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Research letter

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An adipocytokine signature improves diagnostic accuracy for people living with lipoedema

Katja S Mühlberg[1,2] Robin Schürfeld[3] Patricia Kieser,[1] Simone Uhlemann,[1] Michael Stumvoll[3,4] Dierk Scheinert[1] Matthias Blüher[2,3,4] Mathias Fasshauer[5] and Thomas Ebert[3,4,6]

[1]University of Leipzig Medical Center, Department of Angiology, Leipzig, Germany
[2]Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Leipzig, Germany
[3]University of Leipzig, Medical Department III – Endocrinology, Nephrology, Rheumatology, Leipzig, Germany
[4]Leipzig University, LeiCeM – Leipzig Center of Metabolism, Leipzig, Germany
[5]Justus-Liebig-University, Institute of Nutritional Science, Giessen, Germany
[6]Karolinska Institutet, Department of Clinical Science, Intervention and Technology, Division of Renal Medicine, Stockholm, Sweden
Correspondence: Thomas Ebert. Email: thomas.ebert@medizin.uni-leipzig.de
K.S.M. and R.S. contributed equally to this work.

Dear Editor, Lipoedema is a chronic adipose tissue disorder predominantly affecting women and characterized by pain, tenderness and disproportionate, symmetrical fat accumulation in the extremities. Unlike obesity, weight loss has little effect on the abnormal fat distribution, and patients often experience bruising and impaired quality of life.[1,2] Despite increasing awareness, diagnosis remains challenging because clinical assessment relies on subjective symptoms and physical examination, with considerable overlap with obesity and lymphoedema. This diagnostic uncertainty delays appropriate treatment and underscores the need for objective biomarkers. Whereas previous reports implicated adipose tissue inflammation, vascular dysregulation and genetics in lipoedema pathophysiology,[3,4] we hypothesized that circulating adipocytokines could improve diagnostic accuracy for lipoedema.

In a cross-sectional study, we examined 79 women allocated to four groups: lipoedema ($n = 24$), lipoedema with overweight/obesity ($n = 17$), overweight/obesity without lipoedema ($n = 28$) and healthy controls ($n = 10$). Anthropometric data and fasting blood samples were collected under standardized conditions. Serum concentrations of 13 adipocytokines, including leptin, adiponectin, adipocyte fatty acid-binding protein (AFABP), fibroblast growth factor 21 (FGF21), progranulin, chemerin, afamin and growth differentiation factor 15 (GDF15), were measured using enzyme-linked immunosorbent assays. The diagnosis of lipoedema was based on current clinical criteria,[2,5] including characteristic fat distribution, pain and exclusion of other causes. Statistical analyses were performed in R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria) using the packages stats, mdatools, broom, partykit, caret, pROC, PredictABEL and ggplot2. We applied Kruskal–Wallis tests, partial least squares discriminant analysis (PLS-DA), logistic regression with reclassification metrics and conditional inference trees.

Baseline characteristics (Table 1) revealed significant differences across groups in body mass index, waist circumference, fat mass and blood pressure. Serum leptin, adiponectin, AFABP, FGF21 and chemerin differed markedly between lipoedema and anthropometric phenotypes.

PLS-DA identified adiponectin, AFABP, FGF21, chemerin, afamin and GDF15 as relevant biomarkers for discriminating lipoedema, with variance importance in projection (VIP) scores > 1. In models combining adipocytokines and cardiometabolic markers, mean blood pressure, glycated haemoglobin A1c (HbA_{1c}), triglycerides and high-sensitivity C-reactive protein (hsCRP) also contributed to discrimination, but chemerin and FGF21 retained the highest VIP scores, suggesting superior diagnostic power. In women with overweight/obesity with and without lipoedema, results remained virtually the same. When healthy individuals were excluded from the cohort, leptin, AFABP, FGF21 and chemerin were the most relevant adipocytokines for discriminating lipoedema (for summary results tables, see https://doi.org/10.6084/m9.figshare.30715652).

Logistic regression confirmed FGF21 and chemerin as independent predictors of lipoedema. Following z-transformation and adjustment for age, fat mass percentage, HbA_{1c} and hsCRP, a one-standard-deviation increase in FGF21 and chemerin was associated with 79% [odds ratio (OR) 0.208, 95% confidence interval (CI) 0.051–0.579] and 56% (OR 0.445, 95% CI 0.216–0.844) lower odds of lipoedema, respectively. Prognostic performance analyses revealed that adding FGF21 or chemerin improved risk classification: the net reclassification index increased by 71.5% and 57.3% for FGF21 and chemerin, respectively, while integrated discrimination improvement increased by 10.6% and 6.7%, respectively, even though changes in the area under the receiver operating characteristic curve were modest. When healthy women were excluded, FGF21 (OR 0.103, 95% CI 0.019–0.400) and

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Table 1 Baseline characteristics of the study population ($N = 79$ women)

Group	Lipoedema	Lipoedema and overweight/obesity	Overweight/obesity	Healthy controls	*P*-value
N	24	17	28	10	NA
Age (years)	32 (10)	33 (11)	32 (15)	29 (21)	0.782
Diabetes (%)	1 (4)	1 (6)	7 (25)	0 (0)	0.101
BMI (kg m^{-2})	24.4 (3.0)	31.6 (7.9)[a]	39.2 (16.4)[a]	22.4 (3.5)[b,c]	**< 0.001**
Waist circumference (cm)	78.5 (9.8)	95.0 (13.0)[a]	109.5 (28.0)[a]	80.0 (12.0)[b,c]	**< 0.001**
WHtR	0.47 (0.05)	0.58 (0.06)[a]	0.65 (0.17)[a]	0.47 (0.06)[b,c]	**< 0.001**
Fat mass percentage	30.2 (7.3)	41.9 (10.1)[a]	41.7 (16.0)[a]	26.9 (8.8)[b,c]	**< 0.001**
Mean BP (mmHg)	91 (10)	97 (13)	97 (17)	87 (10)	**0.003**
HbA_{1c} (%)	5.0 (0.3)	5.2 (0.3)	5.4 (0.7)[a]	5.2 (0.3)	**< 0.001**
TG (mmol L^{-1})	0.8 (0.6)	0.8 (0.8)	1.4 (0.8)[a]	0.7 (0.4)[c]	**< 0.001**
Cholesterol (mmol L^{-1})	4.7 (1.4)	4.5 (0.8)	4.9 (2.1)	5.3 (0.9)	0.256
HDL cholesterol (mmol L^{-1})	1.9 (0.5)	1.7 (0.3)	1.4 (0.7)[a]	2.3 (1.3)[c]	**< 0.001**
LDL cholesterol (mmol L^{-1})	2.9 (1.0)	2.6 (0.8)	3.2 (1.9)	2.6 (1.1)	0.631
hsCRP (mg L^{-1})	1.0 (2.2)	3.3 (5.6)	5.0 (10.6)[a]	1.1 (2.1)[c]	**< 0.001**
Leptin (µg L^{-1})	16.3 (8.5)	32.9 (22.1)[a]	37.7 (35.1)[a]	9.2 (9.9)[b,c]	**< 0.001**
Adiponectin (mg L^{-1})	12.4 (7.5)	11.9 (4.7)	8.4 (5.6)[a,b]	10.4 (6.6)	**0.003**
AFABP (µg L^{-1})	21.5 (12.3)	37.1 (32.3)[a]	43.7 (39.8)[a]	25.5 (15.7)[c]	**< 0.001**
FGF21 (ng L^{-1})	33.6 (57.6)	61.5 (77.4)	96.3 (225.0)[a]	41.6 (52.5)	**0.009**
Progranulin (µg L^{-1})	35.9 (6.0)	34.6 (13.7)	39.0 (8.8)	35.9 (7.5)	0.091
Chemerin (µg L^{-1})	166.6 (55.9)	194.2 (50.8)	236.0 (50.5)[a]	158.4 (38.6)[c]	**< 0.001**
Afamin (mg L^{-1})	63.4 (19.7)	72.0 (22.2)	75.2 (27.7)	67.3 (17.3)	0.075
GDF15 (ng L^{-1})	447.6 (174.2)	490.7 (242.6)	535.4 (466.8)	580.8 (257.3)	0.250
Fetuin A (mg L^{-1})	262.9 (72.2)	270.3 (74.9)	291.8 (86.8)	250.6 (61.9)	0.081
Fetuin B (mg L^{-1})	1.67 (0.86)	1.79 (0.81)	1.94 (1.34)	1.98 (1.54)	0.243
Irisin (mg L^{-1})	3.51 (1.16)	3.73 (1.07)	3.19 (1.56)	3.92 (1.19)	0.073
Lipocalin 2 (µg L^{-1})	52.5 (38.0)	44.9 (19.0)	51.0 (40.6)	40.8 (33.3)	0.558
Myostatin (µg L^{-1})	6.0 (102.8)	7.1 (85.2)	20.9 (123.0)	8.9 (1849.5)	0.688

Continuous variables are presented as medians (interquartile ranges); categorical variables are presented as total numbers (percentages). AFABP, adipocyte fatty acid-binding protein; BMI, body mass index; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; HbA_{1c}, glycated haemoglobin A1c; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NA, not applicable; TG, triglycerides; WHtR, waist-to-height ratio. Continuous variables were analysed using the Kruskal–Wallis test followed by post hoc analysis, whereas the χ^2 test was used for categorical variables. *P*-values refer to overall group differences. *P*-values in **bold** font indicate significant differences; superscript letters indicate $P < 0.05$ compared with patients with lipoedema,[a] overweight/obesity and lipoedema,[b] or overweight/obesity[c] in post hoc tests.

chemerin (OR 0.335, 95% CI 0.143–0.700) remained significantly associated with an 89.7% and 66.5% reduced risk of a diagnosis of lipoedema, respectively.

Decision tree modelling further illustrated the clinical utility of these biomarkers (https://doi.org/10.6084/m9.figshare.30715622). In the entire cohort, a decision tree based on chemerin and adiponectin achieved an accuracy of 74.7%, sensitivity of 95% and specificity of 52.6%. In nonhealthy individuals (i.e. excluding lean controls), a second decision tree analysis incorporating chemerin, FGF21 and adiponectin improved performance, yielding an accuracy of 85%, sensitivity of 93% and specificity of 75%. Thus, these three adipocytokines consistently emerged as the most informative biomarkers, outperforming traditional metabolic indicators in multivariate models.

Pathophysiologically, elevated adiponectin levels in lipoedema may indicate a metabolically healthier expansion of subcutaneous adipose tissue compared with that seen in visceral obesity, even when fat mass percentage is similar.[6–8] Consistent with this, FGF21 is upregulated by metabolic and inflammatory stress to modulate lipolysis and adjust adipokine secretion.[7] Thus, lower FGF21 in lipoedema may reflect a more beneficial adipose tissue phenotype compared with adipose tissue dysfunction in obesity. Furthermore, chemerin regulates adipogenesis, angiogenesis and immune-cell recruitment, linking adipose dysfunction to local inflammation and microvascular remodelling.[7,8] In lipoedema, a trend toward lower chemerin levels might indicate disproportionate expansion of subcutaneous adipose tissue, with less hypoxia and low-grade inflammation compared with adipose tissue function in obesity.[7,8]

Limitations of this study include its cross-sectional design, modest sample size and lack of external validation. Future studies should confirm these findings in larger, diverse cohorts and explore mechanistic links between adipocytokines and disease development.

In conclusion, an adipocytokine signature, particularly chemerin and FGF21, improves diagnostic accuracy for lipoedema and may complement clinical assessment. Integrating these biomarkers into diagnostic pathways could represent a major advance in the management of this underrecognized disorder.

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Data availability: For confidentiality reasons, the data that support the findings of this study are generally not available under current regulations. However, the analysed data are available at https://doi.org/10.6084/m9.figshare.30715652 and https://doi.org/10.6084/m9.figshare.30715622. Requests for additional analyses may be considered upon reasonable request to the corresponding author.

Ethics statement: The study was approved by the local Ethics Committee of the University of Leipzig (approval number: 222/17-ek).

Patient consent: All participants provided written informed consent.

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ACR 50, ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

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