge for 20 min. The plasma was immediately separated from the serum and stored at −80°C until analysis. Parameter determinations were conducted using commercial kits according to the manufacturer's instructions and in a single analysis to reduce inter-assay variability. Quantitative plasma LEAP-2 measurement was performed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Human LEAP-2 ELISA kit, Phoenix Pharmaceuticals, Inc), previously validated (Barja-Fernández et al., 2021; Mani et al., 2019). Intraassay and interassay coefficients of variation were <10% and <15%, respectively. The sensitivity limit of the assay was 0.15 ng/mL. Total ghrelin (pg/mL) was measured using an ELISA kit (Invitrogen-Thermofisher scientific) for the detection of human ghrelin, with a specificity of 100%. The intra-assay variation coefficient was <6%, and the inter-assay variation coefficient <8.5%. The sensitivity limit of the assay was 11.8 pg/mL (Pena-Bello et al., 2015). Plasma adiponectin (ng/mL) and leptin (ng/mL) were measured using a solid-phase sandwich ELISA kit (Invitrogen-Thermofisher scientific) with a specificity of 100%. The intraassay and interassay coefficients of variation were <4% and <5%, respectively, and the assay sensitivity limit was 100 pg/mL for adiponectin and <3.5 pg/mL for leptin. Each sample's absorbance was measured in duplicate using a microplate spectrophotometric reader at a wavelength of 450 nm (Epoch 2 microplate reader, Biotek Instruments, Inc).

***Neuropsychological variables.*** *Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III)* (Wechsler, 1999): The WAIS-III involves defining words of increasing difficulty presented orally. It was used to assess vocabulary expression, as a measure of estimated intelligence (De Oliveira, Nitrini, Yassuda, & Brucki, 2014).

*Iowa Gambling Task (IGT)* (Bechara, Damasio, Damasio, & Anderson, 1994, 2000): The IGT is a computerized task for evaluating risk-/reward-based and punishment-influenced decision-making. Participants must select 100 cards from four decks of cards (i.e., A, B, C, and D) and, after each card selection, either a monetary gain or a loss is obtained. The participants are told that the ultimate goal of the task is to win as much money as possible. The test is scored by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D. Whereas decks A and B are not advantageous, since the final loss is greater than the final gain, decks C and D are advantageous since the penalties are smaller (as are the rewards). Higher scores indicate better performance, while negative scores reflect more choices from disadvantageous decks. The test score for each block (IGT-1, 2, 3, 4, and 5) is calculated by subtracting the number of choices from disadvantageous decks to the number of choices from advantageous decks draws. The total task score (IGT-Total) is obatined by adding the scores of the five blocks. The learning score (IGT-Learning) measures the differences between the two first blocks (where the participant has not learned which decks are advantageous and disadvantageous) and the two last blocks (where the participant could have already detected which decks involve a risky choice and then, the experience gained through the trial can produce changes in choice patterns). Additionally, the risk score (IGT-Risk) is measured considering the scores from the two last blocks.

*Wisconsin Card Sorting Test (WCST)* (Grant & Berg, 1948): The WCST evaluates cognitive flexibility. It is comprised of four types of stimulus cards and 128 response cards that show different shapes, colors, and numbers of figures on each one. Participants must match the response cards to the stimulus cards in a way that seems justifiable to them before they receive feedback (i.e., correct or incorrect). After ten correct consecutive responses, the categorization criteria change. Total trials, total errors, perseverative errors and non-perseverative errors, the number of complete categories, conceptual, and trials to complete first category are recorded.

*Trail Making Test (TMT)* (Reitan, 1958): TMT part A consists of 25 circles on a piece of paper with the numbers 1 to 25 written randomly in each. The person is tasked with drawing a line from one circle to the next in ascending numerical order, from 1 to 25, as quickly as possible. The lines between the circles are referred to as the "trail." For part B, the dots go from 1 to 13 and include letters from A to L. As in the first part, the person must connect the dots in order while alternating letters and numbers, as in 1-A-2-B-3-C…, in the shortest time possible without lifting the pen from the paper. The task assesses visual conceptual and visual-motor tracking, entailing motor speed, attention, and the capacity to alternate between cognitive categories (set-shifting). Each part is scored according to the time spent to complete the task.

*Stroop Color and Word Test (SCWT)* (Golden, 1978): The SCWT consists of three separate lists. First, a word list contains the names of colors in black ink. Then, a color list includes the letter "X" printed in different colors. Lastly, a color word list consisting of color names in a color ink that does not match the written name. Three final scores are obtained based on the number of items the participant can read on each of the three lists within 45 seconds. The SCWT assesses cognitive interference, which occurs when the processing of one stimulus feature affects the simultaneous processing of another attribute.

***Clinical variables.*** *Yale Food addiction Scale 2.0 (YFAS 2.0)* (Gearhardt, Corbin, & Brownell, 2016): The YFAS 2.0 consists of a self-report scale for assessing FA based on 11 symptoms related to SUDs that are adapted to the context of food consumption. The YFAS 2.0 consists of 35 items and produces two measurements: (1) a continuous symptom count score that reflects the number of diagnostic criteria met (from 0 to 11), and (2) a binary measure (present vs. absent) that is based on the number of symptoms (at least 2) and self-reported clinical distress or impairment. In addition, it also provides severity thresholds: mild (2-3 symptoms), moderate (4-5 symptoms) and severe (6-11 symptoms). The Spanish validation of the YFAS-2 (Granero et al., 2018) generated an internal consistency of Cronbach's alpha ($\alpha$) = 0.94. The internal consistency of our sample was $\alpha = 0.97$.

*South Oaks Gambling Screen (SOGS)* (Lesieur & Blume, 1987): The SOGS includes 20 items for the identification of problem gambling and associated negative consequences. Total scores obtained as the summation of the items have been used as a measure of problem-gambling severity, with a score of five or more reflecting "probable pathological gambling." The Spanish validation of the scale showed very good psychometric results in the adaptation study (test-retest reliability $R = 0.98$, internal consistency $\alpha = 0.94$ and convergent validity $R = 0.92$) (Echeburúa, Baez, Fernández-Montalvo, & Páez, 1994). The internal consistency for this scale in the study sample was $\alpha = 0.74$.

*Diagnostic Questionnaire for Pathological Gambling According to DSM criteria* (Stinchfield, 2003): Spanish adaptation (Jiménez-Murcia et al., 2009). This instrument is a self-report questionnaire containing 19 items coded on a binary scale (yes-no), which is used for the diagnosis of GD according to the DSM-IV-TR (APA, 2000). This questionnaire has been updated according to DSM-5 (APA, 2013) criteria. The internal consistency of this scale in the study sample was $\alpha = 0.80$.

*Symptom Checklist-90-Revised (SCL-90-R)* (Derogatis, 1994): The SCL-90-R is a self-report questionnaire of 90 items that assesses a broad range of psychological problems and psychopathology, based on nine primary symptom dimensions (Somatization, Obsessive-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism). Three global indexes are included (global severity index, positive symptom distress index and total positive symptom). The validation of the scale in the Spanish population (Derogatis, 2002) showed a mean internal consistency of $\alpha = 0.75$. The internal consistency in the study was $\alpha = 0.98$.

*Temperament and Character Inventory-Revised (TCI-R)* (Cloninger, 1999): The TCI-R is a 240-item questionnaire

scored on a 5-point Likert scale that measures personality features derived from three character dimensions (Self-Directedness, Cooperativeness, and Self-Transcendence) and four temperament dimensions (Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence). Evaluation of the Spanish revised version (Gutiérrez-Zotes et al., 2004) had an internal consistency of $\alpha = 0.87$. This questionnaire was administered in its Spanish adaptation, in which the original author participated (Gutiérrez-Zotes et al., 2004). The internal consistency in the study was between $\alpha = 0.70$ (Novelty Seeking) and $\alpha = 0.88$ (Persistence).

*Impulsive Behavior (UPPS-P)* (Whiteside, Lynam, Miller, & Reynolds, 2005). Through 59 self-report items, the UPPS-P assesses five aspects of impulsive behavior: negative urgency; positive urgency; lack of premeditation; lack of perseverance; and sensation-seeking. The Spanish validation of the UPPS-P demonstrated good reliability (Cronbach's α between 0.79 and 0.93) and external validity (Verdejo-García, Lozano, Moya, Alcázar, & Pérez-García, 2010). The internal consistency in the study varied between $\alpha = 0.80$ (lack of perseverance) and $\alpha = 0.93$ (positive urgency).

*Difficulties in Emotion Regulation Strategies (DERS)* (Gratz & Roemer, 2004). The DERS is a self-reported 36-item scale that assesses emotion dysregulation. The scale is divided into six subscales (non-acceptance of emotional responses, difficulties in performing goal-directed behaviors when experiencing strong emotions, difficulties in controlling impulses, lack of emotional awareness, limited access to emotion regulation strategies, and lack of emotional clarity). The participants are asked to answer each item using a five-point Likert scale ranging from 1 (almost never) to 5 (almost always). Higher scores suggest greater problems in emotion regulation. The instrument has been validated in the Spanish population (Hervás & Jódar, 2008). The internal consistency of the DERS total score in our sample was $\alpha = 0.92$.

***Other variables.*** Additional data (e.g., socio-demographic, and socio-economic, anthropometric variables, and GD-related characteristics) were collected in a semi-structured face-to-face clinical interview, as described elsewhere (Jiménez-Murcia, Aymamí-Sanromà, Gómez-Pena, Álvarez-Moya, & Vallejo, 2006).

### Procedure

The participants were assessed at the Behavioral Addictions Unit of the Clinical Psychology Unit of Bellvitge University Hospital (Barcelona, Spain). A multidisciplinary team (psychology, psychiatry, and nursing) with more than 15 years of experience in the field of GD and other behavioral addictions conducted the evaluation and data collection. In a first session, a comprehensive semi-structured clinical interview was performed, focusing on gambling behaviors. Moreover, lifetime ED was also assessed. In a second session, the psychometric evaluation and the extraction of biological samples took place. The biological samples were subsequently analyzed at the Singular Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela (Santiago de Compostela, Spain). Finally, in a third session, the psychological assessment was performed by an experienced neuropsychologist for 60 min. We also administered the WAIS-III (Wechsler et al., 1999) vocabulary subtest as a measure of estimated intelligence (Lezak et al., 2004). All measures used in this study correspond to the evaluation done prior to the beginning of specialized treatment in our Unit.

### Statistical analysis

Statistical analysis was performed with Stata17 for Windows (Stata-Corp, 2021). Comparison of socio-demographic and gambling-related problems between the YFAS 2.0 positive versus negative screening groups was done with chi-square tests ($\chi^2$) for categorical data and *T*-tests for quantitative data. For these models, effect sizes of relationships were measured with Cohen's-*h* and Cohen's-*d* coefficients, interpreting mild-moderate effect sizes for values above 0.50 and less than 0.80 and high-large effect size for values above 0.80 (Kelley & Preacher, 2012).

Comparisons of hormonal measures between groups were performed with analysis of covariance (ANCOVA), adjusting for sex, age, and BMI. The association between leptin concentrations and clinical and neuropsychological variables was assessed through partial correlation coefficients, adjusted for sex, age, BMI, and WAIS-vocabulary scores, the latter used to adjust the between-group comparisons for estimated intelligence. Given the relationship between the significance of correlations with sample sizes (small coefficients can achieve highly significant *p*-values in large samples, and vice versa), correlation values with size |R|>0.24 (medium-moderate effect size) or |R| (large-high effect size) were considered relevant in this study (Rosnow, 1996).

This study used Finner's procedure for controlling the increase in the Type-I error due to the use of multiple statistical comparisons. This procedure is sustained by the familywise error rate stepwise multiple method, and it is aimed to adjust significance levels (*p*-values) by controlling for the probability that the statistical tests make at least k false rejections (Finner & Roters, 2001).

### Ethics

The latest version of the Declaration of Helsinki guided conduct in the present study. The Clinical Research Ethics Committee of Bellvitge University Hospital approved this study (ref. PR329/19 and PR338/17), as part of the scientific production within national and competitive research projects developed by our research group (RTI2018-101837-B-I00; 2019I47). Signed informed consent was obtained from all participants.

## RESULTS

### Descriptive for the sample

Most participants in the study were single (53.2%), men (93.6%), with low education levels (52.9%), and of low social status (44.8%). The mean age was 39.6 years old (SD =

14.2), mean age of onset of the gambling problems 29.1 years old (SD = 12.4), and mean duration of gambling problems 5.23 years (SD = 6.0). The percentage of patients who reported non-strategic gambling preference was 49.8%, while 31.0% reported strategic, and 19.2% both non-strategic and strategic gambling. The prevalence of patients with gambling-related debts was 58.9%.

## Comparison of the measures between FA groups

A small percentage (7.7%) of the sample met criteria for FA. Table 1 presents sociodemographic and GD variables stratified by FA status, with significant differences in the SOGS total score and the BMI levels (higher means among patients with FA + group).

The results of the ANCOVA comparing ghrelin, LEAP-2, leptin, and, adiponectin concentrations between patients with and without FA evidenced differences for the leptin values (higher mean concentrations among the FA + group) (see Table 2 and Fig. 1, with the radar chart).

The ANCOVA procedure with the comparison of the clinical profiles between patients with and without FA is showed in Table S1 (supplementary material). Differences between groups were found for the psychopathological state (higher SCL-90R mean scores in the FA + group), and the emotion regulation capacity (higher scores in DERS among the FA+ group, showing concretely difficulties engaging in goal-directed behaviors, limited access to emotion regulation strategies, lack of emotional clarity, and higher total score).

*Table 1.* Comparison between the groups for the sociodemographic and the GD profiles

| | Total (*n* = 297) | | FA− (*n* = 274) | | FA+ (*n* = 23) | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *p* | \|*h*\| |
| Sex | | | | | | | | |
| Women | 19 | 6.4% | 16 | 5.8% | 3 | 13.0% | 0.175 | 0.25 |
| Men | 278 | 93.6% | 258 | 94.2% | 20 | 87.0% | | |
| Education | | | | | | | | |
| Primary | 157 | 52.9% | 143 | 52.2% | 14 | 60.9% | 0.160 | 0.18 |
| Secondary | 112 | 37.7% | 107 | 39.1% | 5 | 21.7% | | 0.38 |
| University | 28 | 9.4% | 24 | 8.8% | 4 | 17.4% | | 0.26 |
| Marital | | | | | | | | |
| Single | 158 | 53.2% | 146 | 53.3% | 12 | 52.2% | 0.074 | 0.02 |
| Married | 103 | 34.7% | 98 | 35.8% | 5 | 21.7% | | 0.31 |
| Divorced | 36 | 12.1% | 30 | 1.9% | 6 | 26.1% | | 0.40 |
| Social index | | | | | | | | |
| High | 8 | 2.7% | 7 | 2.6% | 1 | 4.3% | 0.875 | 0.10 |
| Mean-high | 19 | 6.4% | 18 | 6.6% | 1 | 4.3% | | 0.10 |
| Mean | 24 | 8.1% | 23 | 8.4% | 1 | 4.3% | | 0.17 |
| Mean-low | 113 | 38.0% | 105 | 38.3% | 8 | 34.8% | | 0.07 |
| Low | 133 | 44.8% | 121 | 44.2% | 12 | 52.2% | | 0.16 |
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| |
| Age (years-old) | 39.58 | 14.16 | 39.44 | 14.15 | 41.26 | 14.45 | 0.554 | 0.13 |
| Age of onset of GD (years) | 29.10 | 12.42 | 28.80 | 12.37 | 32.74 | 12.69 | 0.144 | 0.31 |
| Duration of GD (years) | 5.23 | 6.02 | 5.24 | 6.11 | 5.04 | 4.88 | 0.880 | 0.04 |
| DSM-5 criteria | 7.13 | 1.80 | 7.09 | 1.82 | 7.70 | 1.40 | 0.119 | 0.37 |
| SOGS total | 10.85 | 3.23 | 10.74 | 3.17 | 12.13 | 3.73 | **0.048*** | 0.40 |
| | *n* | % | *n* | % | *n* | % | *p* | \|*h*\| |
| Preference | | | | | | | | |
| Non-strategic | 148 | 49.8% | 139 | 5.7% | 9 | 39.1% | 0.551 | 0.23 |
| Strategic | 92 | 31.0% | 83 | 3.3% | 9 | 39.1% | | 0.19 |
| Mixed | 57 | 19.2% | 52 | 19.0% | 5 | 21.7% | | 0.07 |
| Debts due to the GD | | | | | | | | |
| No | 122 | 41.1% | 113 | 41.2% | 9 | 39.1% | 0.843 | 0.04 |
| Yes | 175 | 58.9% | 161 | 58.8% | 14 | 60.9% | | |
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| |
| Body mass index (Kg/m$^2$) | 26.48 | 5.04 | 25.99 | 4.37 | 32.34 | 8.15 | **<0.001*** | **0.97**† |

*Note.* GD: gambling disorder. SD: standard deviation.
FA−: food addiction negative screening group. FA+: food addiction positive screening group.
*Bold: significant comparison. †Bold: effect size into the ranges mild-moderate to high-large.

*Table 2.* Comparison of hormonal measures: ANCOVA (adjusted by sex, age, and BMI)

| | Total ($n$ = 297) | | FA− ($n$ = 274) | | FA+ ($n$ = 23) | | | | YFAS-total |
|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| | *R* |
| Ghrelin (pg/mL) | 941.59 | 753.26 | 945.03 | 758.78 | 938.15 | 643.10 | 0.967 | 0.01 | 0.006 |
| LEAP-2 (ng/mL) | 5.26 | 2.88 | 5.31 | 2.87 | 5.21 | 3.09 | 0.661 | 0.03 | 0.007 |
| Leptin (ng/mL) | 10.05 | 7.85 | 7.88 | 7.42 | 12.23 | 10.47 | **0.013*** | **0.52**† | 0.106 |
| Adiponectin (ng/mL) | 8,678.79 | 4,374.29 | 8,374.86 | 4,429.37 | 8,982.71 | 3,710.43 | 0.543 | 0.15 | 0.022 |

*Note.* SD: standard deviation. R: Partial correlation.
FA−: food addiction negative screening group. FA+: food addiction positive screening group.
*Bold: significant comparison. †Bold: effect size into the ranges mild-moderate to high-large.

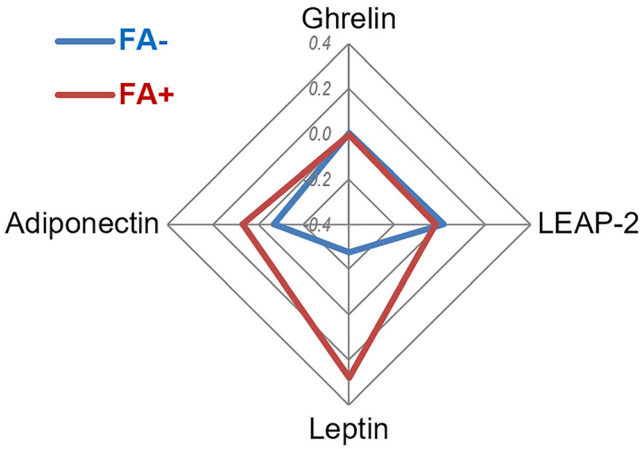


*Fig. 1.* Radar chart with the hormonal profile (z-standardized means are plotted).
*Note.* Z-standardized means are plotted in the graph. Total sample ($N$ = 297).

## Correlational analysis

Table 3 includes the partial correlation matrix assessing the relationship between leptin concentrations and clinical measures, separately for patients with and without FA, and adjusted for sex, age, BMI, and WAIS-vocabulary scores. All correlation coefficients involving the FA− group were into the low effect-size range, suggesting no relationships between leptin and psychological performance, GD severity, psychological state, impulsivity, and emotion regulation capacity among these patients. Within the FA+ group, higher leptin concentrations were related to worse performance on neuropsychological measures (including the WCST, TMT, and SCWT), greater problem-gambling severity (reflected in the number of DSM-5 GD criteria and SOGS scores), higher scores on the SCL-90R obsessive-compulsive and phobic anxiety scales, higher impulsivity levels (UPPS-P: lack of premeditation, sensation-seeking, positive urgency, and total score), and more emotion-

*Table 3.* Partial correlation with the leptin level (adjusted by sex, age, BMI and WAIS-vocabulary)

| | FA− ($n$ = 274) | FA+ ($n$ = 23) | | FA− ($n$ = 274) | FA+ ($n$ = 23) |
|---|---|---|---|---|---|
| IGT: block 1 | −0.026 | −0.055 | SCL-90R Somatization | 0.024 | −0.129 |
| IGT: block 2 | −0.023 | −0.092 | SCL-90R Obsessive/compulsive | 0.020 | **0.322**† |
| IGT: block 3 | 0.030 | −0.071 | SCL-90R Interpersonal sensitivity | −0.081 | 0.019 |
| IGT: block 4 | −0.030 | **−0.334**† | SCL-90R Depressive | 0.004 | −0.134 |
| IGT: block 5 | 0.013 | 0.071 | SCL-90R Anxiety | −0.002 | 0.009 |
| IGT: total | −0.006 | −0.141 | SCL-90R Hostility | −0.073 | 0.138 |
| IGT: learning | 0.012 | −0.076 | SCL-90R Phobic anxiety | 0.061 | **0.300**† |
| IGT: risk | −0.008 | −0.143 | SCL-90R Paranoid Ideation | −0.069 | 0.153 |
| WCST: trials | 0.035 | **0.375**† | SCL-90R Psychotic | −0.041 | 0.140 |
| WCST: errors | −0.034 | **0.244**† | SCL-90R GSI score | −0.023 | 0.042 |
| WCST: errors perseverant | −0.031 | **0.278**† | SCL-90R PST score | −0.041 | 0.110 |
| WCST: conceptual | 0.071 | 0.222 | SCL-90R PSDI score | −0.007 | 0.002 |
| WCST: categories completed | 0.045 | 0.023 | UPPS-P Lack premeditation | −0.056 | **0.285**† |
| WCST: trials for the 1st-categ. | −0.029 | 0.182 | UPPS-P Lack perseverance | 0.019 | −0.029 |
| TMT: A | −0.043 | 0.109 | UPPS-P Sensation seeking | −0.145 | **0.318**† |
| TMT: B | −0.052 | **0.326**† | UPPS-P Positive urgency | −0.155 | **0.435**† |
| TMT: Diff | −0.046 | **0.324**† | UPPS-P Negative urgency | −0.077 | 0.226 |
| Stroop: words | 0.062 | −0.174 | UPPS-P Total | −0.142 | **0.348**† |
| Stroop: colors | −0.002 | −0.064 | DERS Non acceptance emotions | −0.056 | 0.068 |
| Stroop: words-colors | −0.018 | **−0.289**† | DERS Difficulties directed behav. | 0.007 | **0.282**† |
| Stroop: estimated | 0.029 | −0.116 | DERS Impulse control difficult. | −0.025 | 0.139 |
| Stroop: interference | −0.042 | **−0.353**† | DERS Lack emotional aware. | 0.043 | **−0.234**† |
| DSM-5 criteria | 0.049 | **0.240**† | DERS Limited access emotions | −0.045 | 0.163 |
| SOGS total | −0.038 | **0.406**† | DERS Lack emotional clarity | 0.047 | 0.085 |
| | | | DERS Total | −0.022 | 0.135 |

*Note.* †Bold: effect size into the range mild-moderate (\|*R*\|>0.24) to high-large (\|*R*\|>0.37).

regulation difficulties (DERS) related to goal-directed behaviors and lack of emotional clarity.

## DISCUSSION

The present work studied differences in plasma concentrations of appetite-regulating hormones between individuals with and without FA in a sample of patients diagnosed with GD. Likewise, neuropsychological and clinical features were assessed. The results suggested that subjects with FA presented higher BMI, more severe GD measured by the SOGS, greater emotion dysregulation, worse general psychopathological state, and an altered endocrine profile characterized by an elevation of leptin concentrations (after adjusting for BMI), without differences in the other analyzed endocrine factors. Moreover, correlations between leptin concentrations and certain psychological and clinical features were observed in the FA+ group. Higher concentrations of leptin were associated with phobic anxiety and obsessive-compulsive dimensions (SCL-90R), impulsivity, emotion dysregulation, and poorer cognitive flexibility and inhibitory control. Furthermore, in the FA+ group, leptin concentrations were also associated with more severe GD.

The prevalence of FA in the sample (7.7%) was similar to that described in the literature (Granero et al., 2018). As expected, considering both the nature of the studied comorbidity and results from previous studies, patients with FA presented higher SOGS scores and BMI, supporting the notion of more severe GD and a worse metabolic profile in this subgroup of patients (Etxandi et al., 2021; Jiménez-Murcia et al., 2017). This finding reinforces the idea that individuals with GD and FA may benefit from specific therapeutic strategies (e.g., improving healthy eating habits, increasing physical exercise) and that screening for FA in patients with GD may help optimize preventive and therapeutic approaches (Etxandi et al., 2021). No other significant differences were found between sociodemographic profiles nor gambling preferences between both groups, which has also been reported in a prior publication from our group (Etxandi et al., 2021).

Elevated adjusted plasma leptin concentrations in patients with FA, who presented a higher BMI, is consistent with previous studies (Peters et al., 2018) and support the notion that elevated concentrations of this adipocytokine may represent leptin resistance in patients with overweight. According to this hypothesis, leptin would not adequately exert its appetite-suppressing function and could underlie the development of addictive-like eating in these individuals (Peters et al., 2018). Moreover, leptin concentrations showed a positive correlation with trait impulsivity, which is in line with previous studies (Sutin et al., 2013). Leptin can modulate mesolimbic activity both through receptors expressed on dopaminergic cells in the midbrain, and indirectly via its actions in upstream hypothalamic circuits (Adams et al., 2018). Our findings suggest that patients with GD and FA may have leptin resistance that might contribute to dysfunctions in this signaling system and lead to an increased impulsivity. However, increased impulsivity may underlie FA-related eating behaviors leading to increased leptin concentrations, or other possibilities (relating to synergism) may also exist. Elevated impulsivity has been previously reported in both GD and FA (Mestre-Bach et al., 2020; Schulte & Gearhardt, 2021). In patients with GD and co-occurring FA, the dysfunction of circuits linked to impulsivity and leptin signaling may underlie not only the incursion into behaviors related to excessive food intake, but also some common clinical and psychological features related to both GD and FA.

Poor cognitive performance, such as low cognitive flexibility and disadvantageous decision-making, has been implicated in both GD and FA (Etxandi et al., 2022; Lacroix & von Ranson, 2021; Steward et al., 2018). To our knowledge, this is the first study to evaluate the association between leptin concentrations and cognitive performance in people with GD and FA. Interestingly, our results showed a positive correlation between leptin concentrations and poorer cognitive flexibility, as measured by WCST and TMT performance, in GD patients with FA. Some studies focusing on populations of lean body mass have suggested a possible protective factor of this adiponectin (Holden et al., 2017; Lieb et al., 2009), while poorer cognitive performance (specifically in cognitive flexibility and other executive functions) has been related to elevated circulating leptin concentrations in individuals with overweight (Labad et al., 2012). Considering that leptin has an influence on hippocampus-dependent learning and memory (Harvey, Solovyova, & Irving, 2006) and that the hippocampus has been related to cognitive flexibility (Leirer et al., 2010), these results as a whole may suggest that leptin resistance could be involved in the impairment of cognitive flexibility in GD patients with FA (Gunstad et al., 2008).

Recent studies have reported a potential association between leptin concentrations and neuropsychological performance, particularly involving measures of inhibitory control (Wollenhaupt et al., 2019). Interestingly, the results of the present study also demonstrate a positive correlation of leptin concentrations with deficits in inhibitory control, as measured by the SCWT, in patients with FA. Taking all the above into account, the relationship between adjusted leptin concentrations and measures related to impulsivity is highly suggestive, especially when observed in the FA+ group (with higher BMI) and not in the FA-group. Although future studies are warranted to further clarify its role, the results would be in line with the hypothesis that leptin signaling could underlie impulsivity-related dysfunctions in patients with GD and co-occurring FA. Moreover, these results may also contribute to the ongoing debate on the theory and classification of FA. In this regard, the potential involvement of neurobiological factors in the development of impairments in dopaminergic pathways that regulate neural systems associated with reward sensitivity and incentive motivation in FA can reinforce its conceptualization as an addictive disorder.

Individuals with GD, with versus without FA, had higher scores in general psychopathology and emotion dysregulation,

consistent with previous studies (Etxandi et al., 2021; Jiménez-Murcia et al., 2017). FA-related behaviors have been proposed as maladaptive responses to emotional distress, with serious metabolic and clinical implications (Etxandi et al., 2021). Bearing in mind the involvement of leptin signaling in the potential development of anxiety-related behaviors (Liu, Guo, & Lu, 2016), the positive correlation between leptin concentrations and emotion dysregulation and phobic anxiety results resonate with prior findings. Although preliminary, these findings suggest that leptin could be a biological mechanism related to the higher emotion dysregulation found in patients with GD and FA.

Noticeably, in the present study no significant alterations in other endocrine factors concentrations (i.e., ghrelin, LEAP-2, and adiponectin) were identified between GD patients with and without FA. It is very suggestive that in a previous study of our group comparing the same hormones between patients with GD and healthy subjects, differences were observed in ghrelin and adiponectin signaling, but not in leptin concentrations, adjusted for BMI (Etxandi et al., 2022). This finding leads us to hypothesize that leptin could play a specific role in FA, independent of GD, that involves specific neuropsychological and psychopathological domains, including impulsivity, cognitive flexibility, and inhibitory control.

In sum, our results suggest that leptin is linked to FA in patients with GD, underlying clinical and neuropsychological characteristics that exist when adjusting for BMI and other potential confounders. Leptin appears linked to more severe GD symptomatology in the FA+ group. Although promising, these preliminary exploratory results would benefit from more investigation into leptin signaling disturbances in patients with GD and FA.

### Strengths and limitations

Some limitations should be considered when interpreting the results of this study. The cross-sectional nature of the study precludes causal attributions. Future longitudinal research is needed to better characterize a role for leptin in co-occurring GD and FA. The sample was principally composed of treatment-seeking males with GD referred to a specialized unit. The extent to which these findings generalize to other populations, including women with GD, warrants direct investigation. However, the percentage of women in the study is consistent with those in treatment-seeking GD samples. The last limitation is the lack of analysis for potential interaction effects (this was not an objective of the study). Given the pioneering nature of the work, as well as the large number of variables considered (particularly for the neuropsychological area), the number of the potential moderation parameters was too large. We considered more appropriate to provide the results of this first study, aimed to explore and identify the key endocrine and neuropsychological variables within the GD profile, and to plan future studies with larger samples and a limited number of measures (those selected as the most relevant and therefore candidate to analyze the moderation effects).

Some strengths of the present study include a sizable sample, the well-characterized clinical and neuropsychological assessments, and the adjustment of analyses for potential confounding factors. Also, we used several measurement tools, including global scales and subscales, which provide a broad visualization of the psychopathological and functional profile for the patients.

## CONCLUSIONS

The present study provides insight into possible underlying endocrine dysfunctions related to reward processing in FA among patients with GD. Despite its cross-sectional design, this study suggests that leptin signaling may underlie clinical and neuropsychological aspects, especially in terms of impulsivity, cognitive flexibility, and GD severity in the subgroup with FA, with potential therapeutic implications. Future research in this area may contribute to a better understanding of the biology of GD and FA, as well as to the development of more specific psychological and biological treatment strategies in this clinical population.

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*Authors' contribution:* ME, IB, BM-M, and SJ-M contributed to the development of the study concept and design. RG performed the statistical analysis. ME, IB, BM-M, MG-P, LM, AP-G, EV-M, and SJ-M aided with data collection. IB, AP-G, ST, SC, and, CD carried out the procedures related to neuroendocrine variables extraction and analysis. ME, IB, BM-M, IL, NS, and SJ-M aided with interpretation of data

and the writing of the manuscript. MNP, AG, FF-A, JT, and SJ-M revised the manuscript and provided substantial comments. FF-A and SJ-M obtained funding.

*Conflict of interest:* Mikel Etxandi, Isabel Baenas, Bernat Mora-Maltas, Roser Granero, Sulay Tovar, Neus Solé-Morata, Ignacio Lucas, Mónica Gómez-Peña, Laura Moragas, Amparo del Pino-Gutiérrez, Javier Tapia, Eduardo Valenciano-Mendoza, Sabela Casado, Ashley N. Gearhardt, and Carlos Diéguez report no disclosures. Fernando Fernández-Aranda and Susana Jiménez-Murcia received consultancy honoraria from Novo Nordisk, and Fernando Fernández-Aranda received editorial honoraria from Wiley. Marc N. Potenza has consulted for and advised Opiant Pharmaceuticals, Idorsia Pharmaceuticals, Baria-Tek, AXA, Game Day Data and the Addiction Policy Forum; has been involved in a patent application with Yale University and Novartis; has received research support from the Mohegan Sun Casino and Connecticut Council on Problem Gambling; has participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders, or other health topics; has participated in trainings, medical education and journal editorial work; and has consulted for law offices and gambling entities on issues related to impulse control or addictive disorders.

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## SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2023.00051.

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