







Article

Adipolin, Chemerin, Neprilysin and Metabolic Disorders Associated with Obesity

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Abstract: Adipolin, neprilysin, and chemerin have pleiotropic properties; therefore, their concentrations may influence health complications associated with obesity. The study aimed to search the relationship between adipokine levels and anthropometric and metabolic parameters as well as blood pressure values, taking into account the influence of gender and age. The study group consisted of 88 people aged 30–60 years. It was found that chemerin concentration is positively correlated with glycaemia in the 120' OGTT ($rs = 0.412$; $p = 0.030$) in obese women. There was a negative correlation between adipolin and LDL-C serum concentration ($rs = -0.414$; $p = 0.044$) in obese individuals with normal glucose tolerance and a positive correlation between chemerin concentration and triglyceridemia ($rs = 0.333$; $p = 0.033$) in the men. Moreover, high chemerin levels (above median values) were observed 3.79 times more frequently ($OR = 3.79$; 95% CI: 1.03–13.91; $p = 0.040$) in the male population characterized by elevated triglyceride levels (above 1.7 mmol/L). In the logistic regression analyses, we found that the frequency of high plasma adipolin concentrations increases with age ($p = 0.005$) only in people with a BMI $< 30 \text{ kg/m}^2$. It was also shown that the concentrations of the studied adipokines are interrelated. Adipolin, neprilysin and chemerin concentrations are associated with selected anthropometric and metabolism exponents.

Keywords: adipokines; adipolin; chemerin; neprilysin; obesity; insulin resistance; hypertension



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1. Introduction

Obesity disrupts the homeostasis of the secretion of adipokines, which are biologically active molecules secreted by adipose tissue. Adipokines have many essential functions in the human body—among others, they regulate metabolic and inflammatory processes and participate in adipogenesis [1–3]. The number of newly discovered adipokines is systematically increasing, and due to their pleiotropic effects, they have become an interesting research area. High hopes lie in their use as early biomarkers associated with the development of metabolic syndrome in overweight individuals.

The adipokines analyzed in this study—adipolin, chemerin, and neprilysin—were chosen due to their impact on tissue metabolism and insulin sensitivity [3,4]. Their mechanisms of action are not fully understood, and the results of studies determining the relationships between their blood concentrations and anthropometric and metabolic parameters in humans are inconclusive. According to scientific reports, adipolin has potentially

beneficial metabolic effects, while the other two—neprilysin and chemerin—show adverse metabolic effects.

Adipolin is one of the few adipokines with anti-inflammatory and insulin resistance-reducing effects. The FAM132A gene encodes adipolin (C1q/TNF-related protein 12, CTRP12). Overexpression of the FAM132A gene in obese mice improves insulin sensitivity, as reflected by a reduction in fasting glucose levels, a decrease in the Homeostasis Model Assessment—Insulin Resistance (HOMA-IR) score, or improved glucose tolerance [5]. In contrast, gene ablation increases body weight and insulin resistance in male mice with high-fat diets. For females, the opposite effect—a decrease in body weight despite a high-fat diet—has been observed [6]. Humans with a fragment of chromosome 1 (1p36.33) that includes the FAM132A locus deletion developed hyperphagia, obesity, hyperinsulinemia, and impaired glucose tolerance [7].

Chemerin (Retinoic Acid Receptor Responder Protein 2), encoded by the RARRES2 gene, is a protein primarily synthesized by visceral adipose tissue cells [8]. Chemerin can modulate insulin action and glucose consumption. Administration of chemerin worsens glucose tolerance and reduces cellular glucose uptake in obese mice. Decreased blood levels of this adipokine are linked with improved insulin sensitivity as expressed by the Insulin Sensitivity Index (ISI) [9]. The results of this study suggest the effect of elevated chemerin concentration on the development of health dysfunctions accompanying visceral obesity. The adipokine in question may be a predictive factor for developing insulin resistance, hypertension, atherosclerosis, and numerous cardiovascular complications [10].

Neprilysin is a conserved zinc metalloprotease that hydrolyses oligopeptides by cleaving on the N-terminal side of hydrophobic amino acid residues [11]. Recent studies have shown that neprilysin is involved in the development of obesity and its metabolic consequences. In *in vivo* analyses using an experimental mouse model, several times higher neprilysin levels were observed in the blood of mice with obesity relative to normal-weight animals [12]. Neprilysin-deficient mice were also characterized by increased islet β -cell mass when fed a high-fat diet, suggesting neprilysin's role in modulating this cell type's metabolism [13].

The aim of the study was to look for the relationships between adipolin, chemerin, and neprilysin levels and anthropometric and metabolic parameters, as well as blood pressure values, taking into account the influence of gender and age of the participants.

2. Materials and Methods

2.1. Examined Population

The study continued previous research [14], so the population group was the same. Eighty-eight people, including 47 women and 41 men aged 30–60 years, were examined. The median age of the investigated population was 45.22 ± 8.08 years. The study group ($n = 51$), which included 27 women (47.71 ± 8.12 years) and 24 men (46.83 ± 8.01 years), was divided into two groups. The distribution criterion was the result of the 75 g oral glucose tolerance test (OGTT) [15]:

- normal glucose tolerance (NGT)—glycemia at 120' OGTT < 7.8 mmol/L
- abnormal glucose tolerance (AGT)—glycemia at 120' OGTT ≥ 7.8 mmol/L

Thirty-seven subjects without obesity (20 women (45.3 ± 8.21 years) and 17 men (43.29 ± 6.44 years)) were included in the control group. The characteristics of the investigated population are shown in Table 1.

2.2. Inclusion and Exclusion Criteria

Subjects with BMI > 30 kg/m², waist circumference in women ≥ 88 cm, and in men ≥ 102 cm were included in the study group. These were patients who were referred for the first time for an OGTT. They had no previously diagnosed or treated glucose tolerance disorders. The control group included those with a BMI < 30 kg/m² and waist circumference in women < 88 cm and in men < 102 cm. Furthermore, individuals with long-term illnesses affecting the endocrine and gastrointestinal systems, chronic kidney

conditions, and previous occurrences of malignancies or cardiovascular events within the last 5 years were not considered for the study. Additionally, none of the participants engaged in competitive sport, nor did they follow a weight loss or alternative diet, and their body weight had remained constant for 3 months leading up to the research.

Table 1. Characteristics of the study population.

	Obesity (<i>n</i> = 51)			No Obesity <i>n</i> = 37 (<i>w</i> = 20, <i>m</i> = 17)	<i>p</i> **
	NGT <i>n</i> = 24, (<i>w</i> = 15, <i>m</i> = 9)	AGT <i>n</i> = 27, (<i>w</i> = 12, <i>m</i> = 15)	<i>p</i> *		
Weight [kg]	112.71 ± 24.44	115.37 ± 24.38	0.699	72.24 ± 14.778	<0.001
Height [cm]	172.25 ± 9.87	170.89 ± 10.02	0.628	171.0 ± 10.121	0.806
BMI [kg/m ²]	37.71 ± 5.98	39.34 ± 6.38	0.352	24.47 ± 3.074	<0.001
Waist circumference [cm]	117.88 ± 15.55	120.19 ± 14.80	0.589	82.38 ± 10.391	<0.001
Hips circumference [cm]	123.25 ± 14.25	122.11 ± 11.89	0.757	99.59 ± 6.829	<0.001
WHR	0.96 ± 0.08	0.99 ± 0.08	0.237	0.82 ± 0.062	<0.001
Fat mass [%]	44.93 ± 7.82	45.45 ± 7.40	0.807	24.54 ± 6.40	<0.001
Lean mass [%]	55.08 ± 7.82	54.49 ± 7.28	0.781	75.46 ± 6.40	<0.001

Values are shown as means ± SD, *n*—number of subjects; *w*—women; *m*—men; *p* *—level of statistical significance comparisons groups NGT vs. AGT; *p* **—level of statistical significance comparisons obese and non-obese groups; NGT—normal glucose tolerance; AGT—abnormal glucose tolerance; BMI—body mass index; WHR—waist-to-hip ratio, partly taken from [14].

2.3. Anthropometric Testing

Participants' anthropometric data were measured in the morning while fasting and wearing only underwear. Participants were instructed to abstain from consuming alcoholic beverages and caffeine, as well as from engaging in exercise, for 24 h prior to the study. Detailed methods of anthropometric analyses for the calculation of BMI and WHR (waist–height ratio) and assessed body composition using a bioimpedance analyzer (Bodystat 1500, Bodystat Ltd., Isle of Man, UK) were described in our previous paper [14].

2.4. Measurement of Blood Pressure

Before measurement, participants sat and rested for 5 min. Blood pressure measurements were performed three times using a certificated sphygmomanometer (705IT, Omron Corporation, Kyoto, Japan). There was a two-minute pause between measurements. Results were averaged as recommended by the European Society of Hypertension and the European Society of Cardiology [16].

2.5. Biochemical Tests

Venous blood samples were taken in the morning on an empty stomach. Most analyses, i.e., assessment of glucose, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and insulin, were carried out immediately after collection. In our previous paper [14], we provided a detailed description of the formula for an index of insulin resistance and the commercial tests used to measure glucose, TG, TC, and HDL-C levels. These tests utilize colorimetric enzymatic methods for their determination.

Serum samples needed to assess adipokine concentrations were stored at −80 °C. The following certified immunoassay kits were used to determine adipokine concentrations: C1QTNF12 ADIPOLIN ELISA (Fuju Fine Chemical, Tianjin, China), Human Neprilysin (Shanghai Sunred Biochemistry Co., Ltd., Shanghai, China) and Chemerin ELISA (Mediagnost, Reutlingen, Germany).

The read absorbance of the standards and samples was measured on an MR-96 plate reader from CLINDIAG SYSTEMS B.V.B.A. (Pollare, Belgium). Serum adipokine concen-

trations were determined by plotting a 4-parameter standard curve in each case using Sigma Plot 11.00 software.

2.6. Statistical Analyses

The statistical analysis was performed using STATISTICA 13.3 software (StatSoft Inc., Tulsa, OK, USA), as well as SPSS Statistics 29.0 (IBM Corp., Armonk, NY, USA) software. To determine the normality of data distribution for small groups, the Shapiro–Wilk test was used, while the Kolmogorov–Smirnov test was employed for large groups. When the quantitative variables satisfied the conditions of normal distribution and homogeneity of variance (according to Levene’s test), the Student’s *t*-test was used. Conversely, if the data did not meet the normal distribution requirement, the non-parametric Mann–Whitney U test was applied. In cases where differences in variance were observed for data that met the normal distribution condition, the Welch test was utilized. Pearson’s and Spearman’s tests were used to analyze the correlation of the variables studied. Pearson’s test was utilized for data that met the assumptions of normality of the distribution of the independent variables analyzed. In contrast, Spearman’s test was used for data that did not meet these assumptions. Frequency tables were generated to organize the collected nominal data. The chi-square and contingency tests were employed to examine potential connections between adipokine profiles and metabolic disorders. In cases where the subsets of data had a smaller sample size, the exact Fisher test of independence was utilized, adhering to Cochran’s condition. The precision of the odds ratio (OR) was estimated using the 95% confidence interval (95% CI). The statistical analysis of the relationship between anthropometric parameters and adipolin, chemerin, and neprilysin was expanded using decision trees based on the Chi-Squared Automatic Interaction Detection (CHAID) algorithm, which was proposed by Kass [17]. CHAID, a decision tree algorithm, partitions data into more homogeneous groups through merging, splitting, and stopping steps. Additionally, the influence of variables on values of adipokines (above the median vs. median and below) was examined using logistic regression models. The significance of variables in the logistic regression models was tested using Wald Chi-Squared statistics and the corresponding *p*-value. The Hosmer–Lemeshow statistic, R² Nagelkerke coefficient, and the area under the curve (AUC) in the receiver operating characteristics curve (ROC) were used to assess the goodness-of-fit of the logistic regression models. The fulfillment of the assumption of sample size was checked according to the popular formula $n \geq 10(k + 1)$, with *k* = the number of tested parameters [18]. When the study was being designed, we established a minimum number of assays, considering calculations from statistical software. This determination was based on the results of pilot studies and the assumption that the test’s strength would be 0.8 and the type I error would be 0.05, which are commonly used parameters in medical studies. The results of all statistical analyses were considered statistically significant when the significance level was $p < 0.05$.

3. Results

3.1. Comparative Analysis of Assessed Parameters

Anthropometric parameters, metabolic parameters, blood pressure values, and adipokine concentrations in the group with and without obesity and in the group with normal and abnormal glucose tolerance were summarized. Statistical analyses were also carried out, taking gender into account.

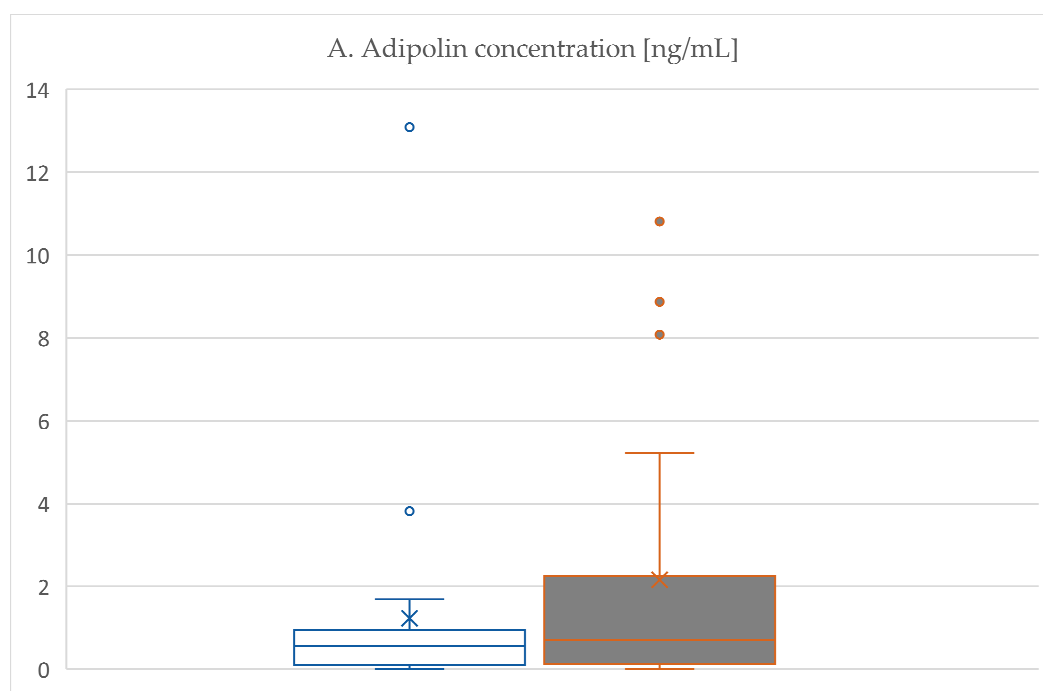
Obese subjects had statistically significantly higher fasting glucose and insulin levels and a higher HOMA-IR than non-obese subjects. In addition, obese people had higher triglyceridemia and higher blood pressure values but lower HDL-C levels. Other parameters analyzed, including adipokine concentrations, were comparable (Table 2).

Table 2. Metabolism parameters, blood pressure, and adipokine concentrations in the study population.

	Obesity (<i>n</i> = 51)	No Obesity (<i>n</i> = 37)	<i>p</i>
Fasting glucose [mmol/L]	5.65 (5.15; 6.12)	4.99 (4.55; 5.38)	<0.001
Fasting insulin [μ U/L]	12.3 (8.95; 18.45)	6.4 (4.1; 8.4)	<0.001
HOMA-IR	3.12 (2.22; 4.38)	1.37 (0.91; 1.92)	<0.001
Total cholesterol [mmol/L]	5.58 \pm 1.35	5.33 \pm 0.86	0.339
Triglycerides [mmol/L]	1.89 (1.38; 2.67)	1.06 (0.78; 1.38)	<0.001
LDL cholesterol [mmol/L]	3.67 (2.83; 4.38)	3.31 (2.66; 3.90)	0.124
HDL cholesterol [mmol/L]	1.11 (0.94; 1.30)	1.78 (1.34; 1.94)	<0.001
SBP [mm Hg]	140 (137.5; 154)	125 (106; 132)	<0.001
DBP [mm Hg]	90 (80; 100)	80 (75; 91)	<0.001
Adipolin [ng/mL]	0.60 (0.14; 1.33)	1.08 (0.13; 3.29)	0.354
Neprilysin [pg/mL]	810.63 (736.56; 1131.56)	785.94 (637.81; 1304.38)	0.736
Chemerin [ng/mL]	47.71 (35.50; 68.48)	44.59 (28.33; 74.20)	0.853

Values are shown as means \pm SD or as medians and 25%; 75% percentiles, *n*—number of subjects; HOMA-IR—Homeostatic Model Assessment—Insulin Resistance; LDL cholesterol—low-density lipoprotein cholesterol; HDL cholesterol—high-density lipoprotein cholesterol, partly taken from [14].

Comparing the results of obese subjects with NGT or AGT, there was a marked difference in glycemia at 120' of OGTT [mmol/L] (5.72 ± 1.20 vs. 9.49 ± 2.26 , $p < 0.001$) insulinemia [mU/mL] (5.20 ± 0.42 vs. 6.21 ± 0.93 , $p < 0.001$) and HOMA-IR 2.33 (1.80; 3.45) vs. 4.00 (2.72; 5.63) $p < 0.001$ and systolic blood pressure values 140.00 (135.00; 146.25) vs. 150.00 (140.00; 165.00) [mmHg] $p = 0.038$. The values of the other parameters analyzed, i.e., lipid metabolism exponents and DBP, were similar [14]. There were also no differences between the concentrations of the analyzed adipokines in these groups (Figure 1A–C).

**Figure 1.** Cont.

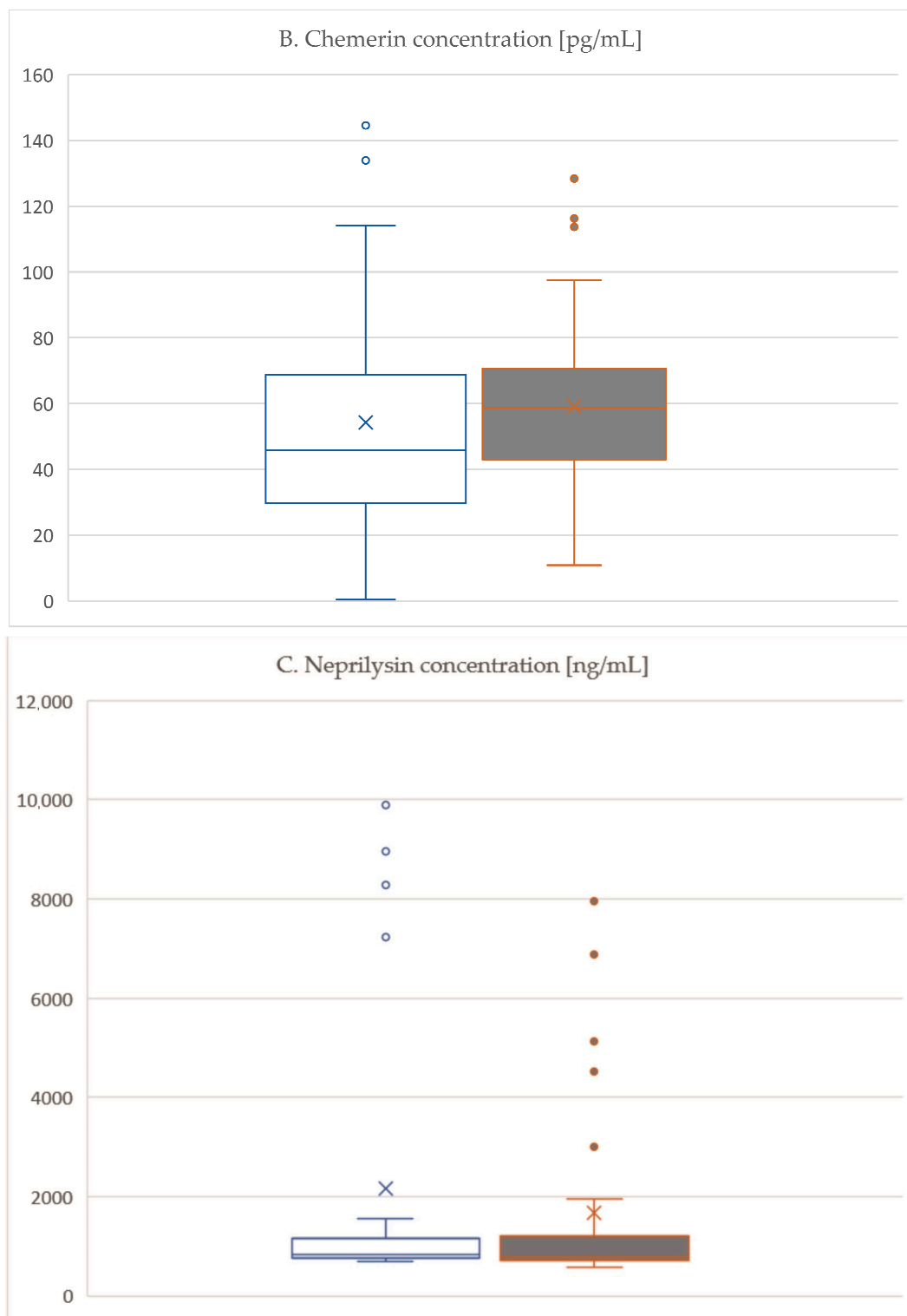


Figure 1. Adipokine concentrations ((A)—adipolin, (B)—chemerin, (C)—neprilysin) in NGT (normal glucose tolerance) group ($n = 24$; assigned as light boxes) and AGT (abnormal glucose tolerance) group ($n = 27$; assigned as grey boxes); n —number of subjects.

In the analyzed groups, there were no statistically significant differences in the concentrations of adipolin, chemerin, and neprilysin when gender was considered. Detailed information is included in the supplement (Tables S1–S16).

The chi-square test conducted in the obesity group divided into two groups (with CRP above 5 ng/mL and below this value) indicated no statistically significant differences in frequency of elevated glycemia in 120' OGTT (above vs. below 7.8 mmol/L), elevated insulinemia (above vs. below 12 μ U/L), elevated triglyceridemia (above vs. below 1.7 mmol/L), elevated blood pressure (above 130 mmHg for SBP and/or above 85 mmHg for DBP vs. below), reduced HDL cholesterol (below vs. above 1.0 mmol/L in male group and 1.3 mmol/L in the female group), (Table 3).

Table 3. Characteristics of selected metabolic disorders in two groups (with high or low CRP values) of obesity populations ($n = 51$).

Parameters	High CRP Group	Low CRP Group	<i>p</i>
Glycemia in 120' OGTT [mmol/L]			
AGT group	40.00%	60.00%	0.561
NGT group	43.76%	56.14%	
Fast insulinemia [μ U/L]			
≥ 12	50.00%	50.00%	0.437
< 12	33.33%	66.67%	
Triglycerides [mmol/L]			
≥ 1.7	41.18%	58.82%	0.924
< 1.7	40.00%	60.00%	
HDL cholesterol [mmol/L]			
≥ 1.0 (m) and ≥ 1.3 (w)	41.18%	58.82%	0.924
< 1.0 (m) and < 1.3 (w)	40.00%	60.00%	
Blood pressure (BP) [mmHg]			
systolic BP ≥ 130 and/or diastolic BP ≥ 85	39.29%	60.71%	0.376
systolic BP < 130 and/or diastolic BP < 85	66.67%	33.33%	

CRP—C reactive protein; OGTT—oral glucose tolerance test; High CRP group—the group with CRP value above 5 ng/mL; Low CRP group—the group with CRP value below 5 ng/mL; *p*—level of statistical significance in the chi-square test or exact Fisher test; AGT (abnormal glucose tolerance group)—the population with glycemia at 120' OGTT ≥ 7.8 mmol/L; NGT (normal glucose tolerance group)—the population with glycemia at 120' OGTT < 7.8 mmol/L; m—men; w—women.

3.2. Adipokines and Anthropometric Parameters

Adipolin concentrations were associated with age only among non-obese subjects ($r_s = 0.464$; $p = 0.004$). In the obese group ($r_s = -0.072$; $p = 0.612$) and the entire population ($r_s = 0.110$; $p = 0.300$), there were non-statistically significant correlations. Blood adipolin concentration correlated positively with body weight ($r_s = 0.484$; $p = 0.031$), BMI ($r_s = 0.471$; $p = 0.036$), waist circumference ($r_s = 0.517$; $p = 0.019$), WHR ($r_s = 0.529$; $p = 0.016$) and body fat percentage ($r_s = 0.545$; $p = 0.013$) in the non-obese women's group and with body weight ($r_s = 0.434$; $p = 0.024$) and waist circumference ($r_s = 0.393$; $p = 0.043$) among obese women. Among lean men, blood adipolin levels correlated positively with body fat percentage ($r_s = 0.577$; $p = 0.015$). In addition, there was a positive correlation between adipolin concentration and WHR in subjects with normal glucose tolerance ($r_s = 0.543$; $p = 0.006$).

Neprilysin and chemerin concentrations were associated with anthropometric parameters only among non-obese subjects. The strongest association with waist circumference was observed for neprilysin ($r_s = -0.777$; $p < 0.001$) in the non-obese male group. In this population, neprilysin concentration was also shown to correlate negatively with body weight ($r_s = -0.540$; $p = 0.025$), BMI ($r_s = -0.532$; $p = 0.028$), and WHR ($r_s = -0.636$; $p < 0.001$). Similar correlations were not observed among women. For chemerin, a negative association was found between its concentration and BMI ($r_s = -0.348$; $p = 0.035$) in the control group.

3.3. Adipokines and Parameters of Carbohydrate Metabolism

We found that neprilysin concentration correlated negatively with fasting glycemia ($r_s = -0.279$; $p = 0.047$) among obese subjects overall, and the relationship was more significant among obese women ($r_s = -0.489$; $p = 0.009$). There was also an association between neprilysin levels and blood glucose in the 120' OGTT among obese patients ($r_s = -0.273$; $p = 0.049$). In addition, there was a negative correlation between neprilysin concentration and fasting insulin ($r_s = -0.703$; $p = 0.002$) and HOMA-IR ($r_s = -0.673$; $p = 0.003$) in non-obese men. In non-obese women, such a correlation was not confirmed.

A positive correlation was shown between chemerin levels and glycemia in the 120' OGTT ($r_s = 0.412$; $p = 0.030$) among obese women, and a negative correlation with fasting glycemia values in obese subjects with NGT ($r_s = -0.418$; $p = 0.042$). No association between adipolin levels and glucose metabolism exponents was found.

3.4. Adipokines and Lipid Metabolism Parameters

Correlations between adipolin and chemerin concentrations and lipid metabolism parameters were observed. In contrast, no mentioned correlations occurred for neprilysin. There was a positive correlation between adipolin concentration and triglyceridemia ($r_s = 0.729$; $p < 0.001$) in non-obese women and a negative correlation with blood LDL-C levels in obese subjects with normal glucose tolerance ($r_s = -0.414$; $p = 0.044$). A positive association with triglyceridemia was also shown for chemerin ($r_s = 0.333$; $p = 0.033$). It was present in obese and non-obese men participating in the study. The chi-square test conducted in men indicated that high concentrations of chemerin (above the median value) were observed 3.79 times more frequently (OR = 3.79; 95% CI: 1.03–13.91) in the population characterized by elevated triglyceride levels—so above 1.7 mmol/L ($\chi^2(df1) = 4.193$; $p = 0.040$). Such observations did not occur in the group of women ($\chi^2(df1) = 1.880$; $p = 0.170$).

3.5. Adipokines and Blood Pressure

Positive correlations between adipolin levels and systolic ($r_s = 0.458$; $p = 0.004$) and diastolic blood pressure values ($r_s = 0.396$; $p = 0.015$) and a negative correlation between neprilysin levels and systolic blood pressure values in lean subjects ($r_s = -0.356$; $p = 0.031$) were observed. Among obese patients, these relationships were not documented.

3.6. Relationships between Concentrations of Individual Adipokines

The present study examined whether there was a correlation between blood concentrations of individual adipokines. A negative correlation was observed between adipolin and neprilysin concentrations in the study population ($r_s = -0.293$, $p = 0.006$). In addition, a positive correlation was shown between chemerin and neprilysin concentrations among patients in the control group ($r_s = 0.334$; $p < 0.043$).

The decision tree for adipolin concentrations in the general population showed that the highest concentrations of this adipokine occurred in the group of people with chemerin concentrations below 17.32 ng/mL ($F = 28.475$ (df1), $p < 0.0001$; Figure 2).

Based on the results of the subsequent decision tree (Figure 3) on the shaping of chemerin concentrations conducted in the whole population, it was shown that the highest concentrations of this adipokine were found in the group of individuals with high levels of neprilysin (above 605.064 pg/mL, $F = 9.374$ (df1), $p = 0.026$).

3.7. Logistic Regression-Based Analyses

According to logistic regression, the frequency of having high adipolin values (above the median) increased with age in the non-obesity group (OR = 1.32; 95% CI: 1.09–1.61; $p = 0.005$, Figure 4). The size of the population was relative to the analyzed parameters, and the results obtained in the LRT (log-likelihood test), the Hosmer–Lemeshow test, and the R2 Nagelkerke index indicated good fits of the model. In addition, high AUC values indicated relatively high sensitivity and specificity of the model (R2 Nagelkerke

= 0.468; LRT = -17.364 ($p = 0.0001$); the Hosmer–Lemeshow statistic = 6.033 ($p = 0.643$); AUC = 0.844 ± 0.062 , Table 4, Figure 5).

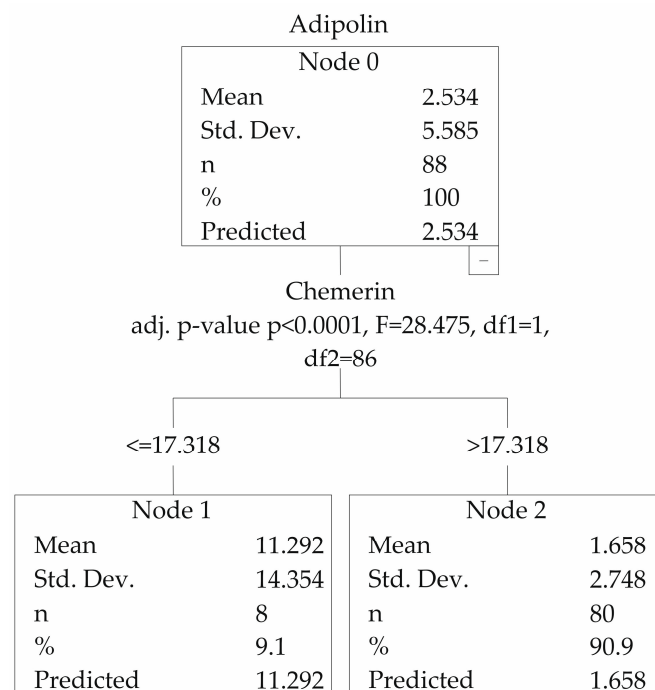


Figure 2. CHAID decision tree for shaping adipolin concentrations in the general population—after considering all anthropometric parameters studied and levels of other adipokines; Std. Dev.—standard deviations; n —number of subjects; adj. p -value—adjusted p value; F — F statistics.

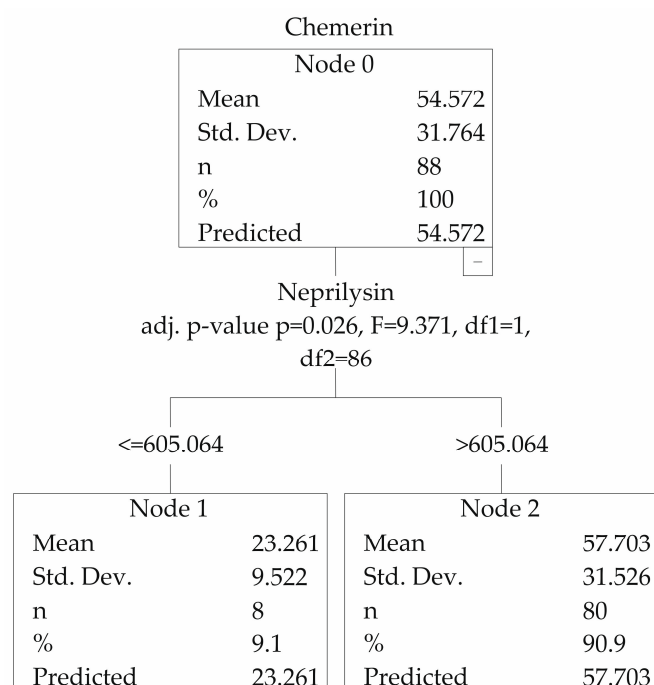


Figure 3. CHAID decision tree for shaping chemerin concentrations in the general population—after considering all anthropometric parameters studied and levels of other adipokines; Std. Dev.—standard deviations; n —number of subjects; adj. p -value—adjusted p value; F — F statistics.

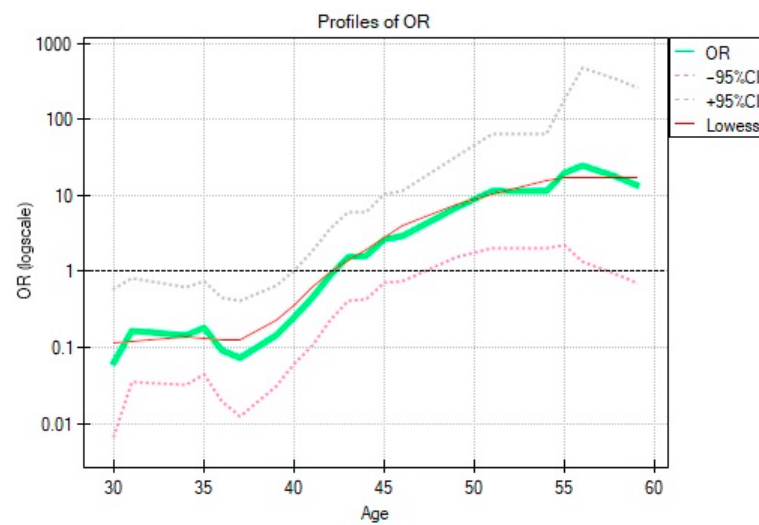


Figure 4. Profiles of odds ratio (OR) of adipolin levels above median value in different ages of individuals from the no-obesity group ($n = 37$).

Table 4. Logit model estimation results for model 1 (adipolin levels in no-obesity group, $n = 37$) and model 2 (adipolin levels in obesity group, $n = 51$).

Factors	Model 1	Model 2
R ² Nagelkerke	0.468	0.00003
LRT		
X ²	−17.364	0.0001
<i>p</i>	0.00007	0.991
AUC	0.844	0.504
SE (AUC)	0.062	0.085
<i>p</i>	0.00004	0.962

LRT—log-likelihood test; AUC—the area under the curve in the receiver operating characteristics curve (ROC), *p*—level of statistical significance; *n*—number of subjects.

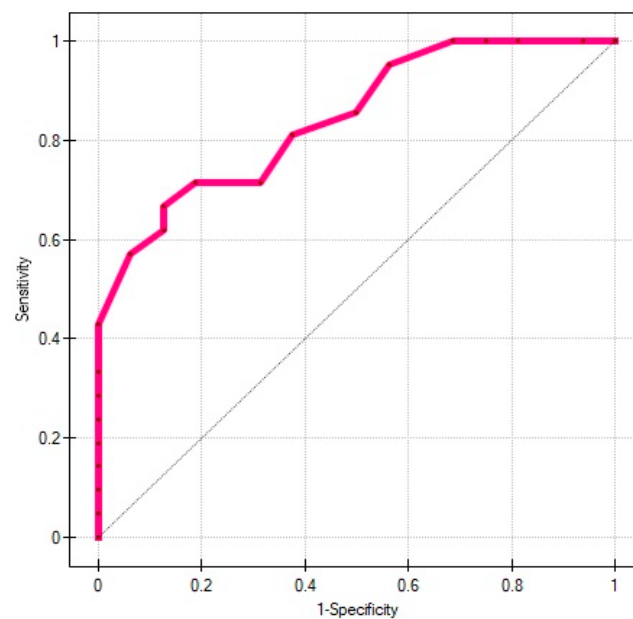


Figure 5. Receiver operating characteristic curves (ROC) for serum adipolin levels in the no-obesity group ($n = 37$); grey line = classifications due to change with the area under the curve (AUC) = 0.5; pink line = ROC curve with AUC = 0.844.

Such observations were not found in the obesity group for adipolin levels ($AUC = 0.504 \pm 0.085$; Table 3) nor in the entire population (obesity and no-obesity together; $AUC = 0.606 \pm 0.060$) and in neither group (obesity/no-obesity/entire population) for chemerin ($AUC = 0.551 \pm 0.082$; $AUC = 0.545 \pm 0.098$ and $AUC = 0.520 \pm 0.063$, respectively) or neprilysin levels ($AUC = 0.549 \pm 0.084$; $AUC = 0.677 \pm 0.092$ and $AUC = 0.508 \pm 0.062$, respectively). The probability relationship between changes with age and adipolin levels (and connected chemerin levels) in the obesity and no-obesity groups and high or low risk of insulin resistance are illustrated in Figure 6.

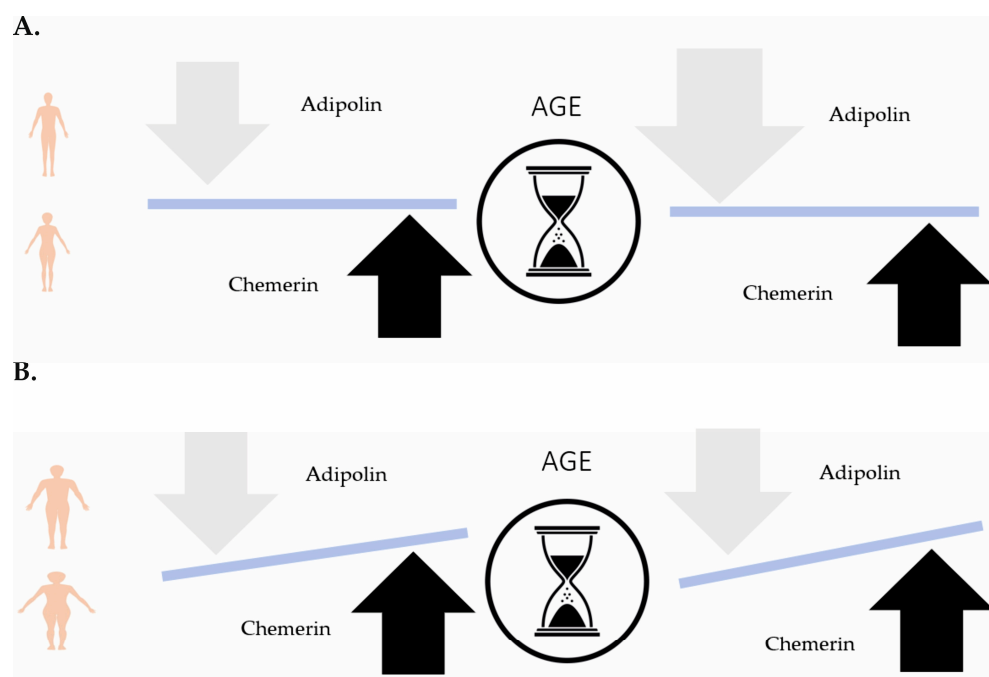


Figure 6. Insulin resistance (blue line) risk in non-obese (A) and obese (B) populations.

4. Discussion

4.1. Adipokines and Anthropometric Parameters

The first analyzed molecule, adipolin, is an adipokine with potentially beneficial effects on human metabolism [19]. According to some researchers, adipolin concentration decreases with increasing body weight. For example, Alipoor et al. showed that blood levels of this adipokine are negatively correlated with waist circumference in patients with type 2 diabetes [4]. Babapour et al. found a negative correlation between adipolin levels and WHR [20] among overweight individuals. A similar relationship with the WHR among obese women was observed by Tan et al. In addition, in this group, it was shown that adipolin concentration also correlated negatively with BMI [21]. The occurrence of a negative correlation with BMI in subjects without obesity was also observed by Fadaei et al. [22].

Kasabri et al. found, contrary to the majority of researchers, that blood adipolin concentrations in overweight and obese individuals were higher than in normal-weight participants [23]. This result is partly consistent with our observations. Indeed, in the control group, it was observed that adipolin concentrations correlated positively with body fat percentage and, among women in this group, also with body weight, BMI, waist circumference, and WHR. Among obese participants, a positive correlation between adipolin concentration and body weight and waist circumference was also found in the women's group. These studies show how difficult it is to define the relationship between adipolin levels and body weight clearly.

There is some evidence that plasma neprilysin concentration correlates positively with BMI. It was shown by Standeven et al. among men, some of whom had metabolic syndrome.

However, not all studies support this [24]. For example, Tuten et al., evaluating neprilysin levels in pregnant women, did not find that it correlated with BMI [25]. In our study among obese individuals, no association between neprilysin concentrations and anthropometric indices was observed. However, somewhat surprising results were obtained in a control group, specifically among non-obese men. The neprilysin concentration in this group correlated negatively with body weight, waist circumference, BMI, and WHR.

Interventional studies provided exciting findings. Ghanim et al. observed a significant decrease in blood neprilysin concentrations among people with morbid obesity and diabetes 6 months after bariatric surgery, compared with values before surgery [26]. In contrast, Henke et al. investigated how blood neprilysin concentrations were affected by a six-month weight-reduction diet leading to weight loss. The researchers showed a significant decrease in blood levels of this adipokine due to the dietary intervention in the low-fat diet group, which they did not find with the low-carbohydrate diet, despite comparable weight loss in both groups [27]. On this basis, it can be suggested that neprilysin concentrations depend more on the diet (which can lead to weight gain or loss) than on the subjects' weight. This observation may explain the discrepancy in the results obtained in the different study centers.

According to most researchers, blood levels of chemerin increase with increasing body weight. For example, Fatima et al. showed that circulating blood levels of chemerin were significantly higher in individuals with a BMI above 25 kg/m² compared to a group with a BMI below 25 kg/m² [28]. Similarly, Chang et al. found higher levels of chemerin in the blood of obese individuals than in lean individuals [29]. Aursulesei et al., in their study, also showed that patients with morbid obesity had significantly higher blood chemerin concentrations than non-obese individuals and observed that its concentration correlated positively with waist circumference and WHR [30]. Similar conclusions were reached by Rowicka et al. after evaluating the concentration of chemerin in children before puberty. Moreover, they showed that it correlated positively with BMI among children with obesity [31]. In our study, no differences in chemerin concentrations between subjects with and without obesity were observed. In addition, a surprising negative association between chemerin concentrations and BMI in the group without obesity was found. This result may be an area for further analysis and inquiry into the reasons for this relationship. Perhaps individuals whose concentrations of this adipokine with adverse metabolic effects decreases with increasing body weight will be less exposed to developing metabolic disorders accompanying obesity.

4.2. Adipokines and Glucose Metabolism

The hypoglycemic effects of adipolin primarily consist of inhibiting hepatic gluconeogenesis and stimulating glucose uptake by hepatocytes and adipocytes through activation of the PI3K-Akt signaling pathway and improved insulin sensitivity [21].

Adipolin can improve glucose homeostasis and IR. It is involved in the regulation of insulin signaling by phosphorylating proteins such as AMP-activated protein kinase (AMPK), protein kinase B (PKB), and insulin receptor substrate (IRS). Experimental studies have demonstrated that adipolin administration decreased levels of enzymes engaged in hepatic gluconeogenesis, such as glucose-6-phosphatase, and increased levels of phosphoinositide 3-kinases (PI3K) related to the insulin signaling pathway [32]. In insulin-resistant obese mice and hyperinsulinemic healthy lean subjects, mRNA and serum levels of adipolin, on the other hand, were inhibited [33].

The results of studies evaluating adipolin levels in people with abnormal glucose metabolism are inconclusive. Based on one of them, patients with newly diagnosed type 2 diabetes had lower adipolin concentrations compared to healthy controls [19]. Alipoor et al., evaluating the levels of adipolin in patients with diabetes, found a negative correlation between its levels and insulinemia and the HOMA-IR [4]. A negative association between HOMA-IR and fasting insulinemia was also shown by Fadaei et al. [22]. Kasabri et al. observed a positive correlation between blood adipolin levels and fasting

glycemia, and glycated hemoglobin in subjects with metabolic syndrome, which included groups of patients with both normal and impaired glucose metabolism [23]. In contrast, Babapour et al. found a negative correlation between levels of this adipokine and fasting glycemia in a group of overweight subjects [20]. A similar relationship among women with obesity was shown by Tan et al. [21].

Innovative results were presented by Du et al. in a group of patients with type 2 diabetes. They observed that adipolin levels were inversely correlated with diabetes duration [34]. We cannot relate this observation to our study because all of our patients had newly diagnosed abnormal glucose tolerance, but it can be assumed that the duration was short, and the lack of differences in adipolin concentrations between the study and control group may be due to this. Also, our study disclosed a positive association between adipolin concentrations and WHR values in subjects with obesity and normal glucose tolerance. This relationship was not present in subjects with abnormal glucose tolerance. Therefore, it can be hypothesized that high blood adipolin concentration is a protective factor for obese individuals against the occurrence of metabolic dysfunction. However, this needs to be confirmed in further studies, as no significant correlations were found between blood adipolin levels and exponents of glucose metabolism and insulin resistance in the other groups.

The higher concentration of adipolin in diabetic patients, observed by some investigators, may be a compensatory mechanism leading to the reduction of insulinemia and HOMA-IR values [4]. Therefore, adipolin and other therapeutic agents that increase its blood concentration may be effective treatments for patients with type 2 diabetes and insulin resistance [23].

There is increasing scientific evidence suggesting an effect of neprilysin on glucose metabolism. By activating glucagon, it indirectly acts antagonistically to insulin, thus stimulating an increase in glycemia and enhancing gluconeogenesis, glycogenolysis, and fatty acid oxidation. Some of its substrates, such as glucagon-like peptide-1 (GLP-1), natriuretic peptides, and bradykinin, modulate glucose metabolism [35,36]. Due to the potential role of neprilysin in glucose metabolism, associations between its levels and parameters such as glycemia, insulinemia, and insulin sensitivity exponents in humans have been sought. Li et al. demonstrated a positive relationship between blood adipokine levels and fasting glycemia and insulinemia, HOMA-IR, glycated hemoglobin, and duration of diabetes among patients with type 2 diabetes [37]. Standeven et al. compared neprilysin concentrations in men with metabolic syndrome and healthy men. They observed that its concentration was higher in the former group and increased with the number of components of the metabolic syndrome [24]. In our analyses, a negative correlation between neprilysin levels and fasting glycemia among all obese patients and with fasting insulinemia and HOMA-IR index values in the control group was found. Relating these observations to the findings of Hu et al. [38], who believe not only that serum neprilysin levels are associated with the occurrence of diabetes but also predict future risk of developing diabetes, it can be concluded that our study included individuals who, despite high neprilysin levels, did not have impaired glucose metabolism but may be at risk of developing it in the future.

Chemerin is also an adipokine involved in glucose metabolism. It reduces insulin-stimulated glucose uptake in the 3T3L1 cell line adipocytes and induces insulin resistance in skeletal muscle cells. This mechanism involves its effects at the level of IRS-1 (Insulin Receptor Substrate 1), protein kinase 8, GSK3 (Glycogen Synthase Kinase 3), and glucose transporters [39]. Most researchers believe that chemerin levels increase with the severity of tissue insulin resistance. For example, Fatima et al., comparing the concentration of chemerin in diabetic and normoglycemic subjects, observed significantly higher levels of this adipokine in diabetic subjects [40]. Similar results were obtained by other researchers [41–43]. These observations were partially confirmed in our study. In a group of obese women, a positive correlation was observed between chemerin concentration and glycemia in the 120' OGTT. However, there are several studies in which no correla-

tion between chemerin concentrations and parameters of glucose metabolism has been demonstrated [30,44,45].

In our study, we observed a negative correlation between serum chemerin concentration and fasting glycemia values in obese subjects with normal glucose tolerance. This result contradicts the general view and applies to obese people without abnormal glucose tolerance. This observation demonstrates the need for further research to look for reasons for the lack of negative consequences of obesity observed in some individuals referred to as “metabolically healthy obese”, in which the role of blood chemerin concentration is worth considering.

4.3. Adipokines and Lipid Metabolism and Hypertension

The role of the adipokines assessed in lipid metabolism is not well known. However, Tan et al. observed that CTRP12 (\pm), CTRP12 ($-/-$), and wild-type mice differed in lipid and cholesterol metabolism. Their study showed, among other things, that mice partially deficient in the adipolin gene (CTRP12) had lower secretion of very low-density lipoproteins [6]. Furthermore, Tan et al., in another study, showed that adipolin supply to mouse hepatocytes inhibits triglyceride synthesis [7]. Furthermore, *in vitro* studies proved that overexpression of the CTRP12 gene in mice reduces fasting and postprandial serum triglyceride levels [46]. The positive correlation between adipolin levels and triglyceridemia in non-obese women found in our study can be explained by some compensatory mechanism. Furthermore, the demonstrated negative correlation between adipolin concentrations and LDL-C in obese subjects with normal glucose tolerance confirms its protective effect in the context of disorders associated with obesity. The lack of differences in adipolin concentrations between the study group and the control group may be because some of the subjects in the control group had elevated total cholesterol and LDL-C concentrations. Therefore, the mean values of these parameters were comparable in both groups.

Another study showed reduced adipolin levels in patients with coronary artery disease compared to healthy subjects [22]. A positive association between the concentration of adipolin and the occurrence of ischemic heart disease was observed by Babapour et al. [20]. In contrast, these authors did not demonstrate an association between blood adipolin concentrations and blood pressure values in patients with coronary artery disease [21,22]. In our study, we observed a positive correlation between the concentration of the adipokine in question and systolic and diastolic blood pressure values in the control group. This relationship was particularly noticeable among women. The results of the study conducted so far suggest a possible link between CTRP12 and the pathomechanism of atherosclerosis, but further research is needed in this area. Adipolin appears to be of particular importance not only in glucose metabolism and the formation of tissue insulin sensitivity but also in preventing cardiovascular disease, and efforts to increase its blood levels in at-risk groups seem justified.

One of the few studies evaluating the relationship between neprilysin levels and blood pressure values is that of Li et al., who found a positive relationship between neprilysin levels and systolic blood pressure values [37]. Tuten et al. also found a positive relationship with both systolic and diastolic blood pressure in pregnant women [25]. Our study found a negative relationship with systolic blood pressure but only among those without obesity, but there are no studies with which to compare the results.

The role of chemerin in the pathogenesis of the cardiovascular disease, where dyslipidemia is a significant risk factor, is suggested. Many researchers have reported positive correlations between chemerin levels and triglyceridemia and LDL-C [47–49] and negative correlations with HDL-C [45,50,51]. Our study also showed a positive association of chemerin concentration with triglyceridemia among men. Moreover, high chemerin levels (above median values equal to 46.926 pg/mL) were observed almost four times more frequently in the male population, characterized by elevated triglyceride levels (above 1.7 mmol/L).

Chemerin can affect vascular remodeling, proliferation, and migration [52,53]. Increased adipokine levels are most commonly observed in hypertensive patients [54,55]. Aursulesei et al. observed a positive correlation between chemerin levels and systolic blood pressure values in obese individuals [30]. Furthermore, one of the blood pressure-lowering drugs, amlodipine, has been shown to decrease plasma chemerin concentrations. In contrast, intraperitoneal injection of the adipokine in question at a dose of 6 mg/kg/day for a further 6 weeks significantly increased systolic blood pressure compared with the control group [56]. However, in our study, there was no correlation between chemerin levels and blood pressure values, but it should be taken into account that a significant proportion of the subjects were taking blood pressure-lowering drugs, which may have chronically influenced the results.

4.4. Relationships between Concentrations of Particular Adipokines and Other Factors

Contrary to expectations, the concentrations of adipolin, neprilysin, and chemerin in the study groups were comparable. Presumably, it could be because the control group may have included individuals with the metabolically obese normal-weight (MONW) phenotype. Indirectly, this may be suggested by some results indicating the presence of metabolic disorders in this group of patients. It led to the conjecture that, due to the substantial abnormalities in adipokine secretion in obese individuals, their positive and negative effects may potentiate or cancel each other out. An attempt was made to find correlations between the concentrations of individual adipokines in the blood, and these correlations were found to exist. The decision tree method was used, through which exciting observations were made. Based on decision tree analyses conducted on the whole population, it was shown that the highest concentrations of chemerin were found in the group with high concentrations of neprilysin. It may indirectly confirm that the two adipokines have a similar mechanism of action. It was also shown that the highest concentrations of adipolin were found in the group with low levels of chemerin, which, like the available literature, suggests that these adipokines have opposing mechanisms of action. The blood concentrations of the adipokines analyzed are interrelated, potentially potentiating (in the case of molecules with similar functions) or abolishing (in the case of adipokines with opposing roles) their reciprocal effects. The determination of single adipokine concentrations may have little diagnostic value. In the future, it would be worthwhile to develop a panel of tests that includes the assessment of the concentrations of a more significant number of adipokines influential in shaping metabolic disorders. Their mutual proportions may be crucial in developing many diseases accompanying obesity, significantly affecting adipose tissue's secretory function.

Our logistic analyses have given a special result (which confirms the positive correlations obtained in non-parametric analyses)—an increased frequency of high plasma adipolin concentrations (above the value of 1.08 ng/mL) with the age of subjects, occurring only in people with a BMI below 30 kg/m², so also with a low risk of insulin resistance and low frequency of another risk of factors included in metabolic syndrome. Such results were not observed in the obesity group (in our research, characterized by high BMI (range 31.1–51.6 kg/m²) and high waist circumference in women ≥88 cm (range 93–140 cm) and in men ≥102 cm (range 110–160 cm). Also, in the case of the entire population, we did not receive such a result, similar to the study of Babapour et al., where no statistically significant correlation was observed between the levels of serum adipolin and age in patients with coronary artery disease (CAD) [20]. Moreover, Fadaei et al. found no association of this adipokine level with age in patients with CAD [22]. The papers of other authors connected with adipolin (CTRP12) concentrations lacked information about the analysis of the relationship between this adipokine level and age [4,21,23,34,57]. Only Bai et al. reported that the C1q complement/TNF-related protein (CTRP1) level increased with age in a large cohort (CTRP1 belongs to the same CTRP superfamily as adipolin, the adipokine analyzed by us (CTRP12)) [19]. Reduced serum levels of adipolin (CTRP12) in type 2 diabetes, according to Du et al., are associated with renal dysfunction [34]. This problem probably also occurs

(at least to some degree) in older obese people with multiple disorders associated with metabolic syndrome.

4.5. Limitations

Adipokine concentrations can be influenced by age, gender, physical activity, diet, weight changes, and medication. Every effort was made to ensure that the groups analyzed were comparable. Therefore, several exclusion criteria (Section 2.2) were used, but it resulted in relatively small group size. Some participants from the study population took necessary medications that may have influenced the study results. Usually, it was the treatment for hypertension (chronic effect), as other diseases were exclusion criteria. We excluded from the study people whose eating habits were unconventional or who followed “alternative diets”, e.g., vegetarianism or a ketogenic diet. However, people eat very differently, which could potentially affect (acutely or chronically) adipokine concentrations in the blood. Furthermore, the study exclusively involved participants of Caucasian ethnicity (chronic effect), necessitating caution in generalizing the findings. Additionally, the research encompassed individuals exhibiting varying degrees of different metabolic disorders characterized by dysregulation in glucose and/or lipid metabolism and/or blood pressure. However, the study’s main advantages lie in its thorough examination of biochemical, physiological, and anthropometric factors and how they relate to metabolic disorders in obese patients.

5. Conclusions

1. High plasma concentrations of chemerin are associated with low adipolin and high neprilysin concentrations. Adipolin, neprilysin, and chemerin concentrations are connected with some metabolic parameters, such as fasting and 120' OGTT glycemia, HOMA-IR, and triglyceridemia, which influence health complications.
2. The increasing frequency of high plasma adipolin concentrations with the age of subjects, occurring only in people with a BMI below 30 kg/m², indicates a particular protective role for this adipokine in an older population without obesity but not in obese patients.
3. The plasma chemerin profile in a population with high triglyceride concentrations depends on the sex of the studied subjects. High concentrations of this adipokine in men with high triglyceride concentrations indicate that this adipokine is an additional predictor of changes in lipid metabolism in this group.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/app13148005/s1>, Table S1. Anthropometric characteristics of men population, Table S2. Anthropometric characteristics of women population, Table S3. Adipokines concentrations in the study and control groups by gender, Table S4. Comparison of adipokine concentrations between men and women from the study and control groups, Table S5. Correlations between adipolin concentration and anthropometric parameters in the study and control groups. including gender, Table S6. Correlations between adipolin concentration and glucose metabolism parameters in the study and control groups. including gender, Table S7. Correlations between adipolin concentration and lipids metabolism parameters in the study and control groups. including gender, Table S8. Correlations between adipolin concentration and blood pressure values in the study and control groups. including gender, Table S9. Correlations between neprilysin concentration and anthropometric parameters in the study and control groups. including gender, Table S10. Correlations between neprilysin concentration and glucose metabolism parameters in the study and control groups. including gender, Table S11. Correlations between neprilysin concentration and lipids metabolism parameters in the study and control groups. including gender, Table S12. Correlations between neprilysin concentration and blood pressure values in the study and control groups. including gender, Table S13. Correlations between chemerin concentration and anthropometric parameters in the study and control groups. including gender, Table S14. Correlations between chemerin concentration and glucose metabolism parameters in the study and control groups including gender, Table S15. Correlations between chemerin concentration and lipids metabolism parameters in the study and control groups. including gender, Table S16. Correlations between chemerin concentration and blood pressure values in the study and control groups. including gender

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