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Vaspin gene expression in human adipose tissue: Association with obesity and type 2 diabetes

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Abstract

Recently, vaspin was identified as an adipokine with insulin-sensitizing effects, which is predominantly secreted from visceral adipose tissue in a rat model of type 2 diabetes. In this study, we examined whether vaspin mRNA expression is a marker of visceral obesity and correlates with anthropometric and metabolic parameters in paired samples of visceral and subcutaneous adipose tissue from 196 subjects with a wide range of obesity, body fat distribution, insulin sensitivity, and glucose tolerance. Vaspin mRNA expression was only detectable in 23% of the visceral and in 15% of the subcutaneous (SC) adipose tissue samples. Vaspin mRNA expression was not detectable in lean subjects (BMI < 25) and was more frequently detected in patients with type 2 diabetes. No significant correlations were found between visceral vaspin gene expression and visceral fat area or SC vaspin expression. However, visceral vaspin expression significantly correlates with BMI, % body fat, and 2 h OGTT plasma glucose. Subcutaneous vaspin mRNA expression is significantly correlated with WHR, fasting plasma insulin concentration, and glucose infusion rate during steady state of an euglycemic–hyperinsulinemic clamp. Multivariate linear regression analysis revealed % body fat as strongest predictor of visceral vaspin and insulin sensitivity as strongest determinant of SC vaspin mRNA expression. In conclusion, our data indicate that induction of human vaspin mRNA expression in adipose tissue is regulated in a fat depot-specific manner and could be associated with parameters of obesity, insulin resistance, and glucose metabolism.

Keywords: Vaspin; Obesity; Subcutaneous fat; Intra-abdominal adipose tissue; Type 2 diabetes

Increased abdominal visceral fat is associated with insulin resistance, type 2 diabetes, and coronary heart disease [1–3]. It was recently shown that reduction of visceral fat mass by omentectomy has significant positive and long-term effects on the glucose metabolism, insulin sensitivity, and metabolic profiles in obese subjects [4], whereas decreasing subcutaneous adipose tissue mass does not have beneficial metabolic effects [5]. The main focus to explain the mechanisms for the epidemiologic relationship between visceral fat mass and increased metabolic risk has been the search for adipokines, which are predominantly expressed and secreted from visceral adipose tissue. Over the past years, a number of adipokines with fat depot-specific expression including leptin [6,7], plasminogen activator inhibitor-1 [8], interleukin-6 (IL-6) [9], and visfatin [10,11] have been identified. Recently, visceral adipose tissue-derived serpin (vaspin) was identified as a member of serine protease inhibitor family, which was expressed in visceral adipose tissue of Otsuka Long–Evans Tokushima Fatty (OLETF) rats at the age when obesity and insulin plasma concentrations reach a peak [12]. Vaspin expression was shown to decrease with worsening of diabetes and body weight loss, whereas vaspin serum levels could be normalized by insulin or pioglitazone treatment. Administration of vaspin to obese mice improved glucose tolerance, insulin sensitivity, and altered gene expression of candidate genes for insulin resistance [12]. Taken together, these findings

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suggest that vaspin could play a role in the association between visceral obesity and increased metabolic risk.

We therefore tested the hypothesis that vaspin mRNA expression in fat is related to visceral fat mass, measures of obesity, insulin sensitivity, and glucose metabolism. We used correlational analysis to dissect whether and how vaspin mRNA expression is explained by the variability in anthropometric and metabolic parameters.

Research design and methods

Subjects. Paired samples of visceral and subcutaneous adipose tissue were obtained from 196 Caucasian men ($n = 98$) and women ($n = 98$) who underwent open abdominal surgery for gastric banding, cholecystectomy, appendectomy, weight reduction surgery, abdominal injuries, or explorative laparotomy. The age ranged from 23 to 86 years and body mass index from 20.8 to 54.1 kg/m^2. Thirty-six subjects had type 2 diabetes and 31 subjects had impaired glucose tolerance. All subjects had a stable weight with no fluctuations of more than 2% of the body weight for at least three months before surgery. Patients with severe conditions including generalized inflammation or end stage malignant diseases were excluded from the study. Samples of visceral and subcutaneous adipose tissue were immediately frozen in liquid nitrogen after explantation. The study was approved by the Ethics Committee of the University of Leipzig. All subjects gave written informed consent before taking part in the study.

Assays. Basal, fasting blood samples were taken after an overnight fast to determine glucose, insulin, and standard laboratory parameters. Plasma insulin was measured with a two-site chemiluminescent enzyme immunometric assay for the IMMULITE automated analyzer (Diagnostic Products, Los Angeles, CA, USA).

Measures of body fat content and oral glucose tolerance test. Body mass index (BMI) was calculated as weight divided by squared height. Waist and hip circumferences were measured and waist-to-hip ratio was calculated. Percentage body fat was measured by dual X-ray absorptiometry (DEXA). In addition, in a subgroup of 73 subjects (33 males, 40 females) visceral fat area and the relative ratio of intraabdominal visceral fat to the subcutaneous (SC) fat area using CT scans at the level of L4–L5 were calculated as previously described [13]. The oral glucose tolerance test (OGTT) was performed according to the criteria of the American Diabetes Association (ADA) [14]. Three days prior to the OGTT the patients documented a high carbohydrate diet. The OGTT was performed after an overnight fast with 75 g standardized glucose solution (Glucodex Solution 75 g, Merieux, Canada). Venous blood samples were taken at 0, 60, and 120 min for measurements of plasma glucose concentrations.

Euglycemic–hyperinsulinemic glucose clamp. Insulin sensitivity was assessed with the euglycemic–hyperinsulinemic clamp method [15]. The cut-off for insulin resistance was arbitrarily chosen from the euglycemic–hyperinsulinemic clamp results of more than 120 individuals, who share the same population background and underwent the same clamp conditions as previously reported [11,16].

Analysis of human vaspin gene expression. Human vaspin gene expression was measured by quantitative real-time RT-PCR in a fluorescent temperature cycler using the TaqMan assay and fluorescence was detected on an ABI PRISM 7000 sequence detector (Applied Biosystems, Darmstadt, Germany). Total RNA was isolated from paired subcutaneous and visceral adipose tissue samples using TRIzol (Life Technologies, Grand Island, NY) and 1 μg RNA was reverse transcribed with standard reagents (Life Technologies, Grand Island, NY). Two microliters of each RT reaction was amplified in a 26 μl PCR by using the Brilliant SYBR Green QPCR Core Reagent Kit from Stratagene (La Jolla, CA) according to the manufacturer's instructions. Samples were incubated in the ABI PRISM 7000 sequence detector for an initial denaturation at 95 °C for 10 min, followed by 40 PCR cycles, each cycle consisting of 95 °C for 15 s, 60 °C for 1 min, and 72 °C for 1 min. The following primers were used: human Vaspin (Accession No. NM_173850) 5′-agggcttccattacatcatcca-3′ (sense) and 5′-aacagcgtgttcccaatgct-3′ (antisense); human 36B4 (Accession No. NM_001002) 5′-aacatgctcaacatctcccc-3′ (sense) and 5′-ccgactcctcc gactcttc-3′ (antisense). Because human vaspin gene expression was not detectable in 77% of the visceral and 85% of the subcutaneous adipose tissue samples, a second PCR was performed using the following different primer pair: 5′-tgcacagtcggtgccaaa-3′ (sense) and 5′-tgtgtgtgctggctctgttct-3′ (antisense). SYBR Green I fluorescence emissions were monitored after each cycle. Expression of human vaspin and human 36B4 mRNA was quantified by using the second derivative maximum method of the TaqMan Software (Applied Biosystems, Darmstadt, Germany) determining the crossing points of individual samples by an algorithm which identifies the first turning point of the fluorescence curve. Human vaspin mRNA expression was calculated relative to 36B4, which was used as an internal control due to its resistance to hormonal regulation [17]. Amplification of specific transcripts was confirmed by melting curve profiles (cooling the sample to 68 °C and heating slowly to 95 °C with measurement of fluorescence) at the end of each PCR. The specificity of the PCR was further verified by subjecting the amplification products to agarose gel electrophoresis. In addition, Northern blot analysis confirmed the PCR results in ten subjects with absent and ten subjects with detectable vaspin mRNA expression.

Statistical analysis. Data are shown as means ± SD unless stated otherwise. Prior to statistical analysis, non-normally distributed parameters were logarithmically transformed to approximate a normal distribution. Expression differences between visceral and subcutaneous adipose tissue were assessed using the paired Student's t test. Linear relationships were assessed by least-squares regression analysis. Multivariate linear relationships were assessed by a general linear model. Statistical software from the SAS Institute (Cary, NC, USA) was used. p values <0.05 were considered to be statistically significant.

Results

Visceral and subcutaneous vaspin mRNA expression

The analysis of 196 paired samples of visceral and subcutaneous adipose tissue revealed that vaspin mRNA expression was only detectable in 45 (23%) of the visceral and in 30 (15%) of the subcutaneous (SC) adipose tissue samples. None of the lean subjects (BMI < 25, $n = 55$) had detectable vaspin mRNA expression, whereas frequency of subjects with vaspin mRNA expression increased from overweight to obese individuals (Fig. 1). RT-PCR results were confirmed by Northern blot analysis in ten subjects with absent and ten subjects with detectable vaspin mRNA expression. There was no difference either in visceral or SC vaspin gene expression between men and women (data not shown). Vaspin mRNA expression was significantly more frequently detected in patients with type 2 diabetes (Fig. 1). To identify possible relationships pertaining only to metformin or diet-treated patients with type 2 diabetes, we performed subanalyses for these treatment groups. Metformin treatment in patients with type 2 diabetes did not have any effect on the statistical relationships beyond those reported for all patients with type 2 diabetes or the entire study population.

In subjects with detectable vaspin mRNA expression, no significant correlation between the subcutaneous and visceral vaspin gene expression was detected (Fig. 2). To determine visceral intraabdominal and subcutaneous abdominal fat areas, CT scans from 31 individuals (15 males, 16 females) with detectable visceral and/or SC vaspin gene expression were evaluated at the level of L4–L5

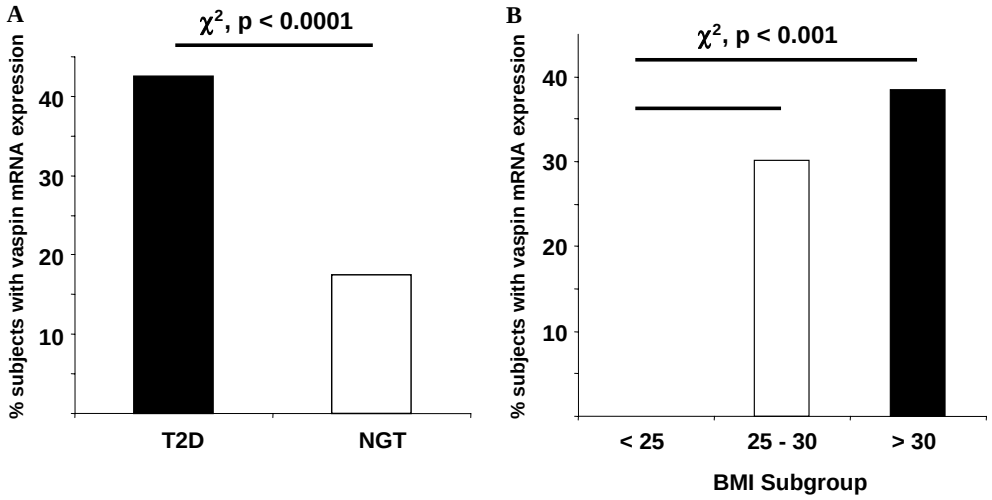

Fig. 1. Frequency of individuals with detectable vaspin mRNA expression in adipose tissue in (A) patients with type 2 diabetes (T2D, $n = 36$) and healthy normal glucose tolerant subjects (NGT, $n = 143$) and in (B) three different BMI subgroups (BMI <25, 25–30, and 30).

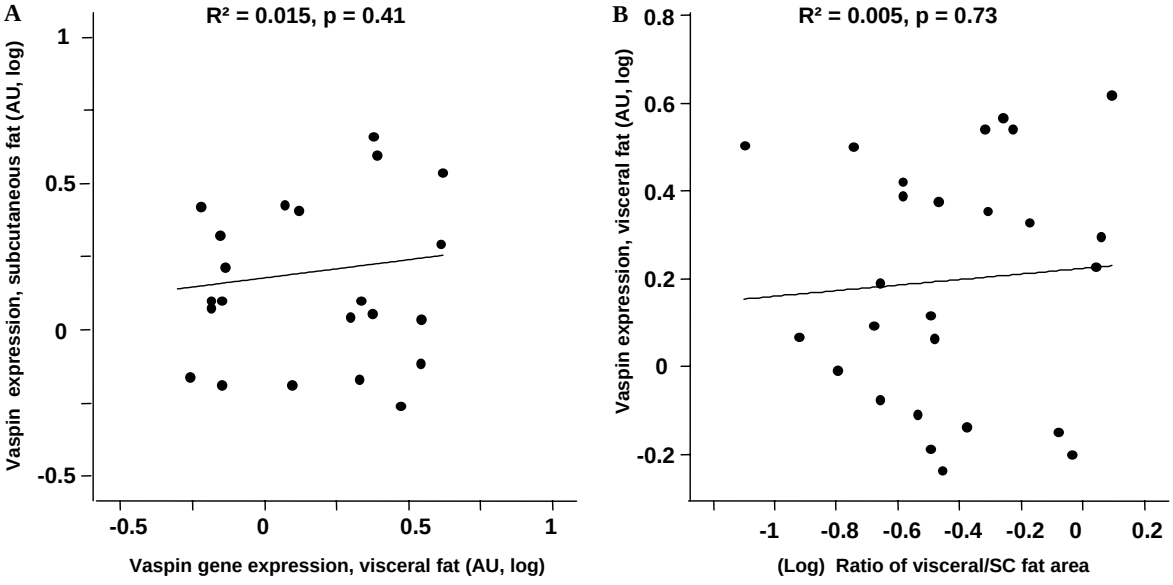

Fig. 2. Correlation between (A) visceral and subcutaneous vaspin mRNA expression and (B) visceral vaspin mRNA expression and the ratio of intraabdominal visceral fat to the subcutaneous fat area in subjects with detectable vaspin mRNA expression ($n = 31$). Data were log transformed to achieve normal distribution.

with an attenuation range of −30 to −190 Hounsfield units. In addition to the visceral fat area, the ratio of intraabdominal visceral fat to the subcutaneous (SC) fat area was calculated as previously described [13]. In this subgroup, we did not find a correlation between visceral vaspin mRNA expression and visceral fat area ($r^2 = 0.0$, $p = 0.56$) or the relative ratio of visceral to SC fat (Fig. 2).

Correlation of vaspin mRNA expression with parameters of obesity, glucose metabolism, and insulin sensitivity

In the entire study population ($n = 196$), multivariate logistic regression models revealed significant and fat depot-specific associations between vaspin mRNA expression in visceral, SC or visceral and SC fat, and % body fat, fasting plasma insulin and glucose concentrations, and the glucose infusion rate during the steady state of an euglycemic–hyperinsulinemic clamp (Table 1). In 51 subjects with detectable vaspin mRNA expression, univariate regression analysis revealed significant correlations between visceral vaspin mRNA expression and BMI ($r^2 = 0.2$, $p = 0.003$), % body fat (Fig. 3), and 2 h OGTT plasma glucose (Fig. 3). Subcutaneous vaspin mRNA expression is significantly correlated with WHR (Fig. 3), fasting plasma insulin concentration ($r^2 = 0.1$, $p = 0.048$), and glucose infusion rate during steady state of an euglycemic–hyperinsulinemic clamp (Fig. 3).

The correlations found by simple linear regression analysis were further analyzed in more detail. Multivariate

Table 1
Multivariate logistic regression analyses showing the association of vaspin mRNA expression in visceral, subcutaneous (SC) or visceral and SC fat with age, anthropometric, and metabolic parameters for the entire study population ($n = 196$)

	Vaspin mRNA expression		
	Visceral odds ratio (95% CI) p value	SC odds ratio (95% CI) p value	Visceral + SC odds ratio (95% CI) p value
Model 1			
Age (years)	0.99 (0.97–1.02) 0.65	0.98 (0.955–1) 0.18	0.99 (0.96–1.02) 0.64
Gender	1.19 (0.56–2.52) 0.66	0.73 (0.332–1.62) 0.44	0.84 (0.35–1.98) 0.69
% Body fat	**0.89** (0.87–0.93) <**0.0001**	0.98 (0.94–1.01) 0.2	0.97 (0.938–1.01) 0.22
Model 2			
FPG (mmol/L)	0.72 (0.48–1.07) 0.1	0.72 (0.47–1.11) 0.14	0.75 (0.49–1.13) 0.17
FPI (pmol/L)	**0.994** (0.991–0.997) <**0.0001**	**0.99** (0.986–0.994) <**0.001**	**0.992** (0.988–0.996) <**0.001**
Model 3			
Age (years)	0.99 (0.963–1.03) 0.79	1 (0.959–1.06) 0.76	0.97 (0.91–1.03) 0.31
% Body fat	**1.09** (1.035–1.145) 0.001	0.95 (0.86–1.04) 0.23	0.93 (0.826–1.04) 0.18
FPG (mmol/L)	1.352 (0.823–2.22) 0.23	**2.24** (1.064–4.83) **0.03**	2.39 (0.01–6.3) 0.08
FPI (pmol/L)	0.99 (0.937–0.98) 0.81	1 (0.99–1.01) 0.96	1 (0.99–1.01) 0.81
GIR	**0.96** (0.937–0.98) <**0.0001**	**0.85** (0.77–0.92) <**0.0001**	**0.77** (0.68–0.88) <**0.0001**

FPI, fasting plasma insulin; FPG, fasting plasma glucose; GIR, glucose infusion rate; during the steady state of an euglycemic–hyperinsulinemic clamp.

linear regression analysis of age, % body fat, fasting plasma glucose, and glucose infusion rate during the steady state of euglycemic–hyperinsulinemic clamp as predictors for the visceral and SC vaspin mRNA expression revealed % body fat as strongest determinant of visceral vaspin mRNA expression (Table 2). Decreased insulin sensitivity, as determined by the glucose infusion rate during the steady state of euglycemic–hyperinsulinemic clamp, was identified as strongest predictor of SC vaspin mRNA expression (Table 2). In addition to insulin sensitivity, increased fasting plasma glucose concentration was identified as significant determinant of SC vaspin mRNA expression.

Characterization of subjects with or without vaspin mRNA expression

According to the vaspin expression pattern, 4 subgroups can be distinguished: Subjects without visceral or SC vaspin expression ($n = 145$), subjects with both visceral and SC vaspin expression ($n = 24$), and subjects with either visceral ($n = 21$) or SC ($n = 6$) vaspin gene expression (Table 3). These subgroups are characterized by significant differences in anthropometric and metabolic parameters (Table 3).

Vaspin mRNA expression in patients with type 2 diabetes

Although frequency of vaspin mRNA expression was significantly increased in subjects with type 2 diabetes (Fig. 1), not all patients with type 2 diabetes had detectable vaspin gene expression. First, we excluded an effect of metformin treatment on vaspin gene expression in adipose tissue of patients with type 2 diabetes (data not shown). To identify possible phenotypical differences associated with vaspin mRNA expression, we compared patients with type 2 diabetes with or without vaspin mRNA expression in adipose tissue (Table 4). In patients with type 2 diabetes, insulin sensitivity was the only significant different parameter discriminating subjects with and without vaspin mRNA expression (Table 4).

Vaspin mRNA expression in obese subjects with normal glucose tolerance

Vaspin mRNA expression was significantly more frequently detected in obese subjects (32%, BMI > 30) as compared to overweight subjects (14%, BMI 25–29.9) without type 2 diabetes. To further characterize the differential phenotypes associated with vaspin gene expression in visceral and/or SC fat, we compared a subgroup of normal glucose tolerant, obese (BMI > 30) subjects with ($n = 16$) or without vaspin ($n = 35$) gene expression in adipose tissue. Subgroup analysis revealed significantly higher % body fat ($37 \pm 6\%$ versus $49 \pm 9\%$, $p < 0.0001$) as the only discriminating parameter between obese, normal glucose tolerant subjects with and without vaspin mRNA expression.

Discussion

Visceral adipose tissue-derived serpin (vaspin) was recently isolated as an adipocytokine from visceral white adipose tissue of Otsuka Long-Evans Tokushima fatty (OLETF) rats [12]. The OLETF rat is a model of type 2 diabetes, which is characterized by abdominal obesity, insulin resistance, hypertension, and dyslipidemia [18]. Vaspin was highly expressed in 30-week old rats, the age when obesity, body weight, and insulin levels peak in OLETF rats [12]. We studied vaspin mRNA expression in paired samples of visceral and subcutaneous adipose tissue from 196 subjects with a wide range of obesity, body fat

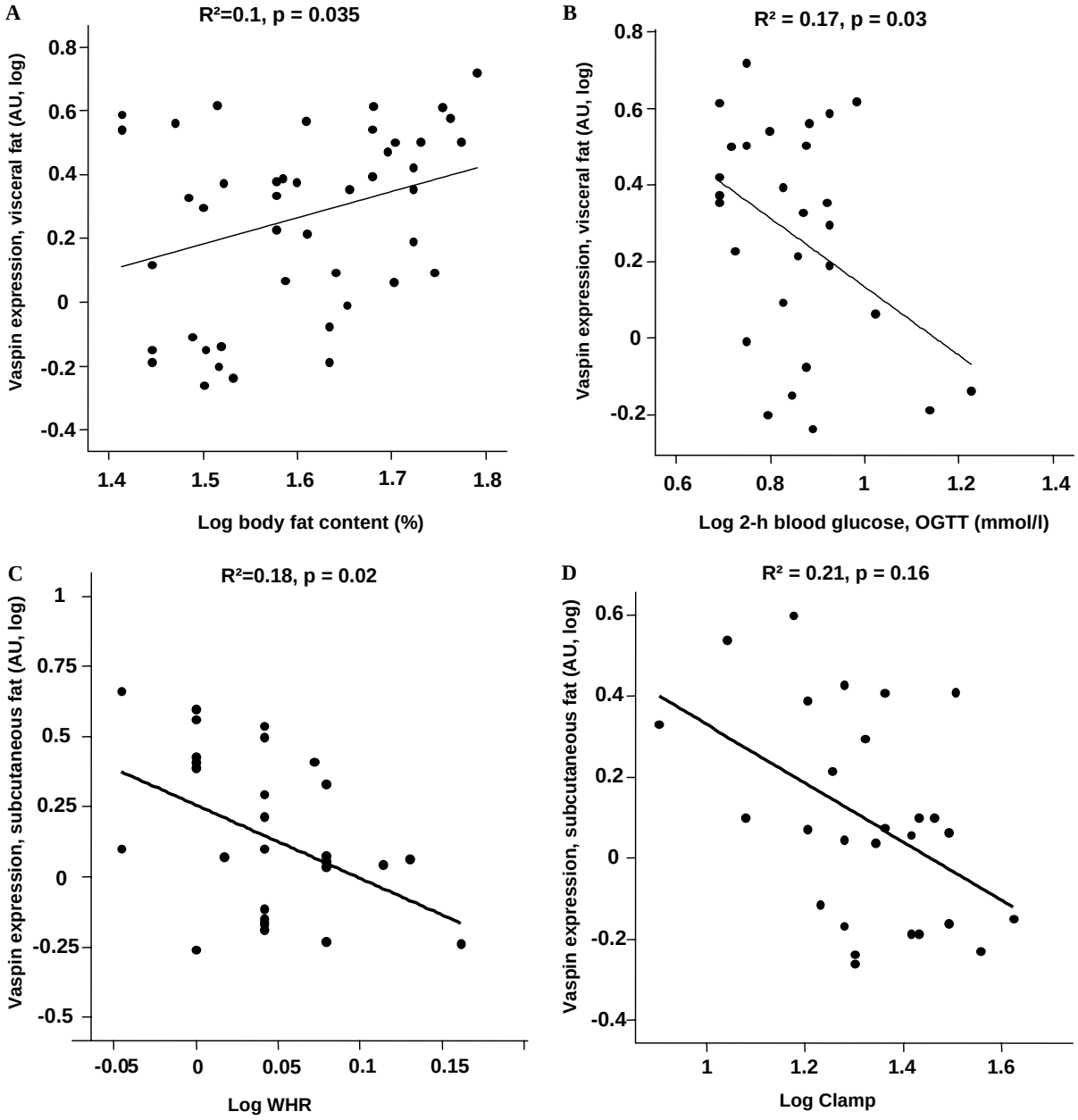

Fig. 3. Correlation between visceral vaspin mRNA expression and (A) % body fat (B) 2 h OGTT plasma glucose concentration. Correlation between subcutaneous (SC) vaspin mRNA expression and (C) waist-to-hip ratio (WHR) (D) glucose infusion rate during the steady state of an euglycemic–hyperinsulinemic clamp. Data were log transformed to achieve normal distribution.

Table 2
Multiple regression analysis between anthropometric and biochemical parameters and vaspin mRNA expression in visceral, and SC adipose tissue in subjects with visceral, SC or visceral and SC vaspin expression ($n = 51$)

	Vaspin mRNA expression (β-Coefficient p value)	
	Visceral	Subcutaneous
Age	−0.11 (0.5)	−0.09 (0.62)
% Body fat	**0.37 (0.025)**	0.003 (0.99)
FPG	−0.01 (0.95)	**0.38 (0.03)**
FPI	−0.1 (0.54)	0.15 (0.42)
GIR	−0.005 (0.98)	**−0.54 (0.004)**

FPI, fasting plasma insulin; FPG, fasting plasma glucose; GIR, glucose infusion rate; during the steady state of an euglycemic–hyperinsulinemic clamp.

distribution, insulin sensitivity, and glucose tolerance. In our cohort, vaspin mRNA expression was only detectable in 23% of the visceral and in 15% of the subcutaneous adipose tissue samples. Interestingly, vaspin mRNA expression was not detectable in lean subjects ($n = 55$, BMI < 25). This observation could be in accordance with the barely detectable vaspin expression in young OLETF rats [12] and suggests that vaspin mRNA expression is inducible by increased body fat and metabolic abnormalities, which develop in older OLETF rats. This view is further supported by the logistic regression models showing an association of vaspin mRNA expression with % body fat, fasting plasma glucose and insulin concentrations,

Table 3
Anthropometric and metabolic parameters in different groups of vaspin mRNA expression patterns from 196 donors of paired visceral and subcutaneous adipose tissue samples

	Vaspin mRNA expression				*p*, ANOVA
n, male/female	No *n* = 145, 73/72	Vis/sc *n* = 24, 11/13	Visceral *n* = 21, 12/9	Subcutaneous *n* = 6, 2/4	0.16
Age (years)	54 ± 14	57 ± 15	57 ± 12	66 ± 12	<0.001
Body fat content (%)	29 ± 9	35 ± 8	48 ± 8	34 ± 7	<0.001
Fasting plasma glucose (mmol/L)	5.5 ± 0.6	6.6 ± 1.7	5.9 ± 1.4	6.5 ± 0.6	<0.001
Fasting plasma insulin (pmol/L)	98 ± 96	285 ± 126	158 ± 120	309 ± 129	<0.001
Glucose infusion rate	75 ± 26	21 ± 7	65 ± 28	35 ± 5	<0.001

Table 4
Anthropometric and metabolic parameters in patients with type 2 diabetes with or without vaspin mRNA expression in adipose tissue

	Vaspin mRNA expression		
n, male/female	No *n* = 13, 6/7	Vis/sc *n* = 15, 6/9	*p*
Age (years)	63 ± 9	52 ± 16	ns
Body fat content (%)	38 ± 10	37 ± 9	ns
Fasting plasma glucose (mmol/L)	6.6 ± 0.8	7.4 ± 1.7	ns
Fasting plasma insulin (pmol/L)	266 ± 92	332 ± 125	ns
Glucose infusion rate	39 ± 17	22 ± 5.4	0.0012
HbA_1C (%)	6.7 ± 0.7	6.7 ± 0.6	ns

and degree of insulin sensitivity as determined by euglycemic–hyperinsulinemic clamps.

In contrast to untreated OLETF rats, in humans, vaspin expression was not restricted to visceral fat. Moreover, in human adipose tissue, vaspin gene expression seems to be differentially regulated in function of the fat depot. There was no correlation between visceral and SC vaspin expression in subjects with detectable vaspin expression in both depots. We found significant correlations between visceral vaspin mRNA expression, and BMI, percentage body fat, and 2 h OGTT plasma glucose. Subjects with no detectable vaspin expression are characterized by significantly lower % body fat, fasting plasma glucose and insulin concentrations, and preserved insulin sensitivity (Table 3). Subcutaneous vaspin mRNA expression is significantly correlated with WHR, fasting plasma insulin concentration, and glucose infusion rate during steady state of an euglycemic–hyperinsulinemic clamp. The relationship between SC vaspin expression and increased insulin plasma concentrations could support the finding that insulin treatment caused induction of SC vaspin expression in OLETF rats [12]. Compatible with these relationships, multivariate regression analysis demonstrated that increased body fat is the strongest predictor for visceral and decreased insulin sensitivity, the strongest determinant of SC vaspin gene expression. Because vaspin was originally identified as a predominantly visceral expressed adipokine, we tested the hypothesis that vaspin mRNA expression in visceral fat is associated with visceral obesity. However, we did not find a correlation between visceral vaspin expression and visceral fat area or the ratio visceral/SC fat areas as determined by CT-analysis.

In our study population, vaspin mRNA expression was significantly more frequently detected in patients with type 2 diabetes. However, not all patients with type 2 diabetes had detectable vaspin mRNA expression. Further analysis of vaspin expression in patients with type 2 diabetes revealed that higher glucose infusion rate during the steady state of an euglycemic–hyperinsulinemic clamp, representing a significantly higher degree of insulin sensitivity, was the only discriminating factor between patients with or without vaspin gene expression (Table 4). We therefore further investigated whether decreased insulin sensitivity might explain induction of vaspin mRNA expression also in normal glucose tolerant, obese (BMI > 30) subjects. However, in this subgroup the only significantly different phenotypical parameter was increased body fat content in subjects with compared to subjects without detectable vaspin expression. These results seem to confirm the initial observation in OLETF rats that insulin resistance and obesity are associated with high expression of vaspin.

Vaspin was shown to improve glucose tolerance and insulin sensitivity in obese ICR mice and normalized altered expression of genes relevant to insulin resistance [12]. Therefore, we postulate that induction of vaspin expression in human fat might be an intrinsic compensatory mechanism of the adipose tissue in response to decreased insulin sensitivity or impairment of glucose metabolism. We found significant correlations between visceral vaspin mRNA expression and BMI, % body fat as well as 2 h OGTT plasma glucose. Since not all insulin resistant, obese, and glucose intolerant subjects in our study population had detectable vaspin expression, the ability to induce vaspin in adipose tissue might define a previously

unrecognized subgroup of these patients. The potential mechanisms, which underly the induction of vaspin expression in this subgroup, require further investigation with more sophisticated methods and study designs. Especially, the identification of the protease substrate for the induction of the protease inhibitor vaspin might help us to elucidate the regulation of vaspin gene expression.

In conclusion, our data suggest that human vaspin mRNA expression in adipose tissue is not detectable in lean normal glucose tolerant individuals, but can be induced by increased fat mass, decreased insulin sensitivity, and impaired glucose tolerance. Regulation of vaspin gene expression seems to be fat depot-specific. Moreover, induction of vaspin mRNA expression in human adipose tissue could represent a compensatory mechanism associated with obesity, severe insulin resistance, and type 2 diabetes.

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