European Journal of Clinical Nutrition (2010) 64, 840–844
 0954-3007/10
www.nature.com/ejcn

ORIGINAL ARTICLE

Specific adipocytokines profiles in patients with hyperactive and/or binge/purge form of anorexia nervosa

J-P Nogueira[1,2,5], M Maraninchi[1,2,5], A-M Lorec[2,3], AB-L Corroller[1], A Nicolay[2,3], J Gaudart[4], H Portugal[2,3], R Barone[2], B Vialettes[1,2] and R Valéro[1,2]

[1]*Department of Nutrition, Metabolic diseases, Endocrinology, University of Aix-Marseille 2, 'La Timone' Hospital, Marseille, France;* [2]*UMR INSERM 476/INRA 1260/University of Aix-Marseille 2, Faculty of Medicine 'La Timone', Marseille, France;* [3]*Department of Biochemistry, University of Aix-Marseille 2, 'Sainte Marguerite' Hospital, Marseille, France and* [4]*Biostatistics Research Unit, Laboratory of Education and Research in Medical Information Processing (LERTIM), Faculty of Medicine, EA 3283 Aix-Marseille University, Marseille, France*

Objective: The aim of our study was to determine whether eating behaviors and/or physical activity level may explain contradicting results in adipocytokines levels in anorexia nervosa (AN).
Subjects/Methods: Fasting levels of circulating adipocytokines (adiponectin, resistin and leptin), insulin, glucose, C-reactive protein, cytokines (tumor necrosis factor-α and interleukin (IL)-1β), body composition and resting energy expenditure were measured in 24 women AN patients and 14 women controls. These parameters were compared according to AN subtypes: 15 patients with restrictive (R-AN) form versus 9 patients with binge/purge (BP-AN) form; 15 patients with hyperactive (H-AN) form versus 9 patients with nonhyperactive (NH-AN) form.
Results: BP-AN patients had significantly higher serum adiponectin levels compared with R-AN patients ($P<0.05$), and H-AN patients had higher serum leptin and lower serum resistin levels compared with NH-AN patients ($P<0.05$ for both).
Conclusions: Our study shows specific adipocytokines profiles depending on the subtype of AN: restrictive versus binge/purge and hyperactive versus Nonhyperactive forms. We suggest that these biological signatures could interfere with the outcome of the disease.
European Journal of Clinical Nutrition (2010) **64,** 840–844; doi:10.1038/ejcn.2010.66; published online 19 May 2010

Keywords: AN; restrictive form; binge/purge form; hyperactive form; adipocytokines

Introduction

Anorexia nervosa (AN) is a severe disease affecting mostly adolescent and adult women. This eating disorder is characterized by chronic self-starvation and is classically divided into two subtypes: the restrictive (R-AN) form and the binge/purge (BP-AN) form (Stoving *et al*., 1999; Thompson-Brenner *et al*., 2008). AN patients may also be classified by the level of their physical activity: hyperactive (H-AN) form or nonhyperactive form (NH-AN). The consequences of such habits can lead to a life-threatening undernutrition. Indeed, the long-term mortality rate of this disease is significantly increased compared with age-matched control women (Lowe *et al*., 2001).

Some adipocytokines secreted by adipose tissue, such as adiponectin, leptin and resistin, have major roles in the regulation of energy metabolism and/or insulin sensitivity (Zou and Shao, 2008). The decrease of serum leptin levels constantly described in the literature was postulated to lead to both amenorrhea and restlessness similar to rat-specific semi-starvation-induced hyperactivity (Hebebrand *et al*., 2007).

However, data concerning serum levels of the other adipocytokines are very conflicting. Serum adiponectin has been found to be either increased (Delporte *et al*., 2003;

Correspondence: Professor R Valéro, Service de Nutrition, Maladies métaboliques et Endocrinologie, Hôpital La Timone, 264 Rue Saint Pierre, 13005 Marseille, France.
E-mail: RVALERO@mail.ap-hm.fr
[5]These authors contributed equally to this work.
Received 17 January 2010; revised 6 April 2010; accepted 7 April 2010; published online 19 May 2010

Pannacciulli *et al*., 2003), normal (Iwahashi *et al*., 2003) or decreased (Tagami *et al*., 2004) in AN patients. Likewise, serum plasma resistin levels have been found to be either decreased (Dostalova *et al*., 2006) or normal (Dolezalova *et al*., 2007). These discrepancies suggest that some confounding factors, such as eating behaviors and/or physical activity level, could interfere with the results.

Accordingly, we compared circulating adipocytokines levels (leptin, adiponectin and resistin) between a group of women patients suffering from AN and a group of healthy control women and also between the different subtypes of the disease: R-AN versus BP-AN form or H-AN versus NH-AN form. Further, we assessed plasma proinflammatory cytokines (interleukin (IL)-1β and tumor necrosis factor-α (TNF-α)), which could be linked to eating behaviors, energy metabolism and adipocytokines levels (Brambilla, 2001). We postulated that some clinical features of AN might lead to different adipocytokines profiles susceptible to interfere with the natural history of the disease. For example, hyperleptinemia during refeeding has been associated with an elevated risk of relapse in AN (Holtkamp *et al*., 2004b).

Subjects and methods

Subjects

This study was conducted in accordance with the Declaration of Helsinki, approved by the institutional ethics committee and a written informed consent was obtained from all patients. Twenty-four women patients meeting the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria of AN and referred to our nutrition department were included in the study (American Psychiatric Association, 1994). Fifteen of them suffered from R-AN and nine from BP-AN according to the DSM-IV classification (American Psychiatric Association, 1994). The mean frequency of vomiting and laxative abuse was once or twice per week. We defined the level of physical activity according to the Structured Interview of Anorexia and Bulimia Nervosa (SIAB) scale (Holtkamp *et al*., 2004a). Fifteen patients were classified in the H-AN group (levels 3 and 4 on the SIAB scale), whereas nine patients were classified in the NH-AN group (levels 0–2 on the SIAB scale). Two patients were treated by antidepressant drugs, two by anxiolytic drugs, one by neuroleptic drugs, one by the association of antidepressant and anxiolytic drugs, two by the association of antidepressant and neuroleptic drugs, two by the association of antidepressant, anxiolytic and neuroleptic drugs, two by estroprogestative drugs and twelve patients received no drugs. In addition, 14 normal-weight healthy women were recruited as controls after a medical interview and a physical examination by a physician specialized in nutrition. None of them had any history of eating disorders or other psychiatric illness.

Methods

Blood samples were collected from each subject in the morning after an overnight fast at the first week of hospitalization in our nutrition department. Specific enzyme-linked immunosorbent assay (ELISA) kits were used to measure serum levels of leptin (Active Human Leptin, DSL Systems, Webster, TX, USA), adiponectin (Quantikine Human Adiponectin, R&D Systems, Minneapolis, MN, USA) and resistin (Quantikine Human Resistin, R&D Systems). Plasma C-reactive protein (CRP) was measured using the turbidimetric method (Synchron LX, Beckman Coulter, Paris, France). The plasma IL-1β and TNF-α levels were measured using ELISA kits (Human IL-1β/IL-1F2, R&D Systems; Human TNF-α/TNFSF1A Immunoassay, R&D Systems). Plasma glucose was measured using the hexokinase oxidase method (Beckman Coulter, Galway, Ireland) and plasma insulin levels through electrochemiluminescence (Roche Diagnostic, Mannheim, Germany). Insulin resistance was estimated using the homeostasis model assessment: HOMA-IR = fasting insulin (mUI/l) × fasting glucose (mmol/l)/22.5 (Matthews *et al*., 1985).

Body composition was assessed using dual-energy X-ray absorptiometry method (Lunar iDXA, GE Healthcare, Chalfont, St Giles, UK): body fat mass (BFM) and body lean mass compartments were considered. Resting energy expenditure (REE) was measured by indirect calorimetry (Quark-RMR, Cosmed, Rome, Italy) after an overnight fast.

Statistical analysis

Statistical analysis was carried out using SPSS software (Statistical Package for the Social Sciences Inc, version 15.0, Chicago, IL, USA). The results are presented as means ± s.d. The Mann–Whitney *U*-test was used for comparisons between groups. Multivariate model stepwise regression analyses were carried out in AN subgroups to determine associations of adipocytokines measures with different parameters. *P*-value <0.05 was considered statistically significant.

Results

Comparison between AN women patients and control subjects

Characteristics of the AN women patients and the control women are presented in Table 1. As expected, AN patients were leaner than control women ($P<0.01$).

The adipocytokines profiles in AN patients versus controls showed no difference in serum adiponectin and resistin levels, but there was a drastic decrease in the serum leptin level in AN patients ($P<0.01$). Plasma glucose was not different but plasma insulin was decreased ($P<0.01$), explaining the reduction of the HOMA-IR index in AN patients compared with controls ($P<0.01$). Plasma CRP and IL-1β levels did not differ between AN patients and control women, whereas plasma TNF-α was significantly lower in AN patients than in controls ($P<0.05$).

Comparison between R-AN and BP-AN patients
Results are presented in Table 2.

Age, body mass index (BMI), body composition, REE, plasma CRP, IL-1β and TNF-α levels were not different between R-AN and BP-AN patients.

The significant difference between R-AN and BP-AN patients was the higher serum adiponectin levels in the BP-AN patients ($P<0.05$). There were no significant differences for serum resistin and leptin levels and HOMA-IR in R-AN compared with BP-AN patients.

In an additional stepwise multivariate analysis, when adjusted for plasma glucose, insulin, HOMA-IR, resistin, leptin, BMI, BFM, body lean mass, REE and binge/purge behaviors, only the BFM ($\beta=0.70$; $P<0.05$) and the presence of binge/purge behaviors ($\beta=6.450$; $P<0.05$) contributed positively and significantly to the variability of adiponectin and explained 66% of the serum adiponectin levels ($r^2=0.66$).

Table 1 Anthropometric, hormonal and biochemical parameters of patients with anorexia nervosa and healthy control women

	AN (n = 24)	*C (n = 14)*
Age (years)	22.75 ± 5.93	24.0 ± 2.14
BMI (kg/m^2)	13.52 ± 1.19[a]	20.36 ± 1.77
Adiponectin (μg/ml)	11.22 ± 6.65	11.09 ± 4.86
Resistin (ng/ml)	11.69 ± 6.85	11.13 ± 3.07
Leptin (ng/ml)	0.75 ± 1.0[a]	11.0 ± 10.25
Insulin (mUI/l)	2.71 ± 2.27[a]	8.02 ± 4.55
Glucose (mmol/l)	4.02 ± 0.74	4.32 ± 0.49
HOMA-IR	0.69 ± 0.71[a]	1.54 ± 0.93
CRP (mg/l)	1.18 ± 0.61	1.83 ± 1.73
IL1-β (pg/ml)	0.206 ± 0.11	0.128 ± 0.44
TNF-α (pg/ml)	2.63 ± 2.89[b]	3.25 ± 1.14

Abbreviations: AN, anorexia nervosa; BMI, body mass index; C, control; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment-insulin resistance; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α.
[a]$P<0.01$ versus control group.
[b]$P<0.05$ versus control group.
Values are mean ± s.d. Statistical significance is from Mann–Whitney *U*-test.

Comparison between H-AN and NH-AN patients
Results are presented in Table 2.

Age, BMI, body composition, REE, plasma CRP, IL-1β and TNF-α levels were not different between H-AN and NH-AN patients.

The H-AN patients showed significantly higher serum leptin levels and lower serum resistin levels compared with NH-AN patients ($P<0.05$ for both). Serum adiponectin levels were not different between the two groups of patients.

In an additional stepwise multivariate analysis, when adjusted for plasma glucose, insulin, HOMA-IR, adiponectin, BMI, BFM, body lean mass, REE and physical activity level, only the HOMA-IR ($\beta=1.003$; $P<0.01$) and the physical activity level ($\beta=2.608$; $P<0.01$) contributed positively and significantly, whereas the BFM ($\beta=-0.11$; $P<0.05$) contributed negatively and significantly to the variability of leptin. These parameters contributed to 93% of the serum leptin levels ($r^2=0.93$). Likewise, only the HOMA-IR ($\beta=2.85$; $P<0.05$) contributed to the variability of resistin as a positive factor and explained 57% of the serum resistin levels ($r^2=0.57$).

Discussion

This study confirmed the constant decrease of serum leptin levels seen in undernourished AN patients (Brichard *et al*., 2003) but shows specific adipocytokines profiles depending on the eating behaviors and the intensity of the physical

Table 2 Anthropometric, hormonal and biochemical parameters of patients with restrictive (R-AN), binge/purge (BP-AN), hyperactive (H-AN) and nonhyperactive (NH-AN) forms of anorexia nervosa (AN)

	R-AN (n = 15)	*BP-AN (n = 9)*	*H-AN (n = 15)*	*NH-AN (n = 9)*
Age (years)	21.13 ± 4.82	25.44 ± 6.89	22.8 ± 7.09	22.66 ± 3.64
BMI (kg/m^2)	13.3 ± 1.30	13.8 ± 0.89	13.43 ± 1.19	13.66 ± 1.24
BFM (%)	11.5 ± 4.44	11.2 ± 6.38	10.6 ± 4.82	12.34 ± 5.88
BLM (%)	89.5 ± 12.15	87.9 ± 14.14	86.2 ± 6.91	86.3 ± 7
REE (kJ/d)	3086 ± 716	3140 ± 645	2805 ± 553	3232 ± 632
Adiponectin (μg/ml)	8.45 ± 6.0[a]	16.3 ± 4.2	11.36 ± 6.56	11 ± 7.20
Resistin (ng/ml)	13.15 ± 7.77	9.81 ± 4.58	9.20 ± 3.53[b]	16.05 ± 9.15
Leptin (ng/ml)	0.91 ± 1.26	0.47 ± 0.06	0.94 ± 1.24[b]	0.42 ± 0.13
HOMA-IR	0.75 ± 0.78	0.59 ± 0.61	0.61 ± 0.72	0.81 ± 0.72
CRP (mg/l)	1.27 ± 0.67	1.02 ± 0.48	1.01 ± 0.36	1.45 ± 0.83
IL-1β (pg/ml)	0.224 ± 0.127	1.179 ± 0.08	0.215 ± 0.124	1.191 ± 0.089
TNF-α (pg/ml)	3.17 ± 3.6	1.81 ± 0.7	2.19 ± 1.52	3.18 ± 4.51

Abbreviations: BFM, body fat mass; BLM, body lean mass; BMI, body mass index; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment-insulin resistance; IL-1β, interleukin 1β; REE, resting energy expenditure; TNF-α, tumor necrosis factor-α.
[a]$P<0.05$ R-AN versus BP-AN group.
[b]$P<0.05$ H-AN versus NH-AN group.
Values are mean ± s.d. Statistical significance is from Mann–Whitney *U*-test.

activity. The comparison of these adipocytokines profiles was facilitated by the absence of difference in terms of age, BMI, body composition and REE between our subgroups of AN patients.

The subgroup of BP-AN patients showed significantly higher adiponectin levels compared with R-AN patients. These results are not in agreement with the study of Housova *et al*. (2005), which did not observe any difference between R-AN and BP-AN forms. Other studies showed an increase in serum adiponectin levels in AN but did not deal with AN subtypes (Delporte *et al*., 2003; Pannacciulli *et al*., 2003). However, it is noteworthy that Monteleone *et al*. (2003) documented a significant increase of circulating adiponectin levels in patients with bulimia nervosa and a correlation of this increased adipocytokine secretion with the frequency of binge/purge episodes. The physiological relevance of the plasma adiponectin increase in AN remains unclear and is still debated. The hyperadiponectinemia could contribute to etiopathogenic factor of AN (Housova *et al*., 2005), or on this background of AN with lower plasma insulin levels, could represent a compensatory mechanism for the increase of insulin sensitivity (Monteleone *et al*., 2008). Indeed, a negative correlation has been found between plasma adiponectin and insulin levels in AN (Dostalova *et al*., 2007). However, we did not find a significant difference in insulin sensitivity between the AN patient subtypes.

The most interesting finding of this study is the adipocytokines profile of H-AN patients showing a higher level of serum leptin and a lower level of serum resistin compared with NH-AN patients.

The results of serum leptin levels do not support the hypothesis from Hotkamp's group that low leptin levels in AN can facilitate motor restlessness and intensive exercise behaviors as observed during the semi-starvation-induced hyperactivity model in rodents (Hebebrand *et al*., 2003; Holtkamp *et al*., 2006). However, in this study, the relationship between serum leptin levels and physical activity follows an inverted U-shape curve; physical activity levels are lower in severely undernourished AN patients leading to the hypothesis that the effect of hypoleptinemia on physical activity levels declines with the severity of the undernutrition (Holtkamp *et al*., 2006). In our study, the mean BMI and the mean serum leptin levels of the AN patients were lower than in this previous study (Holtkamp *et al*., 2006).

The intensity of physical activity is rarely taken into account as a predicting factor for the outcome in AN (Davis *et al*., 1997). However, in a large multicentric European study, periodic overactivity was a significant predictor of readmission in a multivariate analysis (Steinhausen *et al*., 2008). This parameter was a stronger predictor of relapse than purge habits, classically a worsening prognostic factor, which did not reach the statistically significant level. Periodic overactivity multiplied the risk of readmission by a factor of 2.51 (Steinhausen *et al*., 2008). Serum leptin levels increased with the recovery of body weight, but hyperleptinemia during refeeding could contribute, through its effects on appetite suppression and energy expenditure, to the difficulties in reaching and maintaining the target weight and is associated with an elevated risk of renewed weight loss in AN (Holtkamp *et al*., 2004b). Although the serum leptin levels of the H-AN patients are low compared with the control subjects, the relative increase of these hormone levels in this H-AN group compared with the NH-AN patients could contribute to the worse outcome observed in H-AN patients.

This is the first study showing a decrease of serum resistin levels in H-AN patients compared with NH-AN patients, despite the fact that we found no difference in serum resistin values in the whole AN group compared with healthy control women, as seen in other studies (Housova *et al*., 2005). The H-AN patients tend to be more insulin sensitive than the NH-AN patients. The decrease of serum resistin levels in H-AN patients was associated positively with HOMA-IR. Consistent with our observations, Rubin *et al*. (2008) in normal-weight adolescents boys and Jones *et al*. (2009) in overweight adolescents previously showed that vigorous physical activity is associated with lower serum resistin levels, suggesting a link between insulin sensitivity and resistin secretion; physical activity having a moderator role in this relationship.

In humans, it is well known that resistin positively regulates proinflammatory factors. However, in our study, there was no link between serum resistin levels and the concentrations of major proinflammatory cytokines, such as TNF-α and IL-1β. The data on production of proinflammatory cytokines in AN patients are very conflicting. We found a decrease in the levels of plasma TNF-α that is consistent with another study (Nova *et al*., 2002). However, these results are not in accordance with other previous studies showing normal (Brambilla *et al*., 2001) or increased (Nakai *et al*., 1999) plasma TNF-α values. In AN, serum resistin levels seem not to be linked to inflammatory status, but are more likely associated to insulin sensitivity in the H-AN form.

To date, the concept of subtypes in AN, which could be relevant in terms of psychological background and prognosis is still debated. Indeed, some authors advocate for spiting the AN in subgroups (Eddy *et al*., 2002) and others contest the accuracy of such classifications, arguing that the various clinical presentations could simply represent distinct steps in a common natural history of the disease (Eddy *et al*., 2002).

In conclusion, we showed specific adipocytokines profiles corresponding to different forms of AN: increased serum leptin together with decreased serum resistin levels associated with the H-AN form and hyperadiponectinemia associated with BP-AN form. Further studies are needed to confirm our results and elucidate whether these specific hormone profiles are secondary to the nutritional status of the AN patient and/or could interfere with the subtype or the natural history of the disease. We pointed out the importance of the different forms of AN, taking into account eating behaviors as well as physical activity level and suggest

that this subclassification is relevant not only in terms of clinical features but also corresponds to a specific biological signature.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Myriam Coffin for her technical help.

References

American Psychiatric Association (1994). *Diagnosic and Statistical Manual of Mental Disorders* 4th edn. American Psychiatric Press: Washington, DC.

Brambilla F (2001). Social stress in anorexia nervosa: a review of immuno-endocrine relationships. *Physiol Behav* **73**, 365–369.

Brambilla F, Monti D, Franceschi C (2001). Plasma concentrations of interleukin-1-beta, interleukin-6 and tumor necrosis factor-alpha, and of their soluble receptors and receptor antagonist in anorexia nervosa. *Psychiatry Res* **103**, 107–114.

Brichard SM, Delporte ML, Lambert M (2003). Adipocytokines in anorexia nervosa: a review focusing on leptin and adiponectin. *Horm Metab Res* **35**, 337–342.

Davis C, Katzman DK, Kaptein S, Kirsh C, Brewer H, Kalmbach K *et al*. (1997). The prevalence of high-level exercise in the eating disorders: etiological implications. *Compr Psychiatry* **38**, 321–326.

Delporte ML, Brichard SM, Hermans MP, Beguin C, Lambert M (2003). Hyperadiponectinaemia in anorexia nervosa. *Clin Endocrinol (Oxf)* **58**, 22–29.

Dolezalova R, Lacinova Z, Dolinkova M, Kleiblova P, Haluzikova D, Housa D *et al*. (2007). Changes of endocrine function of adipose tissue in anorexia nervosa: comparison of circulating levels versus subcutaneous mRNA expression. *Clin Endocrinol (Oxf)* **67**, 674–678.

Dostalova I, Kunesova M, Duskova J, Papezova H, Nedvidkova J (2006). Adipose tissue resistin levels in patients with anorexia nervosa. *Nutrition* **22**, 977–983.

Dostalova I, Smitka K, Papezova H, Kvasnickova H, Nedvidkova J (2007). Increased insulin sensitivity in patients with anorexia nervosa: the role of adipocytokines. *Physiol Res* **56**, 587–594.

Eddy KT, Keel PK, Dorer DJ, Delinsky SS, Franko DL, Herzog DB (2002). Longitudinal comparison of anorexia nervosa subtypes. *Int J Eat Disord* **31**, 191–201.

Hebebrand J, Exner C, Hebebrand K, Holtkamp C, Casper RC, Remschmidt H *et al*. (2003). Hyperactivity in patients with anorexia nervosa and in semistarved rats: evidence for a pivotal role of hypoleptinemia. *Physiol Behav* **79**, 25–37.

Hebebrand J, Muller TD, Holtkamp K, Herpertz-Dahlmann B (2007). The role of leptin in anorexia nervosa: clinical implications. *Mol Psychiatry* **12**, 23–35.

Holtkamp K, Hebebrand J, Herpertz-Dahlmann B (2004a). The contribution of anxiety and food restriction on physical activity levels in acute anorexia nervosa. *Int J Eat Disord* **36**, 163–171.

Holtkamp K, Hebebrand J, Mika C, Heer M, Heussen N, Herpertz-Dahlmann B (2004b). High serum leptin levels subsequent to weight gain predict renewed weight loss in patients with anorexia nervosa. *Psychoneuroendocrinology* **29**, 791–797.

Holtkamp K, Herpertz-Dahlmann B, Hebebrand K, Mika C, Kratzsch J, Hebebrand J (2006). Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. *Biol Psychiatry* **60**, 311–313.

Housova J, Anderlova K, Krizova J, Haluzikova D, Kremen J, Kumstyrova T *et al*. (2005). Serum adiponectin and resistin concentrations in patients with restrictive and binge/purge form of anorexia nervosa and bulimia nervosa. *J Clin Endocrinol Metab* **90**, 1366–1370.

Iwahashi H, Funahashi T, Kurokawa N, Sayama K, Fukuda E, Okita K *et al*. (2003). Plasma adiponectin levels in women with anorexia nervosa. *Horm Metab Res* **35**, 537–540.

Jones TE, Basilio JL, Brophy PM, McCammon MR, Hickner RC (2009). Long-term exercise training in overweight adolescents improves plasma peptide YY and resistin. *Obesity* **17**, 1189–1195.

Lowe B, Zipfel S, Buchholz C, Dupont Y, Reas DL, Herzog W (2001). Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. *Psychol Med* **31**, 881–890.

Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419.

Monteleone P, Fabrazzo M, Martiadis V, Fuschino A, Serritella C, Milici N *et al*. (2003). Opposite changes in circulating adiponectin in women with bulimia nervosa or binge eating disorder. *J Clin Endocrinol Metab* **88**, 5387–5391.

Monteleone P, Castaldo E, Maj M (2008). Neuroendocrine dysregulation of food intake in eating disorders. *Regul Pept* **149**, 39–50.

Nakai Y, Hamagaki S, Takagi R, Taniguchi A, Kurimoto F (1999). Plasma concentrations of tumor necrosis factor-alpha (TNF-alpha) and soluble TNF receptors in patients with anorexia nervosa. *J Clin Endocrinol Metab* **84**, 1226–1228.

Nova E, Gomez-Martinez S, Morande G, Marcos A (2002). Cytokine production by blood mononuclear cells from in-patients with anorexia nervosa. *Br J Nutr* **88**, 183–188.

Pannacciulli N, Vettor R, Milan G, Granzotto M, Catucci A, Federspil G *et al*. (2003). Anorexia nervosa is characterized by increased adiponectin plasma levels and reduced nonoxidative glucose metabolism. *J Clin Endocrinol Metab* **88**, 1748–1752.

Rubin DA, McMurray RG, Harrell JS, Thorpe DE, Hackney AC (2008). Vigorous physical activity and cytokines in adolescents. *Eur J Appl Physiol* **103**, 495–500.

Steinhausen HC, Grigoroiu-Serbanescu M, Boyadjieva S, Neumarker KJ, Winkler Metzke C (2008). Course and predictors of rehospitalization in adolescent anorexia nervosa in a multisite study. *Int J Eat Disord* **41**, 29–36.

Stoving RK, Hangaard J, Hansen-Nord M, Hagen C (1999). A review of endocrine changes in anorexia nervosa. *J Psychiatr Res* **33**, 139–152.

Tagami T, Satoh N, Usui T, Yamada K, Shimatsu A, Kuzuya H (2004). Adiponectin in anorexia nervosa and bulimia nervosa. *J Clin Endocrinol Metab* **89**, 1833–1837.

Thompson-Brenner H, Eddy KT, Franko DL, Dorer D, Vashchenko M, Herzog DB (2008). Personality pathology and substance abuse in eating disorders: a longitudinal study. *Int J Eat Disord* **41**, 203–208.

Zou C, Shao J (2008). Role of adipocytokines in obesity-associated insulin resistance. *J Nutr Biochem* **19**, 277–286.