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The circulating PBEF/NAMPT/visfatin level is associated with a beneficial blood lipid profile

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Abstract Visfatin with the official gene name pre-B cell colony-enhancing factor 1 (PBEF) and the protein name nicotinamide phosphoribosyltransferase (NAMPT) is a recently discovered adipocyte-secreted protein that was shown by some to be associated with visceral fat and insulin resistance. To explore the link between PBEF/NAMPT/visfatin and lipid metabolism, we analyzed the relation of its plasma level with several parameters of adiposity, insulin resistance and the circulating blood lipid profile in a group of general population (n=40) and a group of subjects who are genetically predisposed to insulin resistance and hyperlipidemia (n=35). In both groups and pooled cohort, PBEF/NAMPT/visfatin lacked association with whole body adiposity, but correlated positively with HDL-cholesterol and negatively with triglycerides. The data suggested a negative correlation of the PBEF level with visceral fat and insulin resistance. But this negative correlation completely disappeared after adjustment for lipid profile. We concluded that circulating PBEF/NAMPT/visfatin level is an indicator of beneficial lipid profile in non-diabetic Caucasian subjects. The relation to lipid metabolism does not depend on visceral obesity and insulin resistance, but may be linked to its enzymatic function in NAD metabolism.

Keywords HDL-cholesterol · Insulin resistance · NAD metabolism · Triglycerides · Visceral adiposity

Abbreviations

BMI	body mass index
FCHL	familial combined hyperlipidemia
HOMA	homeostasis model assessment
NAD	nicotinamide adenine dinucleotide
NAMPT	nicotinamide phosphoribosyltransferase
PBEF	pre-B cell colony-enhancing factor 1

Introduction

Visfatin is a recently discovered adipocyte-secreted protein that was shown to be associated with visceral fat in humans and rodents [1]. Visfatin was also shown to mimic the effect of insulin with the same efficacy in rodent cells in vitro and in mouse models [1]. However, subsequent studies in human subjects reported conflicting results with regard to its relation with adiposity [2–4], subcutaneous or visceral fat [2, 3], and insulin resistance [3–5], suggesting that the role of this protein in the development of obesity and insulin resistance remains unclear.

Visfatin is a rediscovery of the cytokine-like protein pre-B cell colony-enhancing factor 1 (PBEF[1]) [6]. It was also

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[1] In the remainder of the text, PBEF was used to refer to the protein PBEF/NAMPT/visfatin.

identified as cytosolic nicotinamide phosphoribosyltransferase (NAMPT), demonstrated by in vitro, in vivo, and structural studies [7–9]. This enzyme is involved in nicotinamide adenine dinucleotide (NAD) biosynthesis [8].

Visceral fat, together with insulin resistance, contributes to an abnormal lipid metabolism [10]. In view of the possible association of PBEF with adipose tissue and insulin resistance, we wondered if the circulating level of PBEF could be related to lipid metabolism in humans. We analyzed the relation of plasma PBEF with several parameters of adiposity, insulin resistance, and with the plasma lipid profile in Caucasian subjects from the general population. In addition, we used another Caucasian group of subjects with predisposed lipid metabolism disorder to strengthen the findings. In this case, familial combined hyperlipidemia (FCHL) family relatives were chosen because FCHL is a disorder of lipoprotein metabolism in the presence of insulin resistance, and it is known that the accumulation of abdominal fat, especially visceral fat, is highly prevalent in FCHL families [11]. To avoid the influence of type 2 diabetes [4, 5], only non-diabetic subjects were enrolled in this study.

Materials and methods

Subjects

The general population group is composed of 40 Caucasian non-diabetic genetically independent males and females. They were extracted from the spouses databank of FCHL families [12] to constitute a broad range of body mass index (BMI). Thirty-five non-diabetic age-matched and gender-matched Caucasian FCHL family members were recruited for the FCHL relatives group. They were selected to cover a broad range of BMI as well and were drawn evenly from 16 unrelated families to avoid profound genetic influences from a single family. All subjects visited the Maastricht research clinic between 2003 and 2005 where the plasma samples were collected. The study protocol has been described in detail elsewhere [12]. Any lipid-lowering medication had been withdrawn during the last 2 weeks before blood sampling. The Medical Ethical Committee of University Hospital Maastricht approved the study, and all subjects gave written informed consent.

Anthropometrical measurements

Body weight, height, and body mass index (BMI) were measured in fasting state as described previously [11]. The skinfold thickness of biceps, triceps, subscapular and suprailiac regions was measured, and percentage body fat was derived from the sum of the four skinfold measurements using the method of Durnin and Womersley [13].

The size of subcutaneous adipose tissue and visceral adipose tissue were measured with an ultrasound method as described elsewhere [12], which has been validated [14].

Biochemical measurements

Fasting venous blood samples were collected in pre-cooled EDTA vacutainer tubes and immediately processed. EDTA–plasma aliquots were stored at −80°C until analysis. Triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol, ApoB lipoprotein, glucose, and insulin were measured as described previously [11]. The homeostasis model assessment (HOMA) score was calculated as an index of insulin resistance [15]. PBEF was measured using a commercial enzyme immunoassay kit (Phoenix, Belmont, NY, USA) according to the manufacturer's instruction. In this assay, the blood samples were threefold diluted. Samples were measured in duplicate and the average was used in the data analysis. The intra-assay and inter-assay coefficients of variation were 12% and 17%, respectively. The detection limit was 1 ng/ml.

Statistic analysis

All analyses were performed with SPSS 12.0 (SPSS, Chicago, IL, USA). All values are expressed as the mean±standard deviation (SD). Variables significantly deviating from normal distribution were logarithmically transformed. For comparing the males and females inside the group, independent-samples *t*-test was used. For comparing the mean of the groups, age-adjusted and gender-adjusted *t*-test was used. The associations among the parameters were assessed by age-adjusted and gender- adjusted partial correlation analysis within the groups, and further group identity-adjusted analysis in the pooled subjects. Subsequently, for parameters of a correlation with PBEF at a significance level <0.10 in the pooled cohort, multiple linear regression analysis was performed to assess the independent relation. Statistical calculations were performed two-tailed and a p value <0.05 was considered statistically significant.

Results

Characteristics of the subjects

Both individually and combined, the general population and FCHL relatives groups comprised a broad range in adiposity: BMI was 20.0–35.6 for the former and 21.0–40.0 for the latter. The same held true for insulin resistance. The HOMA score ranged from 0.43 to 4.16 and from 0.61 to 7.68, respectively. By definition, FCHL relatives had higher

plasma concentrations of triglycerides and cholesterol. As expected, additional differences were seen in adiposity, especially intra-abdominal (visceral) adiposity, and insulin resistance. However, the average plasma PBEF levels did not differ between the two groups (Table 1). In both groups, there was some difference between male and female subjects on the parameters of adiposity and lipid profile, but no difference with respect to the plasma PBEF level.

The relation between plasma PBEF level, adiposity, insulin resistance, and plasma lipid profile

The correlations after adjusting for age and gender between BMI or visceral fat and HOMA score or lipid profile were as expected (Table 2). Although there was no essential difference between the two groups, the relation between visceral fat and HDL-cholesterol was weaker in the group of FCHL relatives, which could be caused by the heterogeneity of predisposing genetic factors that specifically affect the HDL-cholesterol level. Additional relations between metabolic parameters were also as anticipated; both in the general population and FCHL relatives groups. BMI and visceral adipose size were highly correlated (r=0.622, p< 0.001 and r=0.577, p<0.001, respectively), as were total plasma triglycerides and HOMA score (r=0.486, p=0.002 and r=0.441, p=0.010, respectively), while a strong negative association was observed between triglycerides and HDL-cholesterol (r=−0.404, p=0.010 and r=−0.602, p<0.001, respectively). These results confirm that, despite a relatively small sample size, all known relations behaved as expected.

In the general population group, plasma PBEF level was negatively correlated with visceral adipose depot size, but not associated with other adiposity indicators, including BMI, body fat percentage, and size of subcutaneous adipose depots. The PBEF in this group was negatively, but not significantly, correlated with the HOMA score as a measure for insulin resistance. However, PBEF correlated positively with HDL-cholesterol and negatively with triglycerides (Table 3). In the FCHL relatives group, plasma PBEF level showed similar correlations with HDL-cholesterol and triglycerides, and was not correlated with any of the other parameters (Table 3 and Fig. 1).

To assess the independent relation, we performed multiple linear regression. Because the correlations were similar in both groups, we pooled the data with adjustment for group identity to increase the power. In the pooled data, HDL-cholesterol, $\log_{10}$triglycerides, $\log_{10}$HOMA, and $\log_{10}$visceral fat size were significantly correlated with PBEF level. When HDL-cholesterol, $\log_{10}$triglycerides, $\log_{10}$HOMA, and $\log_{10}$visceral fat size together with body fat percentage, age, gender, and group identity were entered as independent variables into a model with $\log_{10}$PBEF as the dependent variable, multiple linear regression showed that HDL-cholesterol, but not body fat percentage, visceral fat size or HOMA score, was an independent predictor of plasma PBEF. Age and gender did not show significant

Table 1 Anthropometrical and biochemical characteristics of the subjects

	General population (n=40)			FCHL relatives (n=35)			p[a]
	Male	Female	p[b]	Male	Female	p[b]	
Number	21	19		15	20		n.s.[c]
Age (years)	50.6±11.2	47.4±7.3	n.s.	49.8±10.2	53.8±7.3	n.s.	n.s.[d]
BMI (kg/m^2)	27.6±4.0	26.0±4.4	n.s.	28.0±4.5	31.6±4.5	0.027	0.007
Body fat percentage	28.6±6.1	37.6±5.9	<0.001	28.9±4.3	42.2±3.4	<0.001	n.s.
Subcutaneous fat (cm)	2.28±1.06	3.33±1.18	0.005	2.31±0.90	3.79±1.10	<0.001	n.s.
Visceral fat (cm)[e]	9.00±2.71	6.36±1.47	0.001	9.90±3.43	10.12±2.91	n.s.	0.001
HOMA score[e]	1.37±0.93	1.44±0.87	n.s.	2.51±1.76	2.99±1.28	n.s.	<0.001
Total cholesterol (mmol/l)[e]	5.19±0.80	5.30±0.94	n.s.	6.26±1.68	6.50±1.45	n.s.	0.001
Triglycerides (mmol/l)[e]	1.59±0.83	1.24±0.51	n.s.	2.61±1.68	2.76±1.64	n.s.	<0.001
HDL-cholesterol (mmol/l)	0.92±0.20	1.04±0.22	n.s.	0.76±0.19	0.92±0.21	0.032	0.007
LDL-cholesterol (mmol/l)[e]	3.56±0.77	3.71±0.87	n.s.	4.32±1.57	4.36±1.30	n.s.	0.029
ApoB (g/l)[e]	0.96±0.18	1.08±0.29	n.s.	1.18±0.29	1.31±0.25	n.s.	0.001
PBEF (μg/ml)[e]	39.3±12.8	35.8±11.0	n.s.	40.9±13.7	39.7±13.5	n.s.	n.s.

Data are expressed as the mean±SD.
n.s.: not significant
[a] Age-adjusted and gender-adjusted *t*-test for the difference between the means of the groups.
[b] Independent-samples *t*-test for the difference between the means of the males and females inside the group.
[c] Only age-adjusted.
[d] Only gender-adjusted.
[e] Log transformed data were used in *t*-test.

Table 2 Correlation (age-adjusted and gender-adjusted) between adiposity and the measures of insulin resistance and lipid metabolism

		General population		FCHL relatives	
		BMI	Visceral fat size[a]	BMI	Visceral fat size[a]
HOMA score[a]	*r*	0.514	0.505	0.449	0.545
	p	**0.001**	**0.001**	**0.009**	**0.001**
Total triglycerides[a]	*r*	0.391	0.655	0.063	0.378
	p	**0.015**	**<0.001**	0.726	**0.030**
HDL-cholesterol	*r*	−0.260	−0.339	−0.299	−0.183
	p	0.115	**0.038**	0.091	0.307

The bold *p* values are significant.
[a] Log transformed data.

influence on the PBEF. However, the group identity made significant contribution to the model. This model could explain approximately 30% of the variance in plasma PBEF level (Table 4).

Discussion

The aim of the present study was to test the link between PBEF and lipid metabolism. Our results showed that in non-diabetic human subjects, plasma PBEF level is correlated to a high HDL-cholesterol/low triglyceride plasma lipid profile. This relation is conserved in subjects predisposed to a disorder of lipoprotein metabolism in the presence of insulin resistance (FCHL relatives). Although the size of the study cohorts was limited, the repeated finding corroborates that circulating PBEF has a relation with lipid metabolism in humans.

The significant associations of circulating PBEF with HDL-cholesterol and triglycerides in Caucasians have not been reported before. Very recently, Smith et al. reported that non-fasting serum PBEF level correlated positively to HDL-cholesterol and apolipoproptein A1 in Asian Indians; but this was not replicated in Caucasians [16]. The difference between their result on Caucasians and ours is probably caused by the non-fasting samples used in their study while our results were obtained from fasting state. The use of fasting samples additionally allowed us to detect the correlation with plasma triglycerides. Together, it indicates that the relation between circulating PBEF and HDL-cholesterol may be universal: in Asians and in Caucasians, in the general population, and in the subjects with genetic predisposition for dyslipidemia. In the study of Pagano et al. [3], the relation between PBEF and lipid profile was not analyzed. However, the Caucasian obese group that had a significantly lower level of HDL-cholesterol and higher level of triglycerides also showed a significantly lower level of plasma PBEF compared to the lean group. This supports our findings.

The relation between PBEF and lipid profile may be explained in the light of the cytosolic function of PBEF as a nicotinamide phosphoribosyltransferase (NAMPT). NAD has been established as a molecule, similar to ATP, that plays an important dual role as energy and signal transducer [17]. This enzyme salvages the nicotinamide that is formed during NAD metabolism to replenish the cellular NAD

Table 3 The correlation coefficients (age-adjusted and gender-adjusted) between plasma PBEF level and other parameters

	General population		FCHL relatives		Pooled[a]	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.009[b]	0.957[b]	0.211[b]	0.230[b]	0.103[b]	0.388[b]
BMI	−0.033	0.846	−0.298	0.092	−0.158	0.369
Body fat percentage	−0.209	0.207	−0.202	0.259	−0.207	0.084
Subcutaneous fat size	−0.040	0.811	0.230	0.198	0.049	0.683
Visceral fat size[c]	−0.345	**0.034**	−0.256	0.150	−0.269	**0.023**
HOMA score[c]	−0.278	0.092	−0.230	0.198	−0.245	**0.039**
Total cholesterol[c]	−0.169	0.309	−0.130	0.471	−0.144	0.229
Triglycerides[c]	−0.402	**0.012**	−0.465	**0.006**	−0.408	**<0.001**
HDL-cholesterol	0.469	**0.003**	0.403	**0.020**	0.439	**<0.001**
LDL-cholesterol[c]	−0.138	0.408	0.023	0.900	−0.073	0.547
ApoB[c]	−0.293	0.074	−0.046	0.799	−0.182	0.129

The bold *p* values are significant.
[a] Adjusted for group identity in pooled groups.
[b] Only adjusted for gender.
[c] Log transformed data.

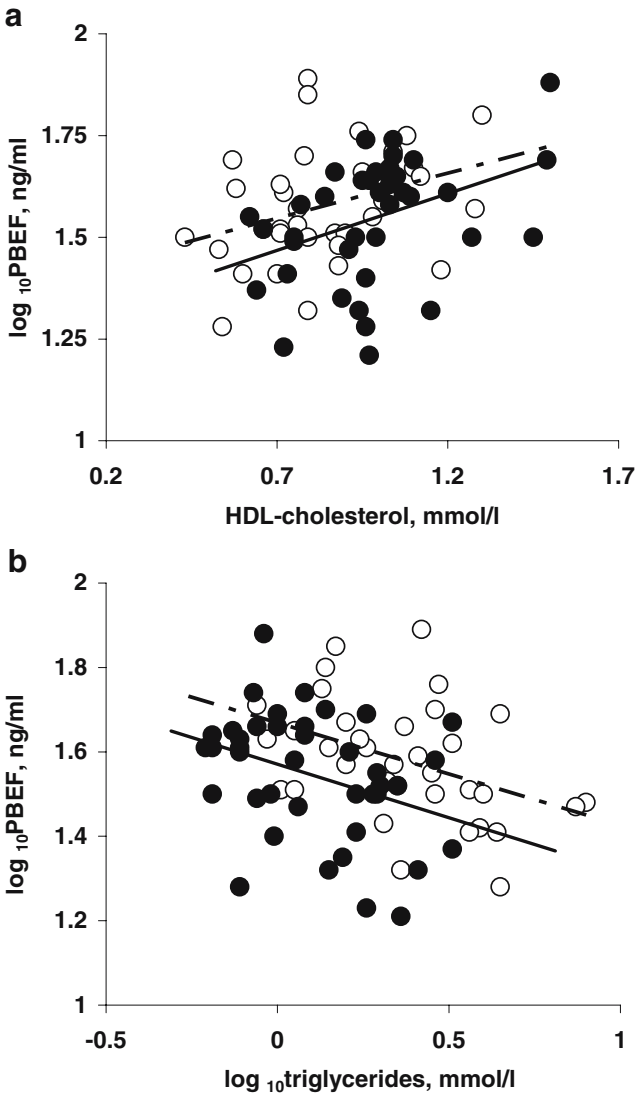

Fig. 1 Scatter plot for plasma PBEF level and lipid profile (**a** HDL-cholesterol, **b** triglycerides). *Filled dots* and *regression line*: the general population group. *Empty dots* and *dashed regression line*: the FCHL relatives group

level. This pathway may have beneficial impact on aging and longevity [9, 18]. It is interesting to note that it has been observed that oral administration of nicotinamide significantly increased cellular NAD level and serum HDL-cholesterol level in hemodialysis patients. The change of HDL-cholesterol correlated significantly with the change of NAD concentration in total blood cells [19]. Another NAD biosynthesis substrate, nicotinic acid, has been reported as the most potent agent for raising HDL-cholesterol [20]. Altogether, these observations strongly suggest that maintenance of the beneficial high HDL-cholesterol/low plasma triglycerides phenotype [21] may be associated with NAD metabolism. Our finding on the association of circulating PBEF with the plasma lipid profile implies that PBEF may serve as the link between those two processes. Presently, it is unclear how the cytosolic function of this protein is reflected in its extracellular level. It has been suggested that the release of PBEF into the culture medium in in vitro studies is most likely due to cell leakage [8]. But the significant amount of the circulating level suggests that extracellular PBEF is not merely derived from cell leakage. Therefore, the source of circulating PBEF still needs to be defined.

Remarkably, the group identity (i.e. general population or FCHL relatives) was significantly associated with plasma PBEF level in the multiple linear regression model, despite the comparable plasma levels of PBEF in the general population and FCHL relatives. This suggests that the genetic predisposition for FCHL may influence the circulating level of PBEF. The relation between FCHL and PBEF may be evaluated in a larger FCHL population including other un-identified factors beyond our model in future investigations, which is beyond the scope of our present study.

Visceral adiposity and insulin resistance are not the reason behind the relation between PBEF and lipid metabolism. We could not find the associations of circulating PBEF with general adiposity and insulin resistance in either of the present groups. This could be due to the limited cohort size. However, this also implies that the link between PBEF and lipid metabolism may be related more to the real role of PBEF. Our result on the negative correlation between the circulating PBEF and visceral fat in the general population group confirmed the previous study in healthy subjects [3]. Our pooled data suggested a negative correlation of the PBEF level with visceral fat and insulin resistance, but they completely disappeared

Table 4 Multiple linear regression model-corrected correlation between plasma PBEF level and other parameters

Model R^2	Model p		Standardized coefficient	p
0.286	0.003	Group identity[a]	0.374	**0.005**
		Gender	−0.126	0.521
		Age	0.190	0.116
		Body fat percentage	−0.169	0.408
		Visceral fat size[b]	−0.045	0.804
		HOMA score[b]	0.026	0.871
		Triglycerides[b]	−0.265	0.115
		HDL-cholesterol	0.337	**0.013**

The bold p values are significant.
[a] General population=0 and FCHL relatives=1 in the dummy variable of group identity.
[b] Log transformed data.

after adjustment for lipid profile. Although PBEF has been regarded as an adipose tissue-related hormone, studies show that PBEF is ubiquitously expressed in the body. Among different human tissues, the maximum gene expression was found in the liver and peripheral blood leukocytes [6, 22]. A large-scale analysis of the human transcriptome indicated that the PBEF gene is highly expressed in whole blood, over 100 times of the median abundance, while the expression in adipocytes is just about 2 times of the median abundance (GEO series GSE1133) [23].

A recent study has shown lack of association between circulating PBEF level and glucose metabolism/insulin resistance in healthy lean and obese subjects [3]. In humans, the normal fasting PBEF level is 10–40 ng/ml [1–5], which equals 180–700 pmol/l for this 55 kDa protein, 3.6–14 times the concentration of the normal fasting insulin level (50 pmol/l). If PBEF could act with the same efficacy as insulin [1], it should contribute importantly to the regulation of glucose metabolism. Therefore, it suggests that the circulating PBEF is not likely to play a major role in the glucose metabolism in humans.

In conclusion, the significant associations, positively with HDL-cholesterol and negatively with triglycerides, suggest that circulating PBEF is an indicator of beneficial lipid metabolism in non-diabetic Caucasian subjects, possibly linked to NAD metabolism. The relation with lipid metabolism does not depend on visceral obesity and insulin resistance. Further mechanistic studies in this direction may help to understand the physiological role of circulating PBEF.

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