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Original article

Elevated total plasma-adiponectin is stable over time in young women with bulimia nervosa

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ABSTRACT

Background: Bulimia nervosa (BN) is characterized by dysregulated eating behaviour and present data suggest adipokines may regulate food intake. We investigated a possible association between BN and adipokine levels and hypothesized that plasma (P)-adiponectin would be elevated and P-leptin and P-leptin-adiponectin-ratio would be reduced in women with BN.
Methods: The study was designed as a cross-sectional study with a longitudinal arm for patients with BN. Plasma-adiponectin and leptin was measured in 148 female patients seeking psychiatric ambulatory care and 45 female controls. Fifteen patients were diagnosed with BN and the remaining with other affective and anxiety disorders. P-adiponectin and P-leptin levels were compared between patients with BN, patients without BN and controls. At follow-up 1–2 years later, adipokines were reassessed in patients with BN and the Eating Disorder Examination Questionnaire was used to assess symptom severity.
Results: P-adiponectin was elevated in patients with BN at baseline and at follow-up when compared to patients without BN and controls ($P < 0.004$ and < 0.008 respectively). The difference remained significant after controlling for body mass index. P-adiponectin was correlated to symptom severity at follow-up in patients with BN without morbid obesity ($\rho = 0.72$, $P < 0.04$). P-leptin-adiponectin-ratio was significantly lower in patients with BN compared to controls ($P < 0.04$) and P-leptin non-significantly lower.
Conclusions: Findings indicate a stable elevation of P-adiponectin in women with BN. P-adiponectin at follow-up correlates to eating disorder symptom severity in patients without morbid obesity, indicating that P-adiponectin should be further investigated as a possible potential prognostic biomarker for BN.

1. Introduction

Bulimia nervosa (BN) has a prevalence of 1% in young women and is characterized by recurrent episodes of binge eating, inappropriate compensatory behaviour to prevent weight gain and self-evaluation unduly influenced by body weight or shape [1,2]. Women with BN are also described as having a need to eat more before reaching the same self-rated level of satiation [3]. Interestingly, the regulation of food intake is proposed to involve the adipokines adiponectin and leptin, hormones mainly produced in white adipose tissue [4–6].

Adiponectin's peripheral actions include elevation of insulin-sensitization and anti-atherogenic functions [6]. It passes the blood-brain-barrier in mice and rats and is found in human cerebrospinal fluid (CSF) [7,8]. Adiponectin is also expressed in the human pituitary and adiponectin receptors are present in the human hypothalamus, pituitary and hippocampus [9,10]. Serum and CSF adiponectin levels decrease in mice after refeeding and increase during fasting [5]. Adiponectin is described as increasing food intake and reducing energy expenditure in mice through stimulation of the AMP-activated protein kinase (AMPK)-pathway and enhancement of orexigenic signals, such as Neuropeptide Y, in the hypothalamus [5,11,12]. Adiponectin is also shown to indirectly stimulate food intake in mice through inhibition of leptin's suppressing actions on AMPK [5]. However, in contrast, one study demonstrated decreased food intake in rats after intracerebroventricular injection of adiponectin [13], while another observed no effect on food intake in mice [14].

Overfeeding increases circulating leptin in healthy humans. Treatment with leptin reduces appetite and weight loss in patients

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Abbreviations: BN, Bulimia nervosa; UPP, Uppsala psychiatric patient samples.

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with leptin deficiency [4]. Leptin deficiency in mice (ob/ob mice) induces hyperphagia and decreases energy expenditure. The ob/ob mice develop non-insulin-dependent diabetes, severe insulin resistance, reduced lean body mass and infertility. When leptin levels are corrected the obesity syndrome in the ob/ob mice is normalized [15]. Studies in rodents show that leptin-induced reduction in food intake may be mediated through suppression of the AMPK in the hypothalamus [4,11,16]. Activation of hypothalamic AMPK stimulates food intake and its activity increases during fasting and decreases during refeeding [5,12].

There is good reason to believe the signalling pathways regulating food intake are disturbed in patients with BN. Most studies show reduced circulating leptin in women with BN compared to healthy controls [17–20]. Monteleone et al. also observed a declined percentage reduction of leptin during fasting in women with BN compared to controls [21]. A recent study indicates an inverse association between pulsatile leptin secretion and disordered eating psychopathology [22]. Studies investigating circulating adiponectin levels in women with BN are few, use different methods and have contradictory results [23–25]. One study describes elevated plasma levels of adiponectin in individuals with BN [23], another reduced serum levels [24] and a third no significant difference in serum levels compared to controls [25]. To our present knowledge, no previous study has investigated leptin-adiponectin-ratio and longitudinal levels of adiponectin in women with and without BN.

1.1. Objectives

The aim of this study was to investigate a possible association between BN and adipokine levels and their longitudinal variation in patients with BN compared to age-matched patients with other psychiatric diagnoses and controls.

Adiponectin/leptin may have a stimulating/suppressing effect on food intake through inverse effects in the hypothalamus and during fasting adiponectin levels increase and leptin levels decrease. Therefore, we hypothesized that P-adiponectin levels would be elevated and P-leptin levels and P-leptin-adiponectin-ratio reduced in women with BN.

2. Methods

2.1. Participants

The data and samples used in the present study were obtained from the patient cohort "Uppsala Psychiatric Patient Samples" (UPP). UPP is based on consecutive new patients, 18–25 years of age, seeking ambulatory care at the "Young Adults" section of Dept. of General Psychiatry at Uppsala University Hospital, Sweden. Data and samples were collected from patients between the years 2012–2014.

All new patients at the "Young Adults" section were invited to participate in UPP ($N = 623$ patients). Out of these, 230 agreed to participate in UPP and data and blood samples were available for 228 patients of whom 179 women were selected for this study; the men were excluded. Thirty-one of the women in the total study population ($n = 179$), none with BN, were excluded due to the fulfilment of one or more of the prerequisite exclusion criteria:

- current/recent systemic inflammatory disorder;
- cancer;
- diabetes mellitus;
- treatment with testosterone;
- treatment with antibiotics within one-month range of blood sample collection;
- pregnancy;
- incomplete diagnostic assessments or if the time between blood sample collection and health examination diverted more than one month for patients with eating disorders and four months for other patient groups.

In total, 148 women were included in the statistical analyses. See Fig. 1 for details.

Controls without current or previous contact as patients within psychiatry were recruited from university students and personnel to UPP between 2013 and 2015. Blood samples from 45 female controls below the age of 30 were used in this study.

Ethics approval was obtained from the local Ethics Committee in Uppsala, Sweden; study number 2012/081 and 2013/219. Participation involved informed consent.

2.2. Study design

The study was initiated as a cross-sectional study and a longitudinal arm was included for patients with BN. Three groups were compared in the study; patients with BN, patients without BN and controls.

2.2.1. Baseline assessments

Psychiatric diagnoses were assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria [1]. The diagnostic process was constituted by two visits. During the first, a medical history was taken, and during the second, a diagnostic interview was performed. Patients were interviewed by trained personnel, psychiatrists or psychologists, using the Swedish version of the MINI International Neuropsychiatric Interview (MINI 6.0) [26] and/or the Structural Clinical Interview for DSM IV axis I disorders (SCID-I) [27].

Participants in UPP undergo an initial routine health examination at the time of inclusion. Blood pressure is measured sitting, weight is measured with a digital scale in kg and waist-and-hip circumferences are measured with the patient standing while wearing light clothing. Body mass index (BMI) was calculated as the body weight (kg) divided by the square of the body height (m^2). Thereafter, questionnaires concerning socio-demographics, medical history, heredity and current medication are answered in conjunction with blood sample collection.

2.2.2. Follow-up assessments for patients with BN

Patients with BN were invited back to the research assistant for weight control and new blood samples to measure P-adiponectin and P-leptin in Spring 2015. The patients were interviewed by telephone thereafter. Partial remission was defined as < 2 episodes of binge-eating and compensatory purging, laxative use or hard exercise per month [28]. Data concerning heredity for eating disorder, symptoms and age at onset, received eating disorder treatment, subjective change in well-being/symptoms between baseline and follow-up and medical treatment received between baseline and follow-up blood sample collection were gathered from the medical record and verified with the patient using a standardized interview protocol. Patients with BN also answered the Swedish version of the self-report instrument, Eating Disorder Examination Questionnaire (EDE-Q), for the month prior to the follow-up blood sample collection [29,30]. The EDE-Q global score and the scores for the EDE-Q subscales "Restraint", "Eating Concern", "Shape concern" and "Weight concern" were calculated in accordance with the recommendations by Fairburn [31].

2.2.3. Blood sample collection and analysis

Whole blood was collected from non-fasting participants during office hours. For patients with BN, blood was sampled twice: at baseline and at follow-up. Plasma was isolated and stored