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ORIGINAL CONTRIBUTION

Adipocyte fatty acid binding protein during refeeding of female patients with anorexia nervosa

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Abstract
Background Adipocyte fatty acid binding protein (A-FABP) has been suggested to play an important role in fat metabolism linking obesity and the metabolic syndrome. Increasing A-FABP plasma levels were observed during greatest weight loss after bariatric surgery suggesting that A-FABP may indicate changes in fat mass in dynamic situations.
Aim of the study As there are no data on weight gain, we investigated the effect of refeeding anorexic patients on body composition and A-FABP plasma levels.
Methods Parameters of glucose and lipid metabolism as well as plasma levels of leptin and A-FABP were prospectively assessed in 16 female patients with anorexia nervosa during inpatient weight restoration. Body composition was determined by multifrequency body impedance analysis.
Results After 28 days, fat mass increased from 4.4 ± 2.5 kg at baseline to 5.5 ± 2.2 kg ($P < 0.01$), constituting 40% of total weight gain. Conversely, A-FABP concentrations decreased from 32.56 ± 35.59 ng/ml at baseline to 21.27 ± 13.68 ng/ml ($P < 0.05$), which corresponds to a significant decrease in the proportion of A-FABP per kilogram fat mass from 7.86 ± 5.23 to 4.09 ± 2.12 ng/ml/kg ($P \leq 0.001$). Variation in A-FABP plasma concentration was predictive for changes in total cholesterol levels (adjusted $r^2 = 0.239$; $P \leq 0.05$), but not for gain in weight, fat mass, or percent body fat.
Conclusion The present results indicate that variation in A-FABP plasma levels reflect alterations in nutritional status in patients with anorexia nervosa.

Keywords A-FABP · Weight gain · Metabolism · Anorexia nervosa

Introduction

Anorexia nervosa is an eating disorder found in adolescents and adults with significantly decreased lean mass and fat mass and a preferential mobilization of fat mass during weight loss [16]. The diagnostic subtype of anorexia nervosa is also reported to have an impact on percentage fat mass [20]. Analyses of regional fat distribution in anorectic patients revealed that adolescents tend to lose fat primarily from the trunk, sparing fat from the extremities, while in adults trunk fat is spared and fat is mainly lost from the extremities [9, 16].

Although the definitive biology and mechanisms of action are not yet clearly understood, adipocyte fatty acid binding protein (A-FABP) has been demonstrated to be an important player in the regulation of the biological function of adipocytes, serving as a critical link between lipid metabolism, hormone action and cellular functions in adipocytes and other cell types [13]. A-FABP levels have been found to be significantly higher in overweight/obese than in lean subjects. Age- and sex-adjusted serum A-FABP correlated positively with waist circumference, blood

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pressure, dyslipidemia, fasting insulin, and the homeostasis model assessment of insulin resistance index (HOMA-IR). An increasing number of components of the metabolic syndrome was found to correspond with higher A-FABP concentrations [34]. In a prospective study we investigated the changes of A-FABP plasma levels during profound weight loss induced by bariatric surgery. In this study, we found maximum increases of serum A-FABP corresponding with greatest weight loss [6]. These results suggest that A-FABP is also a marker of weight changes in dynamic situations. Thus, in situations of profound weight loss, A-FABP serum levels likely mark lipolytic activity in the adipose tissue. However, there are as of yet no data on changes of A-FABP plasma levels during weight gain.

The aim of this prospective study was to examine body composition and metabolic parameters during treatment of hospitalized patients with anorexia nervosa. We likewise examined in detail the effect of early refeeding on the plasma levels of A-FABP, predicting a decrease in A-FABP plasma levels which would parallel weight gain.

Subjects and methods

Subjects

Female inpatients meeting the criteria for the diagnosis of anorexia nervosa both restrictive and binge-eating/purging subtype defined by DSM-IV were recruited consecutively at the Clinical Department for Psychosomatic Medicine and Psychosocial Psychiatry at Innsbruck's Medical University Department of Psychiatry. We included anorexic patients of all ages and with comorbidities such as major depression, anxiety disorder, obsessive compulsive disorder, and only excluded patients with very severe anorexia nervosa (BMI below 13) and patients with psychosis.

Informed consent was obtained from all subjects and the procedures were performed in accordance with institutional guidelines at the Department of Internal Medicine I, Innsbruck Medical University. The local ethical committee at the Innsbruck Medical University approved the study.

Study protocol and outcome measures

All anorexic patients underwent a refeeding program characterized by a strategic increase in caloric nutrition starting with 1,670 kJ (400 kcal) a day at the first days and ending up with a maximum of 13,400 kJ (3,200 kcal) a day after 1–2 weeks depending on BMI, the monitored blood levels such as liver function, electrolytes especially inorganic phosphate and the patients compliance in order to avoid the refeeding-syndrome. The enteral refeeding of the patients is based on a standardized 1.5 kcal/ml high caloric drink (Fresubin® energy fibre) which is administered up to seven times a day and intake is monitored. During refeeding no additional food consumption or physical activity is allowed. This regime is aimed to achieve an average weight gain of $\geq$1 kg/week.

Measurements of BMI and body composition analysis were performed on the patients concomitantly with the blood samplings at baseline and on days 14, 28, and 42 of refeeding. Body composition was determined by segmental multifrequency body impedance analysis (BIA) using In-Body 3.0 (Biospace Europe), which uses an 8-point tactile electrode system that measures the total and segmental impedance and phase angle of alternating electric current at four different frequencies (5, 50, 250, and 500 kHz). Measurements were done after a fasting period of at least 12 h in light clothing according to the manufacturer's instructions.

Besides levels of insulin, glucose, triacylglycerol (TAG), total cholesterol, HDL cholesterol, LDL cholesterol, FFA, and C-reactive protein (CRP) measurements of adiponectin, leptin, and A-FABP plasma levels were performed.

Laboratory measurements

Blood was drawn in the morning following an overnight fast from a peripheral vein. Immediately after collection plasma was separated from erythrocytes by centrifugation at 3,000 rpm for 10 min at 4 °C and stored at −80 °C until time of assay.

Plasma glucose concentrations were measured using a standard enzymatic method (Roche Diagnostic Systems, Basel, Switzerland). Plasma insulin concentrations were measured using a microparticle enzyme immunoassay (Abbott, Vienna, Austria). HOMA-IR, an alternative method to assess insulin resistance based on known relationships between fasting glucose and serum insulin concentrations was calculated by the following formula: fasting serum insulin concentration (μIU/ml) × blood glucose concentration (mmol/l)/22.5 [14]. Lipid parameters were determined using standard methods on a Cobas Mira analyzer (Roche, Vienna, Austria). ELISA kits were used for measurement of leptin (R&D Systems, Wiesbaden, Germany) and total adiponectin levels (Linco Research, St Charles, MO, USA). CRP concentration was determined by the CRP (Latex) ultrasensitive assay (Roche Diagnostic Systems, Basel, Switzerland). Serum A-FABP was determined with a commercially available ELISA (BioVendor Laboratory Medicine, Brno, Czech Republic) and the assay was conducted according to the manufacturer's instructions. Quality controls of the A-FABP ELISA were performed and the CV of the assay in our laboratory was <5%. The reported mean normal value for the assay is

19.58 ng/ml, the 95% confidence interval ranging from 17.56 to 21.60 ng/ml.

Statistical analysis

Statistical analysis was performed using the complete datasets of days 0 and 28 as one patient did not show up at day 14 and three patients dropped out before 42 days follow-up. The Shapiro–Wilks test was applied to assess significant deviations from normal distribution. Parameters, that were not normally distributed, were log transformed to approximate a normal distribution. After confirming homogeneity of variances by the Levene test, the paired-samples t test was used for prospective comparisons. The Pearson's r correlation coefficient calculated to assess correlations between data and linear regression analysis was performed where applicable. All values are expressed as mean ± SD unless otherwise stated. Statistical significance was inferred at a two-sided $P \leq 0.05$. Statistical analyses were calculated using SPSS release 14.0 for Windows (SPSS, Chicago, IL, USA).

Results

Sixteen female patients with a median age of 23 (range 16–63 years) were included in the study. Four patients were classified as binge-eating/purging types and 12 as restricting types.

Baseline demographic and anthropometric characteristics of the study population are given in Table 1. Results after 28 days demonstrated significant increases in terms of weight (3.8 ± 1.2 kg), BMI (1.40 ± 0.44 kg/m^2), fat mass (1.49 ± 0.57 kg), percent body fat (+2.5 ± 1.2%), and lean mass (2.06 ± 0.92 kg) (all $P \leq 0.001$; Table 2). During this time, A-FABP levels decreased by 34.6% ($P \leq 0.05$), while leptin levels increased by 67.8% ($P \leq 0.01$; Table 3). As A-FABP is a hormone exclusively expressed in adipose tissue, we investigated the change of A-FABP levels in relation to change in fat mass by calculating the ratio of A-FABP concentration and kilogram fat mass. During weight gain and concomitant gain in fat mass, the proportion of A-FABP per kilogram fat mass decreased from 7.86 ± 5.23 to 4.09 ± 2.12 ng/ml/kg ($P \leq 0.001$; Fig. 1).

Correlation analysis revealed no significant correlations between A-FABP plasma levels and weight, BMI, fat mass, percent body fat, lean mass, FFA, CRP, leptin, or adiponectin at baseline. After 28 days, fat mass was associated with A-FABP plasma levels ($r = 0.514$; $P \leq 0.05$). The decrease in A-FABP levels was proportionate to initial A-FABP concentration ($r = 0.773$; $P \leq 0.001$). To test whether A-FABP levels can serve as a predictor for weight or fat mass gained, linear regression analysis was performed. Delta values of BMI, fat mass, lean mass, and percent body fat as well as values at study end entered as dependent variables while A-FABP plasma levels at baseline were used as independent variable. Analysis revealed an association between A-FABP levels at baseline and percent body fat at study end (adjusted $r^2 = 0.290$; $\beta = 7.678$; $P \leq 0.05$). With respect to difference values of parameters, A-FABP was correlated only with total cholesterol ($r = 0.535$; $P \leq 0.05$). Variation in A-FABP plasma concentration was predictive for changes in total cholesterol levels (adjusted $r^2 = 0.239$; $\beta = -0.228$; $P \leq 0.05$), but not for gain in weight, fat mass, or percent body fat.

Table 1 Demographic and anthropometric characteristics of study population

	Mean ± SD
Number of patients	16
Restrictive type AN	12
Bulimic type AN	4
Sex	Female
Age (years)	27.8 ± 13.0
Height (m)	1.64 ± 0.08
Weight (kg)	40.5 ± 5.3
BMI (kg/m^2)	14.98 ± 1.04
Fat mass (%)	10.6 ± 5.2

AN anorexia nervosa

Table 2 Anthropometric measurements and BIA data at baseline and follow-up

	Day 0 Mean ± SD	Day 28 Mean ± SD	P value[a]
Weight (kg)	40.5 ± 5.3	44.2 ± 5.3	≤0.001
BMI (kg/m^2)	14.98 ± 1.04	16.38 ± 0.92	≤0.001
Fat mass (kg)	4.4 ± 2.5	5.5 ± 2.2	≤0.001
Fat mass (%)	10.6 ± 5.2	12.0 ± 4.5	≤0.001
Lean mass (kg)	36.8 ± 4.3	38.2 ± 4.4	≤0.001
ICW (l)	17.91 ± 2.27	19.10 ± 2.54	≤0.001
ECW (l)	9.05 ± 0.95	9.53 ± 1.36	≤0.001
ECW/ICW	0.51 ± 0.04	0.50 ± 0.03	0.313
ICW/weight	0.44 ± 0.03	0.43 ± 0.03	0.334
ECW/weight	0.22 ± 0.01	0.22 ± 0.01	0.109
R_{SUM} 50 kHz (Ω)	1,445 ± 206	1,387 ± 142	0.088
Xc_{SUM} 50 kHz (Ω)	132.6 ± 16.3	132.1 ± 27.8	0.779
Pa_{SUM} 50 kHz (°)	5.22 ± 0.73	5.44 ± 0.90	0.426

ICW intracellular water, *ECW* extracellular water, R_{SUM} whole body resistance, Xc_{SUM} whole body reactance, Pa_{SUM} whole body phase angle

[a] P values are given for the comparison of measures at baseline and follow-up by paired-samples t test

Table 3 Biochemical parameters at baseline and follow-up

	Day 0 Mean ± SD	Day 28 Mean ± SD	*P* value[a]
Glucose (mg/dl)	83.1 ± 8.0	79.8 ± 10.1	0.265
Insulin (μU/ml)	5.1 ± 3.4	5.1 ± 2.9	0.673
HOMA-IR	1.06 ± 0.75	1.03 ± 0.65	0.839
TAG (mg/dl)	84 ± 26	90 ± 34	0.511
Cholesterol (mg/dl)	189 ± 41	202 ± 58	0.153
HDL-C (mg/dl)	72 ± 24	70 ± 16	0.729
LDL-C (mg/dl)	100 ± 27	114 ± 45	0.076
FFA (mmol/l)	0.40 ± 0.48	0.27 ± 0.28	0.496
CRP (mg/l)	0.07 ± 0.17	0.34 ± 1.17	0.299
Leptin (ng/ml)	2.39 ± 5.92	4.01 ± 8.61	≤0.001
Adiponectin (ng/ml)	17.43 ± 6.09	22.15 ± 10.87	0.077
A-FABP (ng/ml)	32.56 ± 35.59	21.27 ± 13.68	0.035

HOMA-IR homeostasis model assessment of insulin resistance, *TAG* triacylglycerol, *HDL-C* HDL cholesterol, *LDL-C* LDL cholesterol, *CRP* C-reactive protein, *A-FABP* adipocyte fatty acid binding protein

[a] *P* values are given for the comparison of measures at baseline and follow-up by paired-samples *t* test

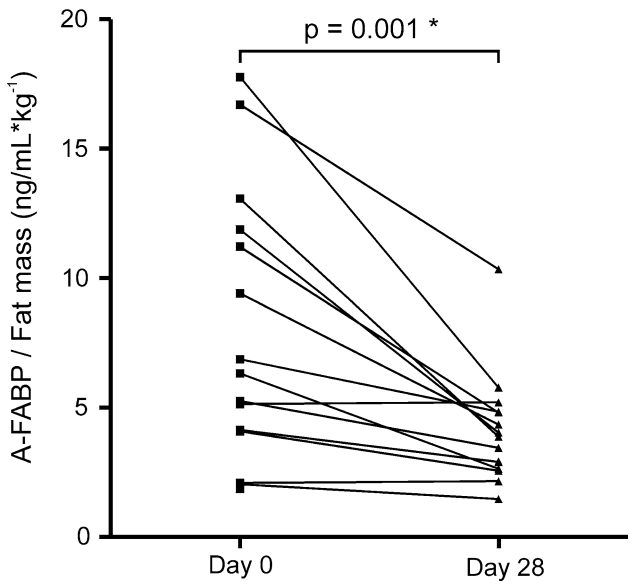

Fig. 1 Change of A-FABP per kilogram fat mass during early weight gain. *Asterisk* represents test probability determined by paired-samples *t* test

Discussion

The evaluation of changes in body composition in refed anorexic patients is a relevant issue as adequate weight restoration during inpatient treatment confers positive long-term outcome and presents as a crucial but challenging element in the treatment of anorexia nervosa [10].

In the present study all anorexic patients gained significantly weight during the first 28 days of refeeding, of which 40% were attributable to gain in fat mass. The literature describes a varying percentage of fat mass contributing to total weight gain ranging from 21 to 77%, depending on the body composition measurement method (skinfold thickness, Dual X-ray absorptiometry, BIA, underwater weighing) [7, 9, 18, 19, 21–23, 32]. With regards to the considerable fluctuations in lean mass that were observed in the majority of our patients during the study period, several factors may be involved. First, when transiting from a catabolic to an anabolic state fluid and electrolyte shifts lead to an expansion in extracellular water which is responsible for most of the changes in lean mass over the first few weeks of refeeding [31]. However, our data did not indicate such a disproportionate increase in extracellular water, as the ratio of extracellular to intracellular water and the proportion of both fluid compartments relative to total body weight remained constant during weight regain. Secondly, an increased level of exercise, seen in 40–80% of anorexic patients during their illness [5], which is then reduced in a controlled hospital setting, may result in loss of muscle mass during treatment.

Fatty acid binding proteins, which are abundantly expressed cytoplasmatic proteins, appear to play a crucial role in lipid signaling transduction by reversibly binding hydrophobic ligands such as saturated and unsaturated long chain fatty acids, eicosanoids, and other lipids [4, 35]. A-FABP is considered to be a circulating biomarker of adiposity linking obesity with components of the metabolic syndrome and may come to represent a diagnostic marker for these diseases in the future [33, 34]. However, despite these reports on associations between A-FABP plasma levels and obesity, insulin resistance, the metabolic syndrome and cardiovascular disease, the nature of plasma A-FABP has not been elucidated yet.

In prior studies which examined changes in A-FABP levels during pronounced weight loss, increases in A-FABP plasma levels paralleled loss of fat mass [6, 11]. This is likely secondary to an increased liberation of fatty acids and glycerol from the TAG storage droplet and their subsequent release into the blood stream due to restricted calorie intake. Adipocyte lipolysis is under tight regulation by hormones, i.e., catecholamines and insulin, of which secretion is under nutritional regulation. Increased lipolysis in anorexia nervosa is a consequence of insulin deficiency but also stimulated by catecholamines [3]. Both low insulin levels and high catecholamine levels lead to activation of protein kinase A and subsequent phosphorylation of cytoplasmic hormone-sensitive lipase (HSL) by increasing intracellular cyclic AMP concentration [12]. HSL hydrolyzes TAG, and with a higher specificity diacylglycerol [36]. On a cellular level, A-FABP forms complexes with HSL positioning A-FABP to bind fatty acids and facilitate lipolysis [26, 27]. In keeping with this mechanism,

A-FABP plasma levels were elevated in most of our patients at study entry after forced self-imposed weight loss. However, basal levels of A-FABP varied from 5 to 160 ng/ml among patients, indicating different degrees of lipolysis. Endogenous glycerol production, serving as a measure of lipolysis, was reported to vary considerably in patients with anorexia nervosa, presumably due to differences in stress hormone responses, caused by either starvation itself or the psychopathology of the disease [28]. The variation in A-FABP plasma levels was also reflected by the different individual amounts of adipose tissue after weight loss. For instance, in the patient with a plasma level of 5 ng/ml A-FABP adipose mass constituted only 5% of body weight, suggesting that fat metabolism was insufficient to provide FFA as the primary source of energy. In contrast, the A-FABP plasma level of 160 ng/ml might be the consequence of high lipolytic activity in the other patient whose fat mass constituted 20% of body weight. This is inline with the report of Xu et al. [34] that fat percentage is a determinant of circulating A-FABP concentrations. The initially high variation in plasma levels diminished in the course of treatment when fat mass began to increase and lipolysis was no longer required as an energy source. This observation is supported by the decrease of A-FABP concentrations per kilogram fat mass during weight gain and concomitant gain in fat mass.

The lack of statistically significant correlations between fat mass and A-FABP levels in the present study may be due to the relatively small study population, the short observation period, and the initially high variation in A-FABP concentrations. Additionally, the mean gain of 1.5 kg in fat mass over this time may be too small to observe a significant correlation unless an appropriately higher number of patients is recruited.

The peripheral adipose tissue derived hormone leptin which acts to signal changes in energy balance to the central nervous system, has an anorexigenic effect and promotes adipolysis [25, 30]. In conditions of negative energy balance, such as fasting or anorexia nervosa, leptin is negatively regulated, whereas in conditions of positive energy balance, such as overfeeding and obesity, leptin levels are elevated [24]. In the current study, low basal leptin levels significantly increased during weight recovery, which is in agreement with previous findings [1, 2, 8, 15, 17, 29]. Although statistically not significant, adiponectin concentrations were higher after 28 days of refeeding than before treatment. This initial increase in adiponectin levels during the first month of weight recovery in anorexia nervosa was also reported in a recent study with a larger group of patients monitored for 5 months, possibly reflecting an early stage of adipocyte differentiation and development characterized by an increase in adiponectin gene expression [17].

To our knowledge, this is the first prospective study investigating changes of A-FABP plasma levels in a cohort of female subjects with anorexia nervosa during early refeeding. Treatment resulted in a significant gain of fat mass which was accompanied by a significant decrease of A-FABP concentrations. Within 4 weeks A-FABP levels per kilogram fat mass decreased highly significantly which is compatible with previous reports on metabolic changes during weight gain in anorectic patients. In addition to our earlier investigation on A-FABP changes during pronounced weight loss, the present results indicate that changes in A-FABP plasma levels reflect alterations in nutritional status and subsequent changes in fat mass. However, further studies are warranted to further elucidate the role of A-FABP during weight changes as we have very little knowledge on the subject so far.

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