ORIGINAL ARTICLE

Plasma visfatin/nicotinamide phosphoribosyltransferase (visfatin/NAMPT) concentration in elderly subjects with metabolic syndrome

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KEY WORDS

insulin resistance, metabolic syndrome, microinflammation, visfatin/NAMPT

ABSTRACT

INTRODUCTION Visceral adipose tissue is the main source of circulating proinflammatory adipokine, visfatin/nicotinamide phosphoribosyltransferase (visfatin/NAMPT), whose role in the pathogenesis of metabolic syndrome (MS) components such as hypertension and carbohydrate and lipid disturbances is still uncertain, due to commonly used low specific C-terminal immunoassays to determine visfatin/NAMPT levels.

OBJECTIVES The aim of the study was to assess the association between the occurrence of MS components and circulating visfatin/NAMPT levels in elderly population.

PATIENTS AND METHODS The analysis included 2174 elderly participants of the PolSenior study without heart failure, severe chronic kidney disease, cancer, and malnutrition. MS was defined according to the modified International Diabetes Federation criteria. Plasma visfatin/NAMPT concentrations were measured by a highly specific enzyme-linked immunosorbent assay. Additionally, high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and insulin levels were assessed, and the homeostasis model assessment for insulin resistance was calculated.

RESULTS Women were diagnosed with MS more often than men (71.2% vs 56.8%; $P < 0.001$) and had a greater prevalence of all MS components except for type 2 diabetes. Women with MS had higher concentrations of hsCRP and IL-6 than those without MS. Visfatin/NAMPT concentrations were higher in women with MS than in those without MS (1.06 ng/ml [0.65–1.87] vs 0.85 ng/ml [0.54–1.40]; $P < 0.001$), but no differences were observed in men (0.97 ng/ml [0.59–1.61] vs 0.90 ng/ml [0.56–1.60], respectively; $P = 0.5$). In women, there was a stronger association between the number of components of MS and increased plasma visfatin/NAMPT levels than in men.

CONCLUSIONS Plasma visfatin/NAMPT levels are increased only in elderly women with MS. It is difficult to distinguish the components of MS specifically associated with increased visfatin/NAMPT levels.

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INTRODUCTION Metabolic syndrome (MS) is a constellation of cardiovascular risk factors including visceral obesity, dyslipidemia, disturbances of carbohydrate metabolism, and hypertension. The cardiovascular risk is proportional to the number of MS components.[1] Insulin resistance (IR), the consequence of visceral obesity, is the key pathomechanism in the development of the remaining MS components.[2]

IR develops as a result of enlarged volume of adipocytes and local inflammation in visceral adipose tissue, related to disturbances in adipokine release and insufficiency in adipocyte energy storage, leading to ectopic lipid accumulation in the liver and skeletal muscles.[3] It should be noted that IR may develop in patients with normal weight (according to body mass index [BMI]) with excessive visceral fat depot known as metabolic obese normal weight.[4] The approved indirect method of visceral fat depot estimation is waist circumference measurement, an assessment of visceral obesity—one of the components of MS according to the International Diabetes Federation (IDF) diagnostic criteria.[5]

As mentioned above, one of the factors participating in IR development is hormonal dysfunction of adipose tissue. Visfatin / nicotinamide phosphoribosyltransferase (visfatin/NAMPT) has been described as an adipokine highly expressed in visceral fat tissue,[6] released by adipocytes and macrophages,[7] with no extracellular receptor established and uncertain extracellular action. It is also known as dimeric NAMPT, the key enzyme involved in the NAD^+ biosynthetic pathway,[8] and as a cytokine pre-B cell colony-enhancing factor (PBEF). Therefore, it is frequently named visfatin/NAMPT or visfatin/NAMPT/PBEF. The initially postulated insulin-mimetic action of visfatin/NAMPT has not been confirmed, and it is now believed that this adipokine has only proinflammatory properties.

Increased visfatin/NAMPT levels have been reported in subjects with IR by a number of studies,[9,10] but have not been confirmed by other investigators.[11-13] Increased circulating visfatin/NAMPT levels have also been reported in subjects diagnosed with obesity and those with MS criteria.[14,15] However, the association between visfatin/NAMPT levels and severity of MS understood as a number of its components has not been assessed so far. In addition, during the analysis of the published studies assessing visfatin/NAMPT levels, we noticed that most of them, including some of our own, estimated visfatin/NAMPT levels with the use of low specific C-terminal enzyme immunoassays (EIA developed by Phoenix Pharmaceuticals, Burlingame, California, United States) or radioimmunoassays, which reported the circulating levels of undefined protein with a molecular weight of ~500 kDa improperly considered as visfatin/NAMPT.[16,17] Therefore, there are no studies that would accurately assess visfatin/NAMPT levels in subjects with MS. Thus, the use of more specific enzyme-linked immunosorbent assay (ELISA) kits in plasma samples of a large group of elderly subjects, participants of the PolSenior study,[18] may provide new data on the role of visfatin/NAMPT in MS. In our recently published study, we have shown that plasma visfatin/NAMPT levels are associated with age, systemic microinflammation, and IR regardless of sex, and with nutritional status only in women.[19]

The aim of the present study was to assess the association between the number and type of MS components and circulating plasma visfatin/NAMPT levels in elderly population.

PATIENTS AND METHODS **Study design and setting** This substudy was based on 2733 banked samples from the PolSenior study[18] stored at –70°C. The PolSenior study conducted in the years 2008 and 2011 recruited 6 age cohorts of a similar size (65–69 years, 70–74 years, 75–79 years, 80–84 years, 85–89 years, and ≥90 years). Trained nurses visited a total of 4979 participants 3 times to conduct a questionnaire survey, comprehensive geriatric assessment, and body mass, height, waist circumference, and blood pressure (BP) measurements. In addition, blood samples were withdrawn in the morning after an overnight fast and urine samples were collected. The study was approved by the Bioethics Committee of the Medical University of Silesia (KNW/0022/KB1/38/II/08/10; KNW-6501-38/I/08) and each subject gave written consent to participate.

Anthropometric measurements The height and body mass were measured in the morning after an overnight fast in subjects without shoes and dressed in light clothes (Tanita scale BC-536, Tokyo, Japan) with the accuracy of 0.5 cm and 0.1 kg.

The waist circumference was measured midway between the last rib and the iliac crest in a standing position in the anterior axillary line leading centimeter dipstick by the umbilicus with the accuracy of 0.5 cm.

BP measurements were performed 3 times in a sitting position after 5 minutes of rest on the left arm, using a fully automatic oscillometric BP measuring device (A&D UA 767, San Jose, California, United States) with a cuff selected according to the arm circumference. Thirty minutes before BP readings were taken, the patient could not smoke cigarettes, drink coffee, or do physical exercise. The nurse recorded the BP values with the accuracy of 1 mmHg. The mean value was calculated from the 2 first BP measurements.

The BMI was calculated according to the standard formula.

Biochemical measurements Blood samples were collected in the morning (8 AM to 9 AM) after a 12-hour overnight fast. Serum levels of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and triglycerides were assessed by an automated system (Modular PPE, Roche Diagnostics GmbH, Mannheim, Germany) in a single certified

laboratory with interassay coefficients of variability below 1.7%, 1.7%, 1.3%, 1.2%, and 1.8%, respectively. The serum insulin concentration was assessed by the electrochemiluminescence method using commercially available kits on the Cobas E411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with an interassay coefficient of variability below 3.8%.

Plasma visfatin/NAPMT levels were measured by ELISA (BioVendor, Brno, The Czech Republic), with the lower limit of sensitivity of 0.03 ng/ml and mean intraassay and interassay coefficients of variance of less than 9.1% and 5.6%, respectively. Our results showed lower concentrations of visfatin/NAMPT in the study populations, whereas previous assays demonstrated higher concentrations of visfatin/NAMPT. The used assay was highly specific for visfatin/NAMPT and did not crossreact with human resistin, adiponectin, vaspin, RBP4, GPX3, progranulin, clusterin, ANGPTL3, ANGPTL4, or ANGPTL6. Moreover, dilution of human serum samples of visfatin/NAMPT showed an expected decrease of visfatin/NAMPT concentrations in subsequent samples showing a recovery range of 85% to 105%. Additionally, in a subset of randomly selected subjects (n = 244), plasma visfatin/NAPMT levels were measured by EIA (Phenix Pharmaceticals, Burlingame, California, United States) with the lower limit of sensitivity of 2.63 ng/ml and intra- and interassay coefficients of variations of 5.2% and 5.8%, respectively.

Data analysis The components of MS were diagnosed according to the modified IDF criteria.[5] The presence of any 3 components in an individual was considered as meeting the criteria of MS: 1) visceral obesity for Europeans (waist circumference of ≥94 cm in men and ≥80 cm in women); 2) serum triglyceride levels of ≥1.7 mmol/l or treatment of hypertriglyceridemia; 3) serum HDL cholesterol concentration: <1.03 mmol/l in men and <1.29 mmol/l in women or treatment of these lipid disturbances; 4) systolic BP of ≥130 mmHg and/or diastolic BP of ≥85 mmHg or previously diagnosed hypertension; 5) fasting plasma glucose of ≥5.6 mmol/l or previously diagnosed type 2 diabetes.

IR was assessed on the basis of homeostatic model assessment of insulin resistance (HOMA-IR) calculated using the standard formula: HOMA-IR = fasting serum insulin (μIU/ml) × fasting glucose (mmol/l)/22.5. IR was diagnosed if HOMA-IR was 2.5 or higher.

Statistical analysis A statistical analysis was performed using STATISTICA 10.0 PL (StatSoft, Kraków, Poland), StataSE 13.0 (StataCorp LP, Texas, United States), and the R software. Statistical significance was set at a P value of less than 0.05. All tests were 2-tailed. Imputations were not done for missing data. Nominal and ordinal data were expressed as percentages, while interval data were expressed as mean value ± standard deviation in the case of normal distribution or as median with lower and upper quartiles in the case of data with skewed or nonnormal distribution. Distribution of variables was evaluated by the Shapiro–Wilk test and homogeneity of variances was assessed by the Levene test. For comparison between the groups with and without MS, the t test was used in the case of data with normal distribution or after normalization with logarithmic function and the Mann–Whitney test in other cases. For comparison of data in relation to the number of MS components and its combinations, the 1-way analysis of variances was used with the Tukey or Dunnet post-hoc tests. Categorical variables were compared using either the χ^2 test or the Asymptotic Linear-by-Linear Association Test.

The Deming regression was used to assess the relationship between visfatin/NAMPT measurements with EIA and ELISA, with the BACON algorithm to check the occurrence of outliers.[20]

To assess the relationship between plasma visfatin/NAMPT levels and other variables, the stepwise backward multivariable linear regression analysis was used. The Cook–Weisberg and Cameron and Trivedi's decomposition tests were used to test the residuals for heteroskedasticity as well as the violation of skewness and kurtosis assumptions in linear regression. Multicollinearity was evaluated by calculating the variance inflation factor, which should not exceed 5. As a measure of the effect size for regression analysis, we used η^2, which is the proportion of the total variance attributed to an effect. Larger values of η^2 indicate greater influence on the dependent variable.

RESULTS

Of 3050 elderly PolSenior study participants with available plasma samples for the visfatin/NAMPT measurement, we excluded 317 subjects (10.4%) with insufficient data as well as subjects diagnosed with cancer (n = 127 [22.7%]), heart failure (n = 133 [23.8%]), stages IV and V of chronic kidney disease with an estimated glomerular filtration rate of less than 30 ml/min/1.7m^2 (n = 63 [11.3%]) or an albumin-to-creatinine ratio exceeding 300 mg/g (n = 61 [10.9%]), underweight (BMI <18.5 m^2/kg [n = 283; 50.6%]). The final analysis included the data of 2174 subjects (45.6% of women). Characteristics of the subjects are presented in TABLES 1 and 2.

Characteristics of the study group A total of 1378 subjects (63.4% of the study group) met the criteria of MS (TABLES 1 and 2). The prevalence of MS was significantly higher among women (71.2%) than among men (56.8%), P <0.001. Women with MS had a greater prevalence of obesity (53.1% vs 38.7%, P <0.001) and visceral obesity (98.2% vs 95.7%, P <0.01), hypertension (95.0% vs 92.0%, P <0.05), hypertriglyceridemia (44.3% vs 39.3%, P <0.001), and low HDL cholesterol levels (55.7 vs 41.2%, P<0.001) compared with men. The frequency of type 2 diabetes was similar among men and women (34.7% and 34.1%, respectively).

TABLE 1 Characteristics and comparison of subgroups according to metabolic syndrome occurrence in women

	All n = 992	MS+ n = 706 (71.2%)	MS– n = 286 (28.8%)	*P* value
age, y	76 ±8	76 ±8	77 ±8	0.1
age ≥80 years	339 (34.2)	231 (32.7)	108 (37.8)	0.1
BMI, kg/m^2	30.0 ±5.3	30.9 ±5.1	27.5 ±5.0	<0.001
obesity	464 (46.8)	375 (53.1)	89 (31.1)	<0.001
waist circumference, cm	98.1 ±13.0	101.0 ±12.0	91.0 ±12.8	<0.001
visceral obesity	918 (92.5)	693 (98.2)	225 (78.7)	<0.001
systolic blood pressure, mmHg	147 ±21	149 ±20	143 ±22	<0.001
diastolic blood pressure, mmHg	86 ±11	87 ±10	84 ±11	<0.001
hypertension	871 (87.8)	671 (95.0)	200 (69.9)	<0.001
type 2 diabetes	249 (25.1)	241 (34.1)	8 (2.8)	<0.001
serum glucose, mmol/l	5.29 (4.81–6.02)	5.61 (5.04–6.38)	4.87 (4.55–5.20)	<0.001
insulin, μIU/ml	12.7 (9.0–18.4)	14.5 (9.9–19.6)	9.8 (7.1–13.2)	<0.001
HOMA-IR	3.11 (2.01–4.70)	3.62 (2.42–5.44)	2.16 (1.49–2.94)	<0.001
HOMA-IR[a]	2.75 (1.80–3.98)	3.18 (2.15–4.36)	2.13 (1.48–2.91)	<0.001
HOMA-IR ≥2.5	631 (63.6)	514 (72.8)	117 (40.9)	<0.001
total cholesterol, mmol/l	5.51 ±1.23	5.43 ±1.31	5.71 ±0.99	<0.001
LDL cholesterol, mmol/l	3.25 ±1.06	3.15 ±1.10	3.47 ±0.90	<0.001
HDL cholesterol, mmol/l	1.39 ±0.36	1.29 ±0.33	1.62 ±0.32	<0.001
triglycerides, mmol/l	1.56 ±0.77	1.73 ±0.83	1.13 ±0.29	<0.001
hypercholesterolemia	791 (79.7)	571 (80.9)	220 (76.9)	0.2
low HDL cholesterol levels	415 (41.8)	393 (55.7)	22 (7.7)	<0.001
hypertriglyceridemia	318 (32.1)	313 (44.3)	5 (1.7)	<0.001
statins	280 (28.2)	258 (36.5)	22 (7.7)	<0.001
fibrates	14 (1.4)	14 (2.0)	0	–
hsCRP, mg/l	2.38 (1.21–4.55)	2.64 (1.33–4.98)	1.89 (1.04–3.60)	<0.001
hsCRP ≥3 mg/l	410 (41.6)	316 (45.1)	94 (33.1)	<.001
interleukin 6, pg/ml	2.1 (1.4–3.2)	2.1 (1.4–3.3)	1.8 (1.2–2.8)	<0.001
serum albumin, g/l	42.9 ±2.93	42.9 ±2.9	43.1 ±2.9	0.5
$eGFR_{MDRDfull,}$ ml/min/1.73 m^2	65.7 ±15.6	64.8 ±15.5	68.0 ±15.8	<0.01
eGFR <60 ml/min/1.73 m^2	356 (35.9)	277 (39.2)	79 (27.6)	<0.001
ACR, mg/g	4.49 (2.01–11.80)	4.34 (2.05–12.19)	4.81 (1.94–11.27)	0.9

Data are presented as number (percentage) of patients, mean value ± standard deviation, or median (lower and upper quartiles).

a excluding diabetics

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; HDL, high-density lipoprotein; hsCRP, high--sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance, LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease

The number of subjects with respective MS components are shown in TABLE 3.

Inflammation Only women with MS were characterized by increased concentrations of inflammatory markers: high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) in comparison with those without MS (TABLE 1). Additionally, more women with MS had increased serum hsCRP concentrations (≥3 mg/l) than the corresponding group of men (45.1% vs 39.6%, P <0.001). An increased number of MS components was not related to the change in serum hsCRP levels either in men or in women, while the changes in the plasma levels of IL-6 have been observed in women but not in men (TABLES 3 and 4).

Insulin resistance HOMA-IR values were higher in subjects with MS both in men and women (TABLES 1 and 2). The prevalence of subjects with HOMA-IR values of 2.5 and higher were similar in men and women with MS (70.8% and 72.8%, respectively). Independently of sex, the prevalence of IR (HOMA-IR ≥2.5) increased with the number of MS components (TABLE 4).

Plasma visfatin/NAMPT levels The differences in plasma visfatin/NAMPT concentrations

TABLE 2 Characteristics and comparison of subgroups according to metabolic syndrome occurrence in men

	All n = 1182	MS+ n = 672 (56.8%)	MS– n = 510 (43.2%)	*P* value
age, y	77 ±8	77 ±8	78 ±8	<0.01
age ≥80 years	478 (40.4)	251 (37.3)	227 (44.5)	<0.05
BMI, kg/m^2	27.9 ±4.3	29.3 ±4.0	26.0 ±3.8	<0.001
obesity	333 (28.2)	260 (38.7)	73 (14.3)	<0.001
waist circumference, cm	102.0 ±12.3	106.6 ±10.2	96.0 ±12.1	<0.001
visceral obesity	933 (78.9)	643 (95.7)	290 (56.9)	<0.001
systolic blood pressure, mmHg	146 ±22	148 ±21	142 ±21	<0.001
diastolic blood pressure, mmHg	82 ±11	83 ±10	81 ±11	<0.001
hypertension	962 (81.4)	618 (92.0)	344 (67.5)	<0.001
type 2 diabetes	256 (21.7)	233 (34.7)	23 (4.5)	<0.001
serum glucose, mmol/l	5.34 (4.88–6.01)	5.79 (5.24–6.67)	4.99 (4.65–5.31)	<0.001
insulin, μIU/ml	10.8 (7.3–16.1)	13.4 (9.3–19.7)	8.2 (5.7–11.6)	<0.001
HOMA-IR	2.61 (1.66–4.20)	3.56 (2.31–5.63)	1.84 (1.24–2.63)	<0.001
HOMA-IR[a]	2.36 (1.53–3.60)	3.22 (2.23–4.56)	1.81 (1.24–2.62)	<0.001
HOMA-IR ≥2.5	619 (52.4)	476 (70.8)	143 (28.0)	<0.001
total cholesterol, mmol/l	5.06 ±1.10	4.99 ±1.18	5.16 ±0.97	<0.01
LDL cholesterol, mmol/l	3.04 ±0.97	2.92 ±1.02	3.19 ±0.88	<0.001
HDL cholesterol, mmol/l	1.25 ±0.34	1.15 ±0.31	1.39 ±0.32	<0.001
triglycerides, mmol/l	1.40 ±0.72	1.65 ±0.83	1.07 ±0.34	<0.001
hypercholesterolemia	776 (65.7)	488 (72.6)	288 (56.5)	<0.001
low HDL cholesterol levels	316 (26.7)	277 (41.2)	39 (7.7)	<0.001
hypertriglyceridemia	275 (23.3)	264 (39.3)	11 (2.2)	<0.001
statins	286 (24.2)	244 (36.3)	42 (8.2)	<0.001
fibrates	17 (1.4)	17 (2.53)	0	–
hsCRP, mg/l	2.03 (0.98–4.57)	2.09 (1.03–4.54)	1.90 (0.91–4.66)	0.1
hsCRP ≥3 mg/l	451 (38.3)	265 (39.6)	186 (36.7)	0.3
interleukin 6, pg/ml	2.2 (1.4–3.6)	2.2 (1.5–3.5)	2.1 (1.4–3.8)	0.3
serum albumin, g/l	43.1 ±3.1	43.5 ±3.0	42.7 ±3.0	<0.001
$eGFR_{MDRDfull}$, ml/min/1.73 m^2	69.8 ±16.3	68.6 ±16.6	71.4 ±15.8	<0.01
eGFR <60 ml/min/1.73 m^2	330 (27.9)	210 (31.2)	120 (23.5)	<0.01
ACR, mg/g	3.86 (1.54–11.74)	4.13 (1.56–12.01)	3.50 (1.49–11.71)	0.5

Data are presented as number (percentage) of patients, mean value ± standard deviation, or median (lower and upper quartiles).

a excluding diabetics

Abbreviations: see TABLE 1

between subjects with and without MS were significant only in women (FIGURE 1), including the subgroup of women not treated with statins (1.03 [0.66–1.93] vs 0.84 [0.54–1.36] ng/dl; P <0.001), but not those on statin therapy (1.08 [0.62–1.66] vs 1.00 [0.59–1.73] nd/dl; P = 0.96). Among women, the lowest visfatin/NAMPT concentration was observed in subjects with 1 MS component, and the concentration increased with the number of MS components, reaching the highest levels in subjects with 4 components (TABLE 3). The number of MS components was more strongly associated with increased plasma visfatin/NAMPT concentrations than the combination of MS components (TABLE 4).

There was no association between the number of MS components and plasma visfatin/NAMPT levels among men, regardless of statin therapy. None of the study subjects received thiazolidinediones.

Finally, we performed the stepwise backward multivariate linear regression analysis of plasma visfatin/NAMPT concentrations, including the following potentially explanatory variables: age, sex, MS, statin treatment, HOMA-IR, and hsCRP, IL-6, and albumin values (TABLE 5). The analysis confirmed that the effect of inflammation on plasma visfatin/NAMPT concentrations is independent from age.

Comparison of visfatin/NAMPT measurements using enzyme-linked immunosorbent assay and enzyme immunoassay From 244 randomly selected plasma samples for the assessment of visfatin/NAMPT

TABLE 3 Visfatin/NAMPT, high-sensitivity C-reactive protein, and interleukin 6 concentrations as well as insulin resistance (defined as HOMA-IR ≥2.5) in relation to the number of metabolic syndrome components in women and men

	Number of MS components						*P* value
	0	1	2	3	4	5	
women							
n	11 (1.1)	64 (6.5)	211 (21.3)	306 (30.8)	274 (27.6)	126 (12.7)	
age, y	77 ±11	77 ±9	77 ±8	77 ±8	75 ±7	75 ±7	0.1
visfatin/NAMPT, ng/ml	0.96 (0.60–1.25)	0.71 (0.51–1.11)	0.93 (0.57–1.50)	1.06 (0.60–1.90)	1.08 (0.73–1.84)	0.98 (0.56–1.88)	<0.001
visceral obesity	0	37 (57.8)	188 (89.1)	293 (95.75)	274 (100)	126 (100)	<0.001
serum glucose ≥5.6 mmol/l or type 2 diabetes	0	1 (1.6)	14 (6.6)	120 (39.2)	184 (67.1)	126 (100)	<0.001
triglycerides ≥1.7 mmol/l or treatment with fibrates	0	0	5 (2.4)	53 (17.3)	134 (48.9)	126 (100)	<0.001
low HDL or its treatment	0	4 (6.2)	37 (17.5)	171 (55.9)	240 (87.6)	126 (100)	<0.001
hypertension	0	22 (34.4)	178 (84.4)	281 (91.8)	264 (96.3)	126 (100)	<0.001
hsCRP, mg/l	2.36 (0.61–4.45)	1.44 (0.98–2.87)	2.11 (1.14–4.07)	2.86 (1.44–5.30)	2.47 (1.26–4.62)	2.81 (1.32–4.68)	<0.001
interleukin 6, pg/ml	2.20 (1.40–4.20)	1.75 (1.15–2.50)	1.85 (1.30–2.90)	2.10 (1.40–3.20)	2.20 (1.40–3.40)	2.00 (1.60–3.10)	<0.01
HOMA-IR ≥2.5	3 (23.3)	25 (39.1)	89 (42.2)	186 (60.8)	213 (77.7)	115 (91.3)	<0.001
men							
n	36 (3.0)	160 (13.5)	314 (26.6)	337 (28.5)	246 (20.8)	89 (7.5)	
age, y	80 ±9	79 ±8	78 ±8	77 ±7	77 ±8	75 ±8	<0.01
visfatin/NAMPT, ng/ml	0.88 (0.61–1.32)	0.75 (0.54–1.67)	0.96 (0.58–1.60)	0.97 (0.56–1.58)	1.02 (0.65–1.66)	0.84 (0.60–1.36)	0.3
visceral obesity	0	50 (31.2)	240 (76.4)	311 (92.3)	243 (98.8)	89 (100)	<0.001
serum glucose ≥5.6 mmol/l or type 2 diabetes	0	9 (5.6)	57 (18.1)	183 (54.3)	195 (79.3)	89 (100)	<0.001
triglycerides ≥1.7 mmol/l of fibrates	0	1 (0.6)	10 (3.2)	50 (14.8)	125 (50.8)	89 (100)	<0.001
low HDL levels or their treatment	0	15 (9.4)	62 (19.7)	165 (49.0)	194 (78.9)	89 (100)	<0.001
hypertension	0	85 (53.1)	259 (82.5)	302 (89.6)	227 (92.3)	89 (100)	<0.001
hsCRP, mg/l	1.47 (0.79–4.22)	1.41 (0.83–3.56)	2.31 (0.98–4.93)	2.02 (0.95–4.53)	2.26 (1.25–4.79)	2.01 (1.05–4.13)	<0.001
interleukin 6, pg/ml	2.05 (1.55–3.60)	2.10 (1.30–3.30)	2.10 (1.40–4.00)	2.20 (1.40–3.50)	2.40 (1.60–3.80)	2.10 (1.50–3.10)	0.4
HOMA-IR ≥2.5	2 (5.6)	32 (20.)	109 (34.7)	194 (57.6)	200 (81.3)	82 (92.1)	<0.001

Data are presented as number (percentage) of patients, mean value ± standard deviation, or median (lower and upper quartiles).

Abbreviations: NAMPT, nicotinamide phosphoribosyltransferase; others, see **TABLE 1**

levels with the EIA method, data from 17 subjects (7.0%) were removed as outliers with the BACON algorithm. Plasma visfatin/NAMPT levels assessed with EIA were 10.1-fold greater than those measured with ELISA (10.72 ng/dl [7.92–13.07] vs 1.03 ng/dl [0.66–1.49] ng/dl). Subsequently, the Deming regression between the EIA and ELISA methods was done with the following results: intercept 0.99 (95% confidence interval [CI], 0.97–1.02), slope 0.12 (95% CI, 0.04–0.22), and R^2 of 0.02 (**FIGURE 2**). The results indicate that there is no relationship between those 2 measurement methods.

DISCUSSION In our study, plasma visfatin/NAMPT concentrations were slightly but significantly higher in women with MS than those without MS (1.06 vs 0.85 ng/ml, respectively), and did not differ in the corresponding subgroups of men (0.97 vs 0.9 ng/ml, respectively). Moreover, in line with the previous study performed using EIA, plasma visfatin/NAMPT concentrations increased with the number of MS components.[21]

As mentioned above, our study is the first to analyze plasma visfatin/NAMPT levels with highly specific ELISA method in subjects with MS. The comparison of EIA and ELISA methods performed

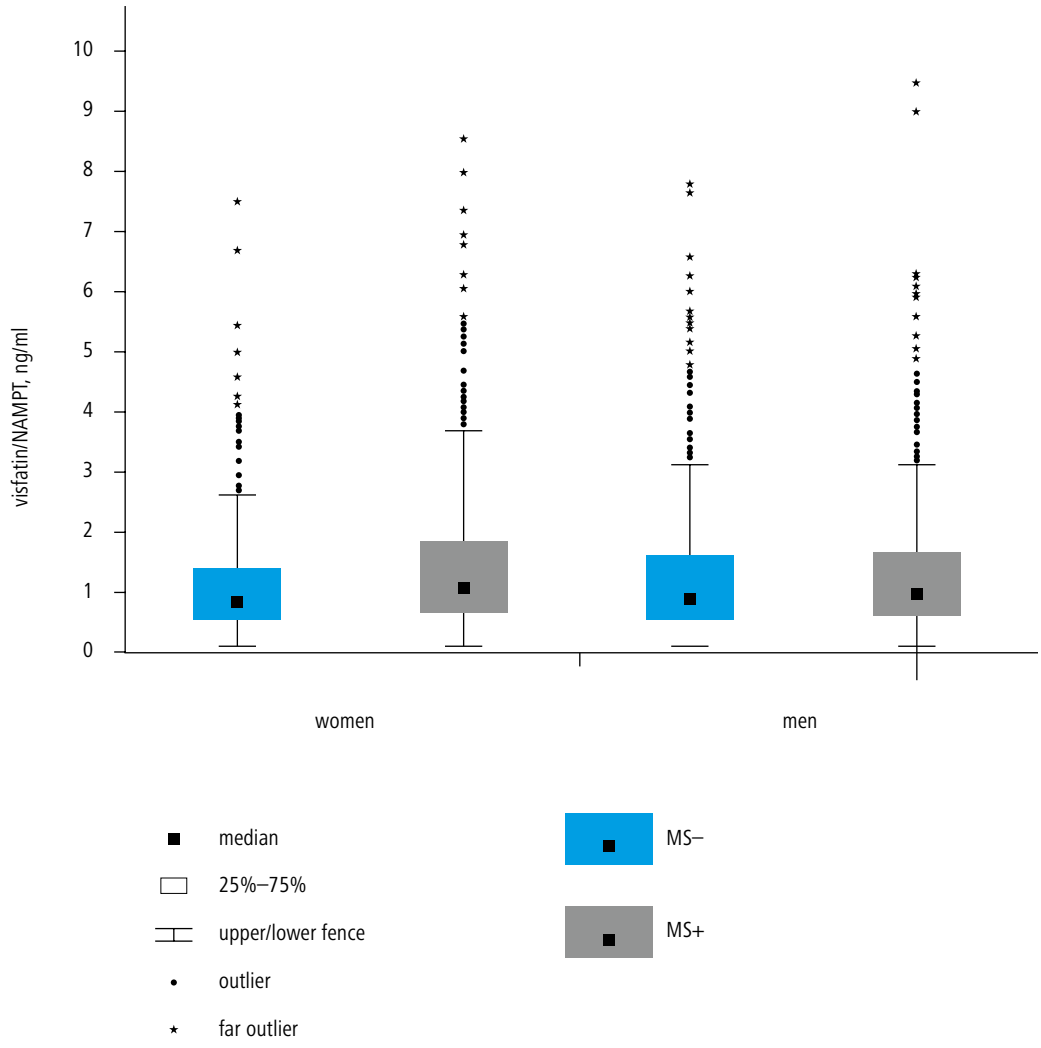

FIGURE 1 Plasma visfatin/NAMPT concentrations in elderly men and women with and without metabolic syndrome (MS). The difference between subjects with and without MS was significant only in women (P <0.001)

in a subset of study subjects showed not only calibration differences (about 10-fold lower concentrations) but also an overall poor agreement of both methods, which is in line with previously published data.[16,17] Nevertheless, we showed that plasma visfatin/NAMPT levels are increased in MS (but only in women), which is in line with a meta-analysis by Chang et al.[22] of studies performed using EIA in subjects with MS based on the IDF criteria for MS.

Visfatin/NAMPT was supposed to be considered as a biomarker of MS, and even as a predictor of MS development.[23] It seems that plasma visfatin/NAMPT levels in subjects with MS mostly reflect the severity of obesity-related systemic microinflammation, rather than IR.[15] The hypothesis of the insulin-like action of visfatin/NAMPT was abandoned. In addition, increased visfatin levels were observed with deterioration of β-cell function.[24]

The link between hypertension and circulating plasma visfatin/NAMPT levels is questionable. Only studies utilizing nonspecific visfatin/NAMPT EIA kits showed higher concentrations in hypertensive patients.[25,26] On the other hand, studies using the ELISA method failed to show such an association.[27,28] However, as IR is an important pathophysiological link between obesity and hypertension[29] and is associated with the increased circulating visfatin/NAMPT levels, the relationship between hypertension and visfatin/NAMPT levels could be expected. It cannot be excluded that it is related to the influence of obesity on the prevalence of hypertension, which decreases with age.[30] As plasma visfatin/NAMPT levels were not assessed by ELISA in young obese patients with hypertension, this hypothesis cannot be verified.

Finally, there are only few (mostly association) studies showing the correlation between lipid disturbances and circulating visfatin/NAMPT levels in subjects with MS.[31] Probably, it is the effect of microinflammation and IR related to obesity. Our recent analysis with structural equation modeling supported a correlation between visfatin/NAMPT levels, nutritional status, and inflammation, but not lipid disturbances, in the PolSenior population.[32] Of interest, statin therapy abolished the association between MS factors and plasma visfatin levels.

The role of visfatin/NAMPT in the pathogenesis of obesity-related cardiovascular complications of MS has not been fully elucidated so far. There is some evidence demonstrating an association between circulating visfatin/NAMPT levels and impaired flow-mediated dilation, suggesting

TABLE 4 Visfatin/NAMPT, high-sensitivity C-reactive protein, and interleukin 6 concentrations as well as insulin resistance (defined as HOMA-IR ≥2.5) in women and men with the most common (n >30) combinations of metabolic syndrome components

Visceral obesity	Carbohydrate metabolism disturbances	High triglycerides levels	Low HDL cholesterol levels	Hypertension	n	Visfatin/NAMPT, ng/ml	HsCRP, mg/l	Interleukin 6, pg/ml	HOMA-IR ≥2.5, n (%)
women									
1	0	0	0	0	37	0.78 (0.54–1.23)	1.5 (1.2–2.6)	1.7 (1.2–2.5)	16 (43.2)
1	0	0	0	1	155	0.95 (0.57–1.50)	2.2 (1.3–4.0)	1.9 (1.3–3.0)	65 (41.9)
1	0	0	1	1	137	1.19 (0.62–1.87) [a]	2.4 (1.2–4.6)	2.2 (1.4–3.4) [a]	67 (48.9)
1	0	1	0	1	36	1.02 (0.66–1.74)	3.3 (1.7–5.6)	2.0 (1.3–2.7)	18 (50.0)
1	1	0	0	1	95	1.02 (0.61–1.92) [a]	3.3 (1.3–5.8)	2.2 (1.4–3.4) [a]	75 (78.9)
1	0	1	1	1	90	1.13 (0.80–1.82) [b]	2.6 (1.3–4.6)	2.1 (1.4–3.3)	53 (58.9)
1	1	0	1	1	140	1.00 (0.70–1.69)	2.6 (1.2–5.0)	2.5 (1.6–3.8) [a]	120 (85.7)
1	1	1	0	1	34	1.32 (0.72–1.98) [a]	2.4 (1.4–5.2)	2.0 (1.3–2.8)	31 (91.2)
1	1	1	1	1	126	0.98 (0.56–1.88)	2.8 (1.3–4.7)	2.0 (1.6–3.1)	115 (91.3)
P_{ANOVA}						<0.05	0.08	<0.01 (1-β = 0.93)	χ^2 =15.1; P <0.001
men									
0	0	0	0	0	36	0.88 (0.61–1.32)	1.5 (0.8–4.2)	2.0 (1.6–3.6)	2 (5.6)
0	0	0	0	1	85	0.73 (0.55–1.60)	1.5 (0.8–5.0)	2.4 (1.6–3.3)	10 (11.8)
1	0	0	0	0	50	0.70 (0.51–1.67)	1.5 (0.9–2.7)	1.7 (0.9–3.1)	16 (32.0)
0	1	0	0	1	32	1.07 (0.56–1.77)	3.0 (0.8–6.0)	1.9 (1.6–4.2)	9 (28.1)
1	0	0	0	1	187	0.97 (0.59–1.63)	2.3 (1.1–5.3)	2.1 (1.3–4.0)	59 (32.0)
0	0	0	1	1	33	0.68 (0.48–1.56)	2.2 (0.9–5.4)	2.8 (1.6–4.6)	14 (42.4)
1	0	0	1	1	116	0.87 (0.56–1.26)	1.9 (0.7–4.7)	2.0 (1.4–3.4)	42 (36.2)
1	1	0	0	1	131	0.86 (0.53–1.64)	2.1 (1.0–5.0)	2.2 (1.4–3.4)	90 (68.7)
1	1	0	1	1	121	1.05 (0.60–1.67)	2.0 (1.2–4.3)	2.5 (1.6–4.0)	97 (80.2)
1	0	1	1	1	51	0.96 (0.67–1.58)	2.8 (1.5–6.6)	2.4 (1.5–4.0)	41 (80.4)
1	1	1	0	1	52	1.05 (0.72–1.64)	2.2 (1.6–5.8)	2.1 (1.6–3.2)	43 (82.7)
1	1	1	1	1	89	0.84 (0.60–1.36)	2.0 (1.1–4.1)	2.1 (1.5–3.1)	82 (92.1)
P_{ANOVA}						0.51	0.30	0.43	χ^2 =85.5; P <0.001

Data are presented as median (lower and upper quartiles).

a P 0.05, **b** P <0.01; statistical significance vs '00001' in women

Abbreviations: ANOVA, analysis of variance; others, see **TABLES 1** and **3**

TABLE 5 Results of the stepwise backward multivariate linear regression analysis

$\log_{10}$(visfatin) × 1000	b	h^2 (%)	±95% CI	t	*P* value
metabolic syndrome, yes	40.88	34.99	11.68–70.085	2.75	<0.01
serum albumin, g/l	5.028	18.13	0.03–10.022	1.97	<0.05
$\log_{10}$ (interleukin 6), pg/ml	55.56	18.63	11.38–109.99	2.00	<0.05
$\log_{10}$ (CRP), mg/l	37.39	20.59	25.51–72.25	2.10	<0.05
age, y	–1.94	19.68	–3.80 to –0.09	–2.06	<0.05
constat	–129.92	–	–415.35 to 155.55	–0.89	0.372

Abbreviations: see TABLE 1

their role in the development of endothelial dysfunction,[12] an early stage of atherogenesis.[33] Additionally, increased plasma visfatin/NAMPT levels were associated with carotid artery intima–media thickness, a surrogate marker of atherosclerosis in subjects with obesity and type 2 diabetes.[34] Furthermore, as demonstrated by our previous analysis, increased plasma visfatin/NAMPT levels are typical especially for obese subjects with low-grade systemic inflammation.[32]

The results of the present study show a more pronounced increase of plasma visfatin/NAMPT levels in women than in men with MS. It could be explained by more severe inflammation in obese women than in men. In line with previously published studies,[35,36] we showed higher serum CRP levels in women with MS than in the corresponding subgroup of men (2.64 vs 2.09 mg/l, respectively). As a result, there was a higher percentage of subjects with CRP levels of 3 mg/l or higher in women than in men with MS (45.1% vs 39.6%, respectively). One of the potential explanations of the difference in CRP concentrations between men and women is the influence of estrogens.[37] However, we analyzed the population of elderly postmenopausal women with a negligible frequency of hormone replacement therapy (0.2%) in the PolSenior population. Therefore, the explanation of the difference is rather a greater percentage of total body fat, and even more

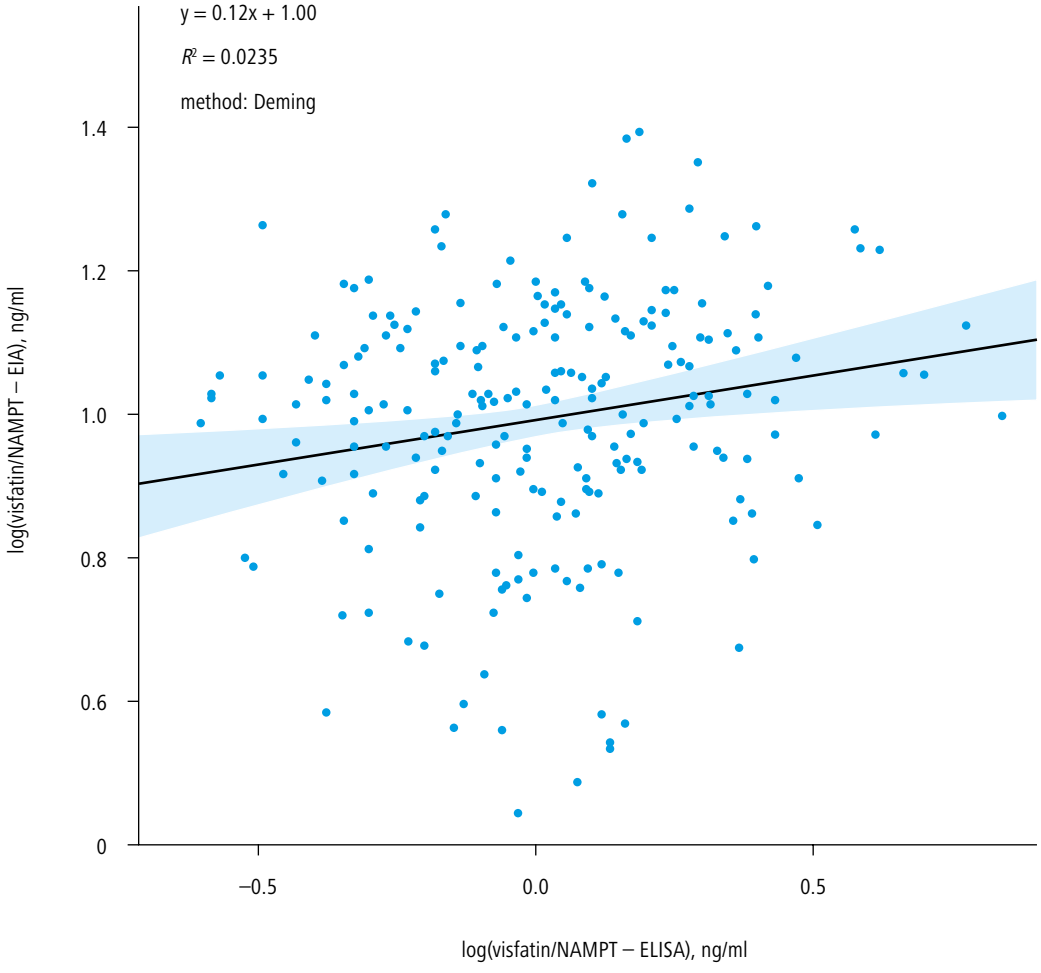

FIGURE 2 Deming regression plot between plasma visfatin/NAMPT concentrations measured with enzyme-linked immunosorbent assay (ELISA) and enzyme immunoassay (EIA) in 227 subjects

considerably, of visceral fat, a source of proinflammatory cytokines and visfatin/NAMPT per se, in women than in men. This hypothesis is also supported by a significantly higher serum IL-6 concentration in women with MS than in those without MS (2.1 vs 1.8 pg/ml, respectively) and a similar concentration in the corresponding groups of men (2.2 vs 2.1 pg/ml, respectively). It is in line with other studies showing higher levels of inflammatory markers in women with MS, possibly the effect of more prevalent visceral obesity among women.[36] One of these obesity-related inflammatory markers is IL-6,[38] a well-known proinflammatory cytokine with increased concentrations in subjects with MS and type 2 diabetes.[39]

In our study, we found a more prevalent low serum HDL cholesterol concentrations and hypertriglyceridemia in women than in men (41.8% vs 26.7% and 32.1% vs 23.3%, respectively) and in subjects with MS than in those without MS (55.7% vs 7.7%, 44.3% vs 1.7% in women, respectively, and 41.2% vs 7.7% and 39.3% vs 2.2% in men, respectively). The results are to a large extent in accordance with other epidemiological studies showing higher prevalence of visceral obesity, low HDL cholesterol concentrations, high BP, and abnormal glucose metabolism with a higher number of MS components in women in analysis of a large cohort of 30 111 women from the Nurses' Health Study and 16 695 men from the Health Professional Follow-up Study.[40]

The percentage of diabetic subjects was higher (although not significantly) among women than among men (25.1% vs 21.7%, respectively). It is in line with previously published data showing higher prevalence of diabetes mellitus in women in developed countries[41] and in China.[42] Only in developing countries, the prevalence of diabetes is greater among men.[43] The greater prevalence is probably due to a higher percentage of visceral fat accumulation in women.[44]

Visceral adipose tissue is the main source of cytokines and free fatty acids involved in the development of liver IR, resulting in abnormalities in the lipid profile. Thus, the frequent prevalence of visceral obesity in women is the cause of low-grade inflammation, IR, dyslipidemia, and hypertension.[45] It should be noted that visceral fat distribution in women increases with age and is particularly common in postmenopausal women.[46] In addition, IR related to visceral obesity may increase hepatic CRP production.[47]

Notwithstanding the more pronounced visceral obesity that leads to a higher level of low-grade inflammation, more advanced metabolic disturbances reported in women in comparison with men with MS, and associated with increased levels of visfatin/NAMPT, may be a marker of the severity of disturbances, classified as MS, and potential indicator of its complications.[48] However, relatively small differences in plasma visfatin/NAMPT levels between the different numbers of MS components preclude their use in clinical practice.

The main new data presented in our study is the lack of the association between visfatin/NAMPT and the number of MS components showed with EIA,[23] but the severity of systemic inflammation associated with excess visceral fat.[15] Moreover, we showed that visfatin/NAMPT levels are higher only in obese women with MS and not in men as reported previously,[49] reflecting that disturbances in adipokine release are secondary to obesity more pronounced in women. The use of a more specific assay for visfatin/NAMPT determination showed that its level is not associated with glucose and insulin levels. This observation is inconsistent with our previously published data obtained with EIA[14] and supports the hypothesis that visfatin/NAMPT should be considered as a marker of inflammation not directly involved in the homeostasis of glucose metabolism.

Our study has a number of limitations related to its cross-sectional design. First, the establishment of the cause–effect relationship was not possible. Additionally, we were unable to demonstrate which of the MS components had a greater impact on plasma visfatin/NAMPT levels. However, the strength of our study are the statistical analyses including a large group of elderly subjects with comprehensive biochemical characteristics and the appropriate method (ELISA) of the visfatin/NAMPT measurement.

In conclusion, our study showed that plasma visfatin/NAMPT levels are increased only in elderly women with MS. It is difficult to distinguish the components of MS specifically associated with increased plasma visfatin/NAMPT levels.

Contribution statement PK, MO-G, and JC conceived the idea for the study. MM, TZ, AS, and AW contributed to the design of the research. MB-W and AB assessed visfatin/NAMPT levels. WK and PO were involved in data collection. AO performed the statistical analysis. JC coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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Stężenie wisfatyny/fosforybozylotransferazy nikotynamidu (wisfatyny/NAMPT) w osoczu u osób starszych z zespołem metabolicznym

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insulinooporność, mikrozapalenie, wisfatyna/NAMPT, zespół metaboliczny

STRESZCZENIE

WPROWADZENIE Tkanka tłuszczowa trzewna jest głównym źródłem wisfatyny/ fosforybozylotransferazy nikotynamidu (wisfatyna/NAMPT), adipokiny prozapalnej, której rola w patogenezie składowych zespołu metabolicznego (ZM) takich jak nadciśnienie tętnicze, zaburzenia gospodarki węglowodanowej oraz zaburzenia gospodarki lipidowej pozostaje niejasna, także z powodu stosowania do oznaczania jej fragmentów C-końcowych zestawów o niskiej swoistości.

CELE Celem badania była ocena związku pomiędzy składowymi ZM oraz osoczowym stężeniem wisfatyny/NAMPT w populacji osób w podeszłym wieku.

PACJENCI I METODY Analizą objęto 2174 osoby w podeszłym wieku z populacji badania PolSenior bez niewydolności serca, ciężkiej przewlekłej choroby nerek, choroby nowotworowej oraz niedożywienia. ZM definiowano na podstawie kryteriów International Diabetes Federation. Stężenie wisfatyny/NAMPT w osoczu oznaczono przy użyciu wysoce swoistej metody ELISA. Oznaczono także stężenia hs-CRP, interleukiny 6 (IL-6) oraz insuliny, a dla oceny insulinooporności zastosowano wskaźnik HOMA-IR.

WYNIKI ZM częściej rozpoznawano u kobiet niż u mężczyzn (71,2% *vs* 56,8%, p <0,001); u kobiet odnotowano również większą częstość wszystkich składowych ZM z wyjątkiem cukrzycy typu 2. U kobiet z ZM stwierdzono podwyższone stężenia hs-CRP, IL-6 w porównaniu z kobietami bez ZM. Stężenia wisfatyny/NAMPT były wyższe u kobiet z ZM w porównaniu z kobietami bez ZM (1,06 ng/ml [0,65–1,87] *vs* 0,85 ng/ml [0,54–1,40]; p <0,001), natomiast nie zaobserwowano różnic w jej stężeniu u mężczyzn (odpowiednio: 0,97 ng/ml [0,59–1,61] *vs* 0,90 ng/ml [0,56–1,60]; p = 0,5). Silniejszy związek liczby składowych ZM ze stężeniem wisfatyny/NAMPT stwierdzono u kobiet.

WNIOSKI Stężenie wisfatyny/NAMPT w osoczu jest wyższe wyłącznie u kobiet w podeszłym wieku z ZM. Trudno wyróżnić składowe ZM szczególnie związane z podwyższonym stężeniem wisfatyny/NAMPT.

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