Cent. Eur. J. Med. • 7(3) • 2012 • 275-283
DOI: 10.2478/s11536-011-0153-7

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Central European Journal of **Medicine**

B-cell activating factor (BAFF) – a new factor linking immunity to diet?

Research Article

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Received 24 May 2011; Accepted 9 January 2012

Abstract: B cell activation factor (BAFF) is a recently discovered member of the TNF ligand superfamily secreted by adipocytes, previously linked to autoimmune and lymphoproliferative disease. The aim of this study was to investigate the relationship between BAFF plasma levels and the non-modified, usual dietary composition as well as obesity-related anthropometric parameters in a cohort of 58 obese and non-obese Central-European Caucasian individuals. We found that BAFF had an independent predictive role for percentage of body fat; moreover, BAFF levels were correlated with waist and hip circumference. BAFF plasma levels were also significantly correlated with investigated dietary composition based on the 7-day food records, as the BAFF levels correlated with the percentage of energy derived from the carbohydrates and with energy derived from the dietary fat. Our results suggest that BAFF may play a role in linking the immune status and metabolic response to diet.

Keywords: *BAFF • Obesity • Dietary composition • Diet • Anthropometry*

1. Introduction

The B cell activation factor (BAFF), also known as THANK, TALL-1 or BLys, is a recently discovered member of the TNF ligand superfamily (TNFSF13B) [1,2]; it is best known for its role in the survival and differentiation of B cells. The biological effects of this type II transmembrane protein are mediated mainly via specific receptors: B cell maturation antigen (BCMA/TNFRSF17), transmembrane activation and calcium modulator and cyclophilin ligand interactor (TACI/TNFRSF13B), and BAFF receptor (BAFF-R/TNFRSF13C) that are present on B cells, plasma cells, but also on specific subpopulations of T cells [3,4]. BAFF is generally produced by myeloid pathway cells, malignant B cells, activated T cells, and the stromal cells of the bone marrow [2,5-7].

In humans, BAFF has been linked mainly to systemic autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis [8-10]. However, BAFF expression has also been reported to increase during adipocyte differentiation [11], whereas BAFF expression was augmented by TNF-α treatment and decreased by rosiglitazone treatment in that study. Kim *et al.* [11] have also reported BAFF secretion to be surprisingly lower in *ob/ob* mice sera compared with controls. Furthermore, those authors reported a considerable difference in mRNA and protein expression between epididymal tissue and visceral adipose tissue [11]. In a study by other authors, the presence of all known BAFF receptors (BAFF-R, BCMA, and TACI) was confirmed in adipocytes, and their expression was upregulated during adipocyte differentiation [12]. To

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summarize, it is highly likely that, apart from its role in the immune system, BAFF can be also considered an adipokine, which might have potentially huge consequences for comprehension of immune mechanisms within the white adipose tissue (WAT). As the BAFF expression is tightly related to the adipose tissue, it probably plays an important role in development of the low grade inflammation that is characteristic of obesity.

To date, little is known about the relationship between BAFF and the diet. Fabris *et al* [13] reported elevated BAFF plasma levels in a small cohort of patients with coeliac disease, and concluded that BAFF might play a pathogenic role in its development. Jee *et al.* [14] observed a relationship between food allergens and BAFF levels in a cohort of children with atopic dermatitis, suggesting that food allergens are more important for atopic dermatitis development than are aeroallergens; however, dietary composition was not investigated in their study.

Previously, it has been suggested that daily fasting serum leptin levels are different when comparing individuals on a diet with a high glycemic index and versus a low-glycemic-index diet [15]. Also, it has been reported that leptin, which is produced by adipocytes present mainly in the perilymphonodal adipose tissue, promotes differentiation of TH1 cells and secretion of pro-inflammatory cytokines (e.g. IFN-γ, TNFα) [16], and that it is highly likely that there is a direct link between the BAFF secretion and leptin plasma levels. In the study by Kim *et al.* [11] that measured BAFF serum levels in lean and ob/ob mice, BAFF secretion was surprisingly decreased in leptin-deficient ob/ob mice – which are generally resistant to the induction of autoimmune diseases. Therefore, we hypothesized that there could be a relationship between circulating BAFF plasma levels and diet composition, mainly in terms of proportion of fat and carbohydrates in the diet.

The aim of this study was to investigate the relationship between plasma levels of BAFF and the non-modified, usualdietary composition in an obese and non-obese Caucasian Central-European population and to evaluate possible associations of BAFF plasma levels with anthropometric parameters related to obesity.

2. Material and methods

2.1. Study subjects

We recruited 58 unrelated Czech Caucasian individuals for the present study in a mass media campaign, as described previously [17]; the inclusion and exclusion criteria have also been described elsewhere [18]. The study was conducted according to the guidelines of the Declaration of Helsinki; all procedures involving human subjects were approved by the Committee for Ethics of Medical Experiments on Human Subjects, Faculty of Medicine at Masaryk University (Brno, Czech Republic). Written informed consent was obtained from all subjects and was archived.

The study cohort was subdivided into two subgroups: the obese arm consisted of 36 obese individuals (BMI ≥ 30 kg/m^2; mean BMI 43.97 ± 6.39 kg/m^2; mean age 50.7 ± 12.8 years). The non-obese arm consisted of 22 healthy non-obese control subjects with no history of childhood obesity or eating disorder (mean BMI 23.14 ± 2.68 kg/m^2; mean age 40.3 ± 10.3 years). All the study subjects were available for leptin, soluble leptin receptor (sObR), and BAFF analyses.

2.2. Anthropometric characteristics

All phenotypic measurements were performed according to the standardized protocol and included weight, height, BMI, lean body mass, fat mass, body fat, waist and hip circumferences, waist-to-hip ratio, and skinfold thickness measured on four different loci. The quality of the measurement was repeatedly monitored during the study. Body composition was assessed by bioelectrical impedance analysis using the single frequency bioimpedance analyser (BodyStat Ltd, Douglas, Isle of Man, UK) with the subject in a supine position. The height measurement was performed with a calibrated stadiometer, and weight (in light indoor clothes and without shoes) was measured with a precisely calibrated set of scales.

2.3. Dietary intake

Participants were furthermore advised to complete 7-day food records augmented by the food frequency questionnaire of Willet *et al* [19] that has been validated for the Central-European population [20]. Food intake data were obtained from the study subjects and were further analyzed to establish the percentage of daily energy intake from carbohydrates, fat, and protein, as well as total energy and macronutrient intake. The nutritional analyses were performed using the Nutrimaster Diet Analysis software (Abbott Laboratories, Abbott Park, IL, USA). Special attention was paid to extreme snacking behaviour (defined as higher than 25% daily energy intake from snacks), eventual dieting, extreme portion sizes, and irregularity in eating. The structure of the daily energy intake was also investigated: a snacking

index (established as a ratio of daily energy intake from snacks versus daily energy intake from the main meals) was calculated.

2.4. Determination of plasma BAFF, leptin and sObR

Venous blood samples were collected into tripotassium EDTA tubes after overnight fasting and immediately centrifuged at 1700 × g for 20 min, then stored at −80 ºC until analysis. Plasma BAFF, leptin and sObR levels were measured by commercially available sandwich ELISA kits (R&D Systems, Minneapolis, MN, USA) with a sensitivity of 3.4, 7.8 and 57 pg/ml, respectively. Plasma samples were 2-, 100- and 5-fold diluted with the applicable calibrator diluent immediately before the BAFF, leptin and sObR assay, respectively. The intra- and inter-assay precisions (CV) were less than 6.0% and 9.0% for BAFF assay, 3.3% and 5.4% for the leptin assay, and 6.1% and 8.6% for the sObR assay, respectively. BAFF values higher than the 97.5th percentile (1374 ng/ml) of the control plasma samples were considered to be elevated in this study.

2.5. Statistics

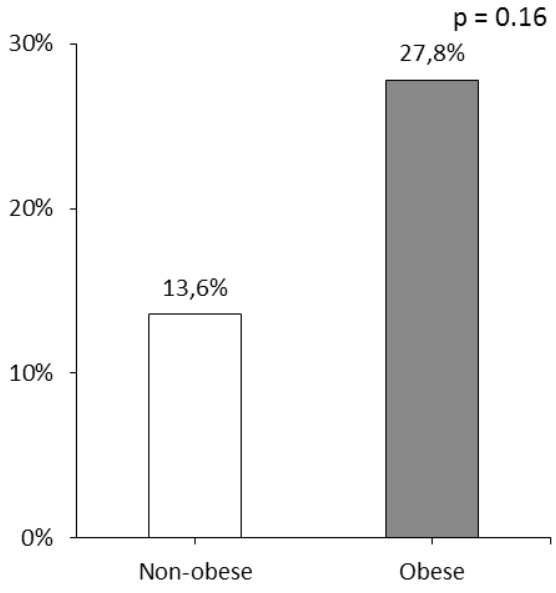
Where applicable, it was first determined whether the variable presented with a normal distribution using the Kolmogorov–Smirnov test, and in cases of skewed variables, logarithmic transformation and further normality testing were performed. For descriptive purposes, mean values and standard deviations are presented using untransformed values.

Statistical analysis was performed using the Mann–Whitney U-test, Kruskal-Wallis test, Fisher's exact test; post hoc Bonferroni's correction for multiple comparisons was employed where required. Univariate linear modelling assessed the relationship between BAFF and quantitative variables; multivariate linear models investigated the predictive role of BAFF on anthropometric and nutritional parameters.

Using sample tertiles, the nutrient variables were categorized in three groups of equal size (upper third, middle third and lower third). Each nutrient variable was then included in logistic regressions as a binary indicator, leaving one category as the reference.

Data analysis was performed using the Statistica v. 8.0 (Statsoft Inc., Tulsa, OK, USA) program package. Values of P <0.05 were considered statistically significant.

Figure 1. Percentage of individuals with elevated BAFF higher than the 97.5th percentile (1374 ng/ml) of the control plasma samples



3. Results

3.1. BAFF levels in obesity

The baseline clinical, anthropometric, and nutritional parameters as well as BAFF levels in the studied cohort are listed in Table 1. Elevated plasma BAFF levels were found in 27.8% of patients with obesity, which was significantly more than the 13.6% observed in the control group (Figure 1).

3.2. BAFF levels by gender

There were no significant differences in plasma levels of BAFF between males and females in our study; however, obese women presented with significantly higher BAFF levels than non-obese women (P = 0.003). When comparing obese males and obese females, the obese females presented higher BAFF levels compared with obese males (P = 0.03).

3.3. Correlation of BAFF levels with anthropometric findings

Table 2 presents anthropometric data stratified into three cohorts: non-obese (18 < BMI ≤ 30), obese (30 < BMI ≤ 40) and morbidly obese (BMI > 40) and the intra-group comparisons of the anthropometric parameters between these cohorts. The mean plasma BAFF levels

Table 1. Clinical, anthropometric and nutritional data in the obese and non-obese cohorts

	Non-obese (18 ≤ BMI < 30)		Obese (BMI > 30)		
	Female	Male	Female	Male	P-value
Subjects (n)	17	5	25	11	
Body composition					
Age (years)	40.2 ± 11.2	40.7 ± 7.9	52.9 ± 12.0	49.1 ± 14.7	< 0.001
BMI (kg/m2)	22.6 ± 2.5	25.0 ± 2.8	43.5 ± 5.7	45.2 ± 7.9	< 0.001
Body fat (%)	30.1 ± 6.7	16.2 ± 3.1	51.0 ± 6.3	39.3 ± 6.0	< 0.001
Dietary intake					
Energy (kJ)	5955 ± 632	8494 ± 1585	7140 ± 799	10050 ± 958	0.509
Protein (% energy)	14.1 ± 1.9	13.0 ± 1.0	15.8 ± 3.6	15.7 ± 3.3	0.007
Carbohydrates (% energy)	51.8 ± 4.8	53.5 ± 2.4	48.7 ± 6.7	48.7 ± 6.2	0.017
Fat (% energy)	34.2 ± 4.3	33.4 ± 2.7	35.5 ± 5.6	35.6 ± 5.1	0.220
Anthropometry					
Waist circumference (cm)	75.9 ± 7.8	87.4 ± 11.2	120.8 ± 12.4	135.8 ± 16.1	< 0.001
Hip circumference (cm)	96.6 ± 5.8	100.3 ± 8.3	134.7 ± 11.9	131.8 ± 15.1	< 0.001
Waist-hip ratio	0.79 ± 0.06	0.87 ± 0.07	0.90 ± 0.08	1.04 ± 0.08	< 0.001
Skinfold thickness (mm)					
Supraspinal skinfold	13.7 ± 4.2	10.4 ± 1.7	31.1 ± 10.9	31.4 ± 11.2	< 0.001
Subscapular skinfold	17.1 ± 5.1	15.0 ± 4.0	34.4 ± 9.2	35.9 ± 9.1	< 0.001
Biceptal skinfold	12.3 ± 3.7	8.0 ± 3.7	26.2 ± 8.1	24.9 ± 9.3	< 0.001
Triceptal skinfold	19.4 ± 5.2	13.4 ± 3.9	32.2 ± 5.7	29.5 ± 7.1	< 0.001
Sum of all skinfolds	62.5 ± 13.0	46.8 ± 9.4	122.6 ± 28.9	115.6 ± 34.2	< 0.001
Systolic blood pressure (mmHg)	112.3 ± 15.7	127.2 ± 8.8	144.0 ± 17.2	149.1 ± 19.9	< 0.001
Diastolic blood pressure (mmHg)	74.6 ± 9.1	80.2 ± 14.6	91.7 ± 12.8	97.5 ± 11.1	< 0.001
BAFF [pg/ml]	1007 ± 211	938 ± 118	1303 ± 333	1037 ± 210	

Results given as mean ± SD. P-value refers to the Mann-Whitney test for the comparison of the obese and non-obese cohort (males and females pooled together)

Table 2. Clinical and anthropometric data from the studied population in the study subgroups

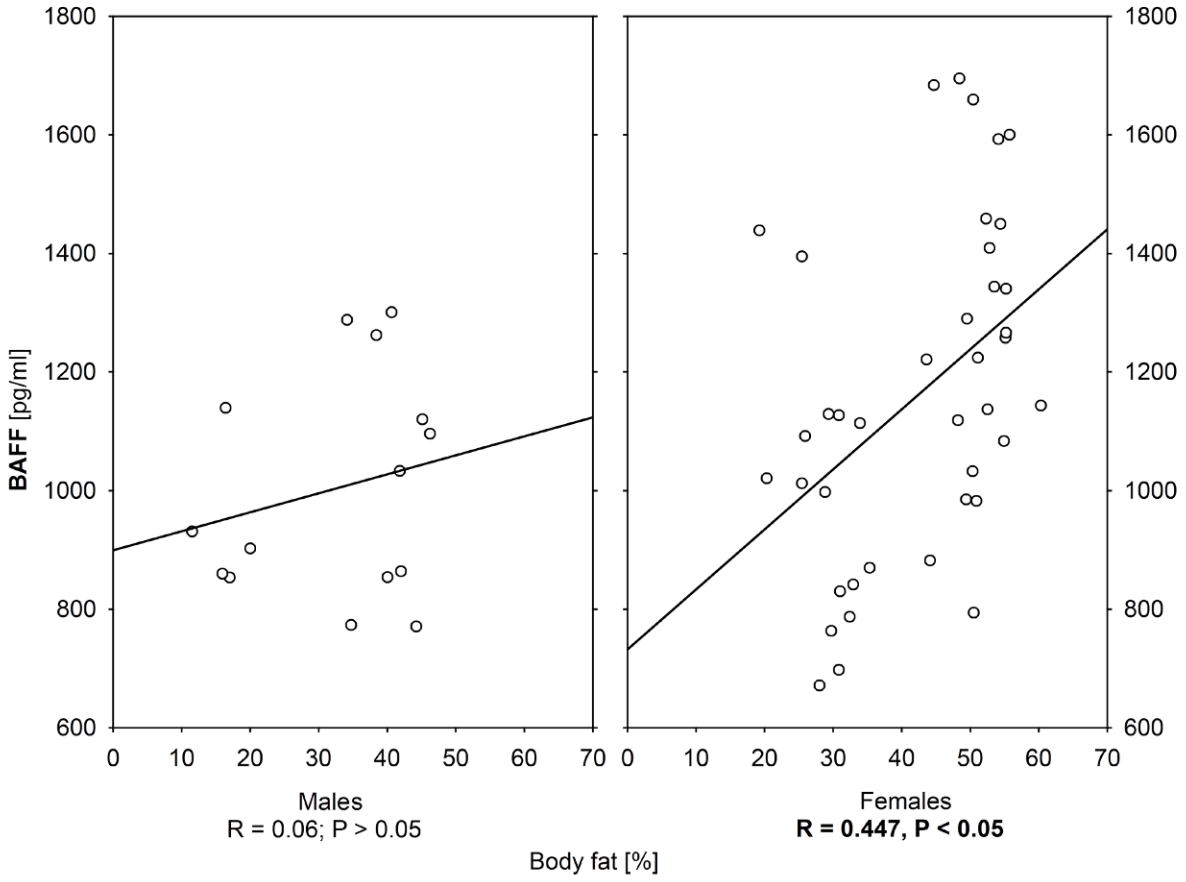
	Non-obese 18 ≤ BMI < 30	Obese 30 ≤ BMI < 40	Morbidly obese BMI ≥ 40	Total	P-value
Gender M/F	5/17	2/6	9/19	16/42	
Age (years)	40.3 ±10.3^{A,B}	55.3 ± 9.7^{A}	50.8 ±13.5^{B}	47.4 ± 13.1	0.004
BMI (kg/m^2)	23.1 ± 2.7^{a}	36.3 ± 4.2^{A}	46.2 ± 5.1^{a,A}	36.1 ± 11.5	< 0.001
% body fat	27.0 ± 8.5^{a}	40.6 ± 9.9	49.4 ± 6.6^{a}	39.7 ± 12.9	< 0.001
Waist circumference (cm)	78.5 ± 9.7^{a,b}	111.9 ± 14.2^{a}	129.2 ±13.3^{b}	107.6 ± 26.5	< 0.001
Hip circumference (cm)	97.5 ± 6.4^{a,A}	122.9 ±11.2^{A}	137.0 ±11.5^{a}	120.0 ± 20.8	< 0.001
Waist-to-hip ratio	0.80 ± 0.07^{a,A}	0.91 ± 0.08^{A}	0.95± 0.11^{a}	0.89 ± 0.11	< 0.001
Sum of skin fold thicknesses (mm)	58.9 ± 13.8^{a}	99.3 ± 21.2	128.3 ± 24.1^{a}	98.0 ± 37.4	< 0.001

Results given as mean ± SD. P-value refers to the Kruskal-Wallis test for the three groups (non-obese, obese, morbidly obese). The inter-group differences were tested using the Tukey-Kramer´s method with a correction for α.
^{A,B} – $P < 0.05$ when comparing the pairs of the groups (non-obese x obese, non-obese x morbidly obese, obese x morbidly obese) on the same line;
^{a,b} – $P < 0.01$

are reported in Table 1, obese females had the highest BAFF levels; however, these observations lacked statistical significance.

In unvariate linear modelling, BAFF was significantly correlated with waist circumference (R = 0.432, $P < 0.05$) and body fat (R = 0.447, $P < 0.05$); this data is presented in Figure 3. In multivariate regression modeling across the entire cohort, BAFF expressed an independent prediction role for BMI (β = 0.380, $P = 0.005$; all P values adjusted for age, gender, smoking status). Moreover, BAFF had an independent predictive role for percentage of body fat (β = 0.310, $P = 0.009$), waist

Figure 2. Correlation between BAFF and percentage of body fat by gender. The correlation coefficient was determined using the Pearson's test; the observed trend is indicated by the solid line.



circumference (β = 0.312, *P* = 0.01), and hip circumference (β = 0.392, *P* = 0.003), but not on waist-to-hip ratio (WHR) (β = 0.06, *P* = 0.547).

3.4. Correlation of BAFF levels with nutritional parameters

In the multivariate regression modeling, BAFF plasma levels were significantly correlated with percentage of energy derived from the carbohydrates (β = 0.38, *P* = 0.01), whereas BMI was also a significant predictor (β = −0.30, *P* = 0.04). BAFF plasma levels also served as an independent predictor for the proportion of energy derived from the dietary fat (β = −0.36, *P* = 0.02) independently of age, gender, smoking status, and BMI. No significant associations of BAFF levels with total daily energy intake, percentage of energy derived from proteins, dietary fibre intake, or dietary cholesterol intake were observed.

As BAFF plasma levels were significantly correlated with the percentage of energy derived from carbohydrates and fats, we investigated the differences in BAFF plasma levels between the highest, middle, and lowest tertile of carbohydrate/fat intake (Table 3). The results of the tertile analysis did not reveal any significant ORs of the categories we investigated (upper, lower tertile of carbohydrate/fat intake) for elevated BAFF in plasma. No association between BAFF plasma levels and abnormal eating behavior (irregular food intake, extreme portion sizes, increased snacking index) was observed.

3.5. Correlation of BAFF with leptin and soluble leptin receptor

In multivariate regression models for prediction of BMI using the available plasma levels of leptin, sObR, and BAFF, only BAFF plasma levels were significantly correlated with BMI (β = 0.438, *P* = 0.003). No significant correlation of BAFF plasma levels with plasma leptin or sObR was observed.

Furthermore, the bivariate analysis was performed to assess possible associations of LEP, sObR and the LEP:sObR ratio, and BAFF and dietary characteristics. To control for possible confounders, the results from the bivariate correlation analysis were consecutively explored using multivariate analysis with logarithmically

Figure 3. Correlation between BAFF and waist circumference by gender. The correlation coefficient was determined using the Pearson's test; the observed trend is indicated by the solid line.

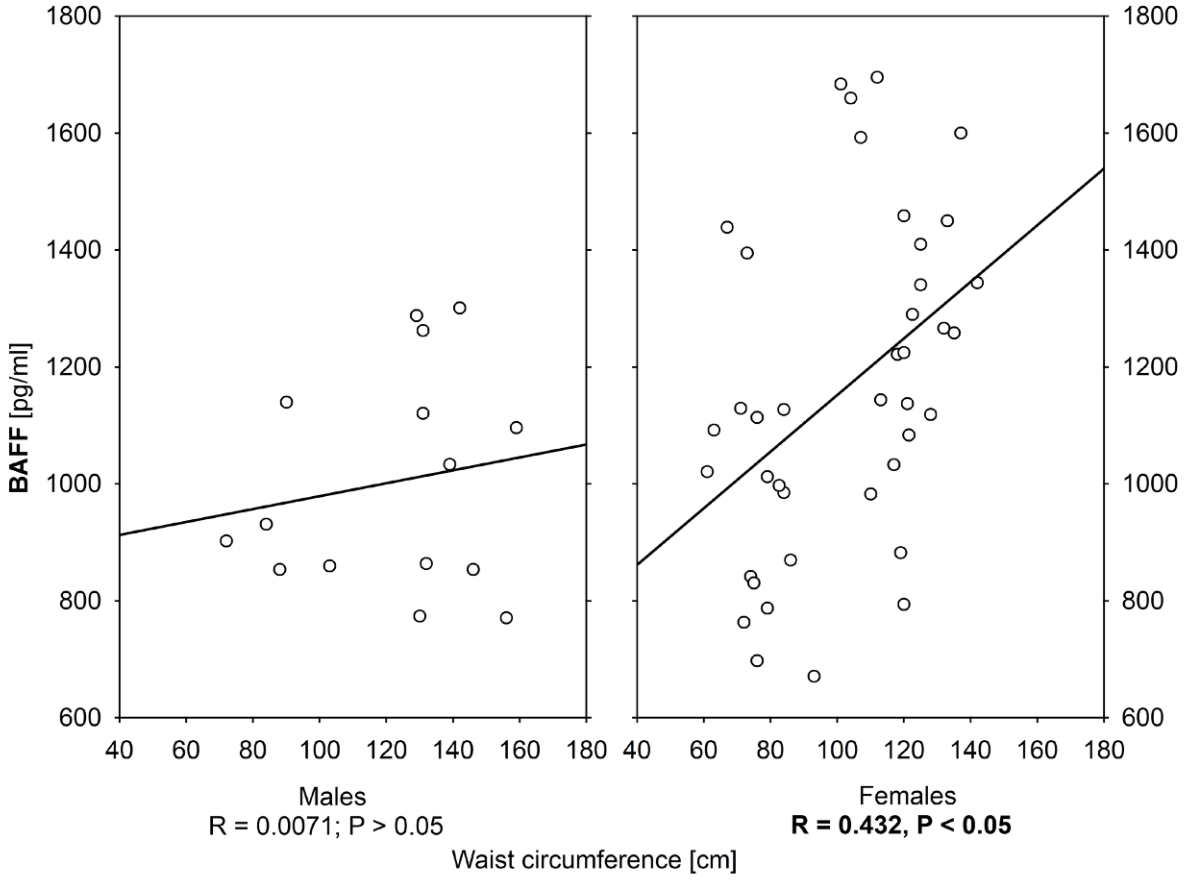


Table 3. Association between the upper and lower tertiles of fat and carbohydrate intake for elevated or normal BAFF plasma levels in the study cohorts

FATS	BAFF elevated	BAFF not elevated	OR	95% CI	P -value
Total	13	45	0.406	0.084–1.947	0.22
Upper tertile	3	16			
Lower tertile	6	13			
CARBOHYDRATES	**BAFF elevated**	**BAFF not elevated**	**OR**	**95% CI**	**P -value**
Total	13	45	0.254	0.044–1.475	0.11
Upper tertile	2	17			
Lower tertile	6	13			

OR – odds ratio,
CI – confidence interval, elevated values defined as BAFF plasma levels higher than the 97.5th percentile (1374 ng/ml) of the control plasma samples

transformed plasma LEP and sObR and LEP: the sObR ratio regressed on total energy intake as well as on the energy intake provided by each macronutrient. However, no significant associations were observed in these analyses.

4. Discussion

BAFF represents a fundamental cytokine of the T-independent IgA class-switching recombination system through the interaction with the common receptor TACI shared also by other proteins, such as APRIL [21]. In this

study, we report elevated BAFF levels among Central-European Caucasian patients with obesity, and we also demonstrate substantial dependence of differences in BAFF plasma levels on gender.

The role of BAFF in obesity is unclear, and it seems to be related to the role of BAFF in the low-grade inflammation typical of obesity. It has been recently demonstrated that BAFF is expressed in adipocytes and that BAFF expression is augmented via TNF-alfa treatment [11]. Moreover, all the three types of known BAFF receptors (BAFF-R, BCMA, and TACI) are expressed in adipocytes and are upregulated during adipocyte differentiation. In agreement with this, is the expression of BAFF mRNA and protein reported in *ob/ob* mice [11].

In a recent study by Hamada et al [22], BAFF levels in the sera and visceral adipose tissue (VAT) of obese mice were investigated. In obese mice, the BAFF levels were preferentially increased in VAT and sera compared with these levels in normal control mice. BAFF also induced alterations in the expression levels of genes related to insulin resistance in adipocytes *in vivo*. In addition, BAFF directly affected the glucose uptake and phosphorylation of insulin receptor substrate-1 in adipocytes. Therefore, the present authors conclude that paracrine BAFF and BAFF-receptor (BAFF-R) interaction in VAT can lead to impaired insulin sensitivity via inhibition of insulin signaling pathways and alterations in adipokine production.

It is difficult to define whether the observed high BAFF phenotype in obese individuals is a priori linked to obesity as a result of a specific shared genetic background, or whether it results from consecutive changes in cytokine profiles during obesity development. Previously, it has been suggested that limited BAFF signaling leads only marginally towards selection against higher affinity autoreactive B cells, whereas BAFF overexpression leads to broad tolerance escape and positive selection of autoreactive cells. In animal experiments, the B cells in BAFF/3H9 mice were elevated in number, used a broad L chain repertoire, including L chains generating high-affinity autoreactivity, and produced abundant autoantibodies [23], making BAFF an outstanding candidate for being a factor linking obesity and autoimmune diseases. It seems to be highly likely that increased BAFF levels favor the development of autoimmune and also lymphoproliferative diseases, which is also consistent with empiric observations that obese individuals are more prone to certain types of autoimmune diseases and cancer [24]. It has also been reported that the presence of an underlying IgA deficiency (IgAD) characterized by increased BAFF levels could represent a further risk factor for lymphoproliferative diseases in course of autoimmune diseases, such as systemic rheumatologic diseases, suggesting also a BAFF-targeted therapeutic interventions might be of advantage under specific circumstances, such as IgAD [25].

Our results show that plasma BAFF levels are gender-dependent, proportional to BMI, waist circumference, percentage of body fat, and significantly different between obese and non-obese individuals. This is consistent with observations that adipocytes are capable of producing BAFF and that they carry BAFF receptors capable of binding BAFF [3,4]. The pivotal role of BAFF in adipogenesis has recently been proposed [12] and the site-dependant differences in BAFF expression might possibly contribute to differences in body fat distribution, making patients with higher BAFF circulating levels more prone to develop abdominal obesity than the others.

In this study, we also observed multiple associations of BAFF plasma levels with dietary composition parameters, the possible explanation of which could be the presence of a leptin-BAFF axis, as proposed recently by Kim *et al.* [11]. Decreased responsiveness to leptin was documented in mice fed a high-fat diet (HFD), probably in relation to gender and/or duration of exposure to diet and/or the strain of mice [26,28]. The reduced activity of STAT-3 in lymphocytes of mice kept on an HFD is consistent with prior reports showing decreased STAT-3 activity in the hypothalamus of HFD mice [29]. This effect of an HFD has recently been found to be associated, at least in part, with an increased level of the suppressor of cytokine signaling 3 (SOCS3), acting also as an inhibitor of leptin signaling [29]. In the study by Papathanassoglou *et al.* [30], ObR/STAT-3-mediated signaling in T lymphocytes was decreased in the diet-induced obese mouse model of obesity and leptin resistance. This research group demonstrated that the leptin receptor (ObR) is expressed on normal mouse lymphocyte subgroups and that leptin plays a role in lymphocyte survival as it alters the ObR/STAT-3-mediated signaling in T cells in relation to the proportion of fat in the diet. On the whole, the data in the Papathanassoglou *et al.* study support the hypothesis that nutrition status acting via leptin-dependent mechanisms might significantly alter the strength and quality of the immune response, and based on our data, it can be suggested that BAFF is a missing piece in this pathway.

The major limitation of our study is its failure to find a significant association between circulating BAFF and leptin levels, which is detrimental to the study hypothesis. However, this study was performed on a small population sample, and we presume the effect could be observed on a larger cohort. Moreover, some of the variations in diet parameters could be at least partially attributed to seasonal variation, and therefore, another

study in a prospective design investigating food records and BAFF levels in various seasons of the year would be also advantageous. Finally, the lack of observation of an association between circulating BAFF and leptin levels does not exclude presence of other mechanisms linking the BAFF plasma levels to dietary composition observed in this study.

In conclusion, we report here multiple associations of BAFF plasma levels with anthropometric determinants of obesity as well as with dietary composition in the Caucasian Central-European population. The results provide some evidence that BAFF might play an important role in linking body composition and risk of autoimmune or malignant diseases.

Acknowledgement

Each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript, in accordance with the definition of an author as stated by the International Committee of Medical Journal Editors.

The present study was supported by a project of the Danone Institute of the Czech Republic (DANONE/2007) focused on genetic variability of adipokines in obese individuals.

The authors are grateful to Jolana Lipková and Marian Hlavna for excellent technical assistance. We thank to Katerina Heczkova, Zlata Piskackova and Lenka Kucerova for their assistance in processing and analysing food records.

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