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# The correlation between two potentially antagonistic human adipocytokines, WISP-1 and CTRP1, and their association with insulin resistance

**Małgorzata Mirr[1,2,A-D] ✉, Anna Braszak-Cymerman[3,A-B], Aleksandra Ludziejewska[4,C], Matylda Kręgielska-Narożna[5,B], Paweł Bogdański[5,A], Maciej Owecki[1,E-F]**

[1] *Department of Public Health, University of Medical Sciences, Poznań, Poland*
[2] *The Doctoral School, University of Medical Sciences, Poznań, Poland*
[3] *Department of Internal Diseases, Metabolic Disorders and Hypertension, University of Medical Sciences, Poznań, Poland*
[4] *Department of Laboratory Diagnostics, University of Medical Sciences, Poznań, Poland*
[5] *Department of Treatment of Obesity, Metabolic Disorders and Clinical Dietetics, University of Medical Sciences, Poznań, Poland*
*A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article*

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## Abstract

**Introduction and Objective.** Wnt-1 signaling pathway protein 1 (WISP-1) and complement-C1q TNF-related protein 1 (CTRP1) are adipokines with possible opposite effects in regulating insulin sensitivity. The study investigated the correlation between circulating WISP-1 and CTRP1 in non-diabetic patients. Correlations between adipokines concentrations and biochemical and anthropometric parameters were also studied.

**Materials and method.** The cross-sectional study enrolled 107 adult patients without diabetes. Patients with obesity accounted for 52.3% of the study group. Clinical, anthropometric, and laboratory data, including serum levels of WISP-1 and CTRP1, were obtained.

**Results.** The moderate positive correlation between serum WISP-1 and CTRP1 concentrations was observed ($p<0.000001$, $r=0.49$). The correlation was more substantial in non-obese patients than in the obese group ($r=0.66$ and $r=0.36$, respectively; $p<0.01$). Circulating CTRP1 correlated positively with fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), total cholesterol, HDL cholesterol, and LDL cholesterol ($p<0.05$). WISP-1 level correlated with total cholesterol and HDL cholesterol concentrations ($p<0.05$). There was no significant difference in WISP-1 and CTRP1 concentrations between the groups with and without insulin resistance. The concentrations of WISP-1 and CTRP1 were significantly higher in females than in males ($p<0.05$).

**Conclusions.** WISP-1 and CTRP1 may represent interrelated factors that antagonistically affect insulin resistance.

## Key words

obesity, insulin resistance, diabetes, adipokines, CCN4, WISP-1, CTRP1

## INTRODUCTION AND OBJECTIVE

Insulin resistance and type 2 diabetes are emerging problems in developed countries, which is the reason for research on the role of individual participants in glucose homeostasis being ongoing [1]. The mechanisms causing insulin resistance are complex and include pancreatic islet cell function, the secretion of gastrointestinal hormones and dietary components, as well as adipocytokines secretion alteration [1–4]. Increased adiposity is associated with an abnormal production of adipokines, which contributes to a pro-inflammatory state, and considered a likely mechanism for enhancing insulin resistance [5, 6]. Adipose tissue secretes numerous substances which regulate carbohydrate metabolism and inflammatory activity [7]. Adipocytokines are increasingly identified as markers and regulators of insulin resistance [2]. The list of adipokines involved in regulating insulin sensitivity is constantly being extended [7].

WISP-1 (Wnt-1 signaling pathway protein 1) is a member of the CCN family that has recently been identified as an adipokine of potential importance in obesity and insulin resistance [8]. WISP-1 is not specific to adipose tissue but is a mediator in various cellular processes in many organs [9]. WISP-1 is secreted, among others, by differentiated human adipocytes [10]. Several studies have shown elevated serum WISP-1 concentrations in obese patients and the correlation of WISP-1 concentrations with the body mass index (BMI) [11–13]. However, some studies have not confirmed this relationship [14, 15]. Several authors have proposed the involvement of WISP-1 in enhancing inflammation in adipose tissue, which would contribute to insulin resistance [10, 12, 13, 16]. WISP-1 mRNA expression in adipose tissue is associated with macrophage infiltration and the secretion of pro-inflammatory cytokines [10]. Also, the possible effect

✉ Address for correspondence: Małgorzata Mirr, Department of Public Health, University of Medical Sciences, Święcicki 6, 60-781 Poznań, Poland
E-mail: malgorzata.tapolska@gmail.com

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of WISP-1 on the induction of inflammation by activation of Toll-like receptor type 4 in hepatocytes and in the skeletal muscle cells of mice, may contribute to skeletal muscle insulin resistance [16]. Some studies show that circulating levels of WISP-1 differ between individuals with normal and impaired glucose tolerance [11, 13, 15, 17, 18], but conflicting reports have also been published [8, 12]. One study presented a correlation between changes in HOMA-IR indexes and serum WISP-1 after the 12-week exercise intervention [19]. It was demonstrated that WISP-1 inhibits insulin-stimulated glycogen synthesis in primary human skeletal muscle cells [11]. WISP-1 treatment decreases the insulin-mediated suppression of the gluconeogenic genes Pck1 and G6Pc in mouse primary hepatocytes [11]. The Pck1 gene encodes phosphoenolpyruvate carboxykinase, an enzyme in the gluconeogenesis pathway catalyzing the formation of phosphoenolpyruvate from oxaloacetate, whose enhanced activity leads to hyperglycaemia and exacerbation of diabetes [20]. Glucose-6-phosphatase encoded by G6Pc mediates the terminal step of gluconeogenesis and glycogenolysis, and its increased activity is reported in diabetes [21]. Therefore, disruption of insulin-mediated inhibition of the above enzymes may be one of the mechanisms of WISP-1's effect on glucose homeostasis [11].

CTRP1 (complement-C1q TNF-related protein 1) is a novel adipokine belonging to the C1q/TNF-related protein family, the best-known representative of which is adiponectin [22]. The plasma concentration of CTRP1 is significantly higher in type 2 diabetes and correlates with fasting plasma glucose, homeostatic model assessment for insulin resistance (HOMA-IR), and body mass index [23–26]. Higher levels of CTRP1 have also been observed in patients with metabolic syndrome [27]. An increase in circulating CTRP1 was observed 2 hours after administration of 75g of glucose in an oral glucose tolerance test in diabetic patients [26]. The postulated mechanism of action of CTRP1 is to improve insulin sensitivity by affecting the multi-insulin receptor substrate 1 [28]. Moreover, significantly lower HOMA-IR values were observed in CTRP1 transgenic (TG) mice relative to wild-type controls via stimulated glucose uptake [29]. A study in obese mice showed that treatment with CTRP1 increased insulin sensitivity [30]. Ren et al. also demonstrated a reduction in food intake in mice induced by CTRP1 treatment [30]. CTRP1 knocked-out mice presented insulin resistance and higher hepatic expression of gluconeogenetic genes G6Pc and Pck1 [31]. It was presented that CTRP1 stimulated glucose uptake in transgenic mice through the glucose transporter GLUT4 [29]. These reports suggest the contribution of the increase in CTRP1 concentrations improving insulin sensitivity as a compensatory mechanism [28].

Based on previous reports, both WISP-1 and CTRP1 proteins may be associated with the regulation of insulin sensitivity. The above-mentioned evidence suggests opposing effects of the two proteins in regulating enzymes responsible for glycemic control, such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 1. This is the first study investigating the correlation between WISP-1 and CTRP1 serum concentrations. Correlations between adipokines' concentrations and biochemical and anthropometric parameters in non-diabetic patients have also been studied.

## MATERIALS AND METHODS

**Study group.** During 2020–2022, a cross-sectional study enrolled 120 patients hospitalized for various causes in the Department of Internal Medicine, Metabolic Diseases & Hypertension, The eligibility criteria were:
– age from 18, both men and women;
– patient's written consent;
– exclusion criteria:
  • history of diabetes or secondary obesity;
  • using pharmacotherapy which may affect body mass or glucose homeostasis, especially glucocorticoids, anti-depressants, anti-psychotics, medroxyprogesterone acetate, beta-blockers or thiazides;
  • acute or chronic inflammatory disease, history of chronic disease of the liver, heart, endocrine glands (except for insulin resistance and well-treated hypothyroidism with normal thyroid-stimulating hormone level) or kidneys, history of neoplasms, current pregnancy.

After performing a physical examination and additional tests, thirteen patients were excluded due to comorbidities diagnosed during hospitalization (three patients meeting the criteria for diagnosing diabetes, two subjects due to newly-diagnosed hypothyroidism, five diagnosed with an adrenal tumour, one with a pancreatic tumour, one with reactive hypoglycaemia, and one participant with hypercortisolemia). Finally, 107 subjects were qualified for the study.

**Anthropometric measurements.** The anthropometric measurements of each participant were performed in the morning, after fasting:
• measurement of body height without shoes;
• measurement of body mass without shoes, in underwear.

Body mass index (BMI) was defined as the body mass divided by the square of the body height (expressed in units of $kg/m^2$).

**Laboratory data.** The following laboratory test results from serum were collected after fasting: glucose, glycated haemoglobin, insulin, total cholesterol, HDL-cholesterol, and triglycerides. The serum concentration of LDL-cholesterol was calculated with Friedewald's formula.

WISP-1 concentrations in sera were measured using a commercially available ELISA kit (Fine Test, Wuhan Fine Biotech Co., Ltd.; Catalog No. EH0330) following the manufacturer's protocol, with an intra-assay coefficient of variation of less than 8%. CTRP1 concentrations in sera were measured using a commercially available ELISA kit (Fine Test, Wuhan Fine Biotech Co., Ltd.; Catalog No. EH1624) according to the manufacturer's instructions, with an intra-assay coefficient of variation of less than 8%.

HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) was calculated according to the mathematical formula: fasting insulin concentration in μIU/ml x fasting glucose concentration in mmol/L / 22.5 [32].

**Statistical analysis.** All analyses were performed using PQ Stat v. 1.8.2 software. The normality of the distribution was checked by the Shapiro-Wilk test. Since most of the examined variables did not achieve normal distribution, further tests were carried out using methods for

ordinal variables (Spearman's rank correlation coefficient and Mann-Whitney U test). A significance level of 0.05 was assumed.

Since the HOMA-IR cut-off point for insulin resistance has not been established for the Polish population, for the following analyses it was assumed that insulin resistance occurs when the HOMA-IR is above two [33]. The patients were divided into two groups, with and without obesity. Obesity was defined as a body mass index ≥30 kg/ $m^2$.

**Ethical Approval.** The study was approved by the Bioethical Committee of the Poznań University of Medical Sciences (Approval No. 1152/19). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all subjects involved in this study.

## RESULTS

Females accounted for 61.7% of the study group. The median age was 59.0 years. Obesity was diagnosed for 52.3% of participants. Table 1 presents the group's basic characteristics. Among analyzed variables only glycated haemoglobin presented normal distribution.

**Table 1.** Group characteristics. Data are reported as medians (interquartile range) except for glycated haemoglobin which is presented as mean ± SD

| | |
|---|---|
| Age (years) | 59.0 (42.0–65.5) |
| Body mass (kg) | 84.5 (73.3–103.6) |
| BMI (kg/$m^2$) | 30.3 (26.4–35.2) |
| Fasting glucose (mmol/L) | 5.2 (4.7–5.6) |
| Fasting insulin (μIU/mL) | 10.6 (7.0–14.7) |
| Glycated haemoglobin (%) | 5.5±0.4 |
| HOMA-IR | 2.6 (1.6–3.8) |
| Total cholesterol (mmol/L) | 5.0 (4.4–5.7) |
| LDL-cholesterol (mmol/L) | 2.9 (2.2–3.5) |
| HDL-cholesterol (mmol/L) | 1.4 (1.1–1.8) |
| Triglycerides (mmol/L) | 1.8 (1.0–2.5) |
| WISP-1 (pg/mL) | 555.4 (469.9–726.3) |
| CTRP1 (ng/mL) | 129.4 (110.2–150.7) |

**Table 2.** Spearman's rank correlation for WISP-1, CTRP1 and other variables. Significant are indicated in bold

| | WISP-1 | | CTRP1 | |
|---|---|---|---|---|
| Variable | *p* | *r* | *p* | *r* |
| Age (years) | 0.161 | 0.136 | 0.292 | 0.103 |
| Body mass (kg) | 0.057 | -0.185 | 0.184 | -0.129 |
| BMI (kg/$m^2$) | 0.176 | -0.132 | 0.632 | 0.047 |
| Fasting glucose (mmol/L) | 0.583 | -0.054 | 0.455 | -0.073 |
| Fasting insulin (μIU/mL) | 0.409 | 0.131 | **0.028** | **0.338** |
| Glycated hemoglobin (%) | 0.075 | -0.301 | 0.844 | -0.034 |
| HOMA-IR | 0.445 | 0.121 | **0.027** | **0.341** |
| Total cholesterol (mmol/L) | **0.040** | **0.199** | **<0.001** | **0.394** |
| LDL-cholesterol (mmol/L) | 0.603 | 0.051 | **0.008** | **0.255** |
| HDL-cholesterol (mmol/L) | **0.032** | **0.207** | **0.001** | **0.307** |
| Triglycerides (mmol/L) | 0.606 | 0.050 | 0.260 | 0.110 |

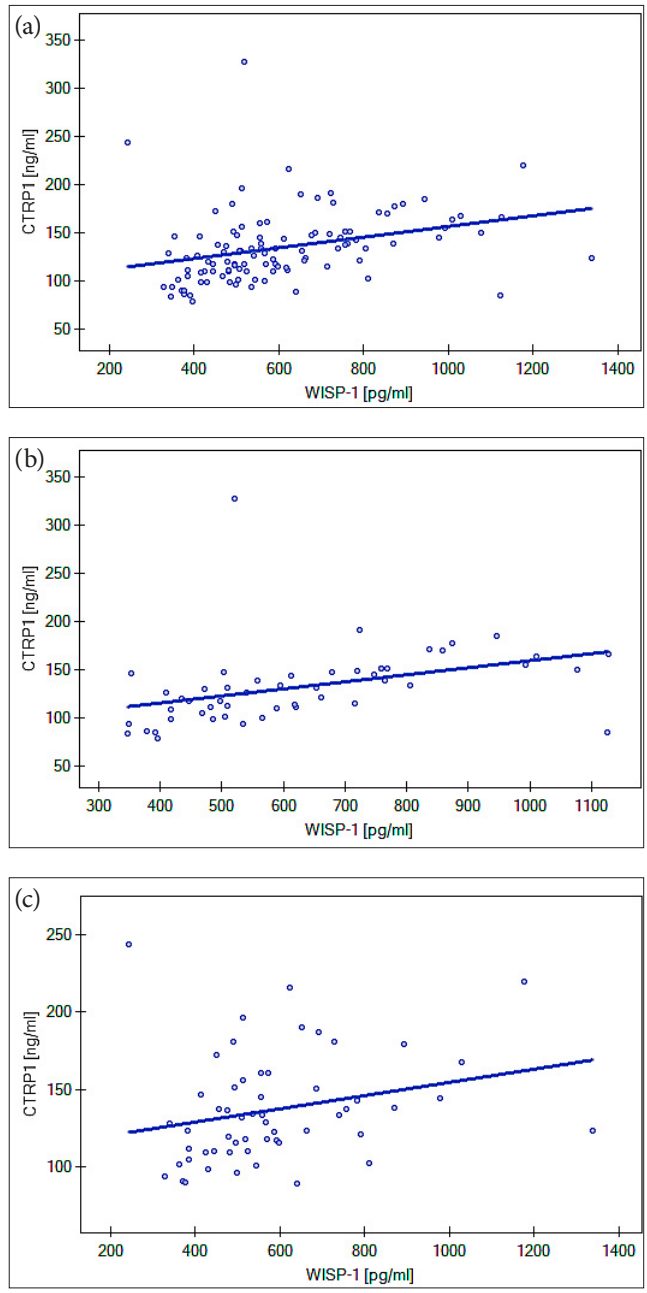


**Figure 1.** Spearman's correlation between circulating WISP-1 and CTRP1 in the whole study group (a), non-obese patients (b), and obese patients (c)

The coefficient of variation for the WISP-1 assay was 3.44%, and for CTRP-1 was 1.71%.

A moderate positive correlation between WISP-1 and CTRP1 concentrations was observed ($p<0.000001$, $r=0.49$). The correlation was more substantial in non-obese patients than in the obese group ($r=0.66$ and $r=0.36$, respectively; $p<0.01$). Figure 1 presents the correlation between WISP-1 and CTRP1 concentrations in the whole study group, in the group of obese patients, and in the group of patients without obesity.

Table 2 summarizes the correlations of WISP-1 and CTRP1, and other variables.

There was no significant difference in WISP-1 and CTRP1 levels between groups with and without obesity ($p=0.282$ and $p=0.460$, respectively). There was no significant difference

**Table 3.** WISP-1 and CTRP1 serum concentration in males and females. Data are reported as medians (interquartile range)

| | Females | Males | *p* |
|---|---|---|---|
| WISP-1 (pg/mL) | 568.1 (494.1–753.6) | 508.2 (417.5–620.1) | **0.036** |
| CTRP1 (ng/mL) | 140.6 (118.5–159.4) | 113.9 (101.5–126.0) | **<0.001** |

in WISP-1 and CTRP1 concentrations between patients with and without insulin resistance (p=0.809 and p=0.402, respectively).

Concentrations of WISP-1 and CTRP1 were significantly higher in females than in males (Tab. 3). The median BMI did not differ significantly between males and females (29.5 and 30.5, respectively; p=0.365).

Table 4 presents a heatmap of correlations between WISP-1, CTRP1 and other variables.

## DISCUSSION

The study shows a positive correlation between WISP-1 and CTRP1 serum concentrations. Previous studies suggest opposing effects of WISP-1 and CTRP1 in regulating insulin sensitivity [11, 23]. WISP-1 may stimulate the synthesis of gluconeogenesis enzymes, while CTRP1 induces glucose uptake and inhibits gluconeogenesis [11, 31]. Antagonistic effects on insulin transmission have also been suggested. Treatment with recombinant WISP-1 of human skeletal muscle cells caused inhibition of insulin signaling, resulting in reduced glycogen synthesis [11]. In turn, Xin et al. showed that CTRP1 improves the insulin sensitivity of adipose tissue by upregulating insulin receptor substrate 1 [28]. Assuming the opposite effects of WISP-1 and CTRP1, the increase in CTRP1 concentrations in insulin resistance may be the result of a compensatory mechanism, which may explain the positive correlation between both adipokines [24–26, 28]. A stronger relationship was observed between the concentrations of both adipokines in the non-obese group than in the obese group. It is possible that the correlation between the concentrations of WISP-1 and CTRP1 is a genetic feature characteristic for people without obesity, while in the group of people with a genotype predisposing to obesity, the balance between the secretion of these adipokines may be disturbed, which leads to obesity, and consequently, insulin resistance. No differences were found in concentrations of adipokines between the group with insulin resistance and normal insulin sensitivity. However, the study was conducted in a group of non-diabetic patients in whom compensatory mechanisms are partially effective. Therefore, the correlations observed in the current study refer to patients in the early stages of insulin resistance. So far, there are no studies examining this relationship in a group of patients with diabetes.

The results of the current study are consistent with previous reports on the positive correlation of CTRP1 with HOMA-IR and levels of fasting insulin [23–26]. As in previous studies, a weak positive correlation was observed between circulating CTRP1 and total and LDL-cholesterol concentrations, which is consistent with reports of higher CTRP1 levels in metabolic syndrome [24–27]. Surprisingly, a positive correlation was also found with HDL-cholesterol, which contradicts other studies [24, 25]. A study by Ren et al. showed that CTRP1 gene transfer in mice significantly down-regulated the expression of some lipogenic genes, including CD36, which encodes an important receptor mediating lipoprotein uptake [30]. Some evidence suggests the involvement of CD36 in HDL-cholesterol uptake, as CD36 knockout mice present an increase in plasma HDL-cholesterol, which may explain the result obtained in the presented study [34]. However, the effect of CTRP1 on lipoproteins is unknown and further research is needed to elucidate these findings. In the current study, there was no significant correlation between CTRP1 concentration and BMI, as presented by some authors [23, 24, 27]. However, in a study by Bai et al., no such correlation was observed, despite analyzing a larger group of patients [26].

The results of this study did not confirm previous reports about the significant correlation of WISP-1 with body weight and body mass index [8, 11, 12]. These studies investigated only Caucasians, as in the current study. However, the influence of ethnic differences on the results of individual studies cannot be excluded. Moreover, in the studies by Hörbelt et al. and Barchetta et al., the study populations were significantly younger than in the current study, which may have influenced the results.

The study by Klimontov et al. showed no significant difference in WISP-1 concentrations between diabetic patients with and without obesity, and no significant correlation between WISP-1 concentration and BMI [14]. The median BMI of patients in the study was similar to the current study [14]. Furthermore, in a study by Cheng et al., no correlation was observed between BMI and WISP-1 concentrations in diabetic patients [15]. Moreover, in a study by Tacke et al. correlation between BMI and WISP-1 was weak (r=0.19), and differences in the WISP-1 levels between normal weight, overweight and obese subjects did not reach statistical significance. [8]. It is concluded that the relationship between obesity and WISP-1 concentrations requires further research.

Significantly higher concentrations were observed of both adipokines in women compared to men. Higher

**Table 4.** A heatmap of correlations between WISP-1, CTRP1 and other variables – r Spearman values are presented. Significant are indicated in bold

| | CTRP1 | WISP1 | HOMA-IR | TC | LDLc | HDLc | TG | BMI |
|---|---|---|---|---|---|---|---|---|
| CTRP1 | | **0.49** | **0.34** | **0.39** | **0.25** | **0.31** | 0.11 | 0.05 |
| WISP-1 | **0.49** | | 0.12 | **0.20** | 0.05 | **0.21** | 0.05 | -0.13 |
| HOMA-IR | **0.34** | 0.12 | | 0.18 | 0.29 | -0.14 | 0.21 | **0.46** |
| TC | **0.39** | **0.20** | 0.18 | | **0.74** | **0.32** | **0.28** | 0.00 |
| LDLc | **0.25** | 0.05 | 0.29 | **0.74** | | -0.07 | 0.15 | **0.26** |
| HDLc | **0.31** | **0.21** | -0.14 | **0.32** | -0.07 | | **-0.49** | **-0.45** |
| TG | 0.11 | 0.05 | 0.21 | **0.28** | 0.15 | **-0.49** | | **0.26** |
| BMI | 0.05 | -0.13 | **0.46** | 0.00 | **0.26** | **-0.45** | **0.26** | |

TC – total cholesterol; TG – triglycerides;, HDLc – HDL-cholesterol; LDLc – LDL-cholesterol; BMI – body mass index

concentrations of other adipokines have also been reported in women, such as leptin, adiponectin, resistin, vaspin and asprosin [35–39]. This may result from a different distribution and higher percentage of white adipose tissue that occurs in women [40]. With a similar BMI, women have a higher percentage of body fat than men [40]. The influence of sex hormones on the secretion of WISP-1 and CTRP1 also cannot be excluded. Androgens reduce the secretion of adiponectin, which is a paralog of CTRP1 belonging to the same family of CTRP proteins [23, 37]. However, the relationship between CTRP1, WISP-1, and sex hormones is unknown.

In the presented study, no significant differences were observed in WISP-1 concentrations between the group with normal and reduced insulin sensitivity or correlation with HOMA-IR. Although a correlation between circulating WISP-1 and HOMA-IR has been reported, the studies were conducted in a group of patients with diabetes [15, 17]. Hörbelt et al. showed a positive correlation between circulating WISP-1 and HOMA-IR, but patients with diabetes accounted for more than one-third of the group [11]. The study by Barchetta et al. showed no difference in WISP-1 levels between healthy and diabetic patients, and no correlation between WISP-1 and HOMA-IR [12]. Similarly, in a study by Tacke et al., there was no significant difference in WISP-1 concentration between normal and impaired glucose tolerance subjects [8]. However, it should be emphasized that in the mentioned studies, taking anti-diabetic drugs was not an exclusion criterion, which could significantly affect the participants' insulin sensitivity and the results [8, 11, 12]. In the current study, diabetic patients were excluded, which may also have influenced the results.

No significant difference was observed in CTPR1 concentrations between the groups with and without insulin resistance. A study by Chalupova et al. showed higher CTRP1 concentrations in patients with metabolic syndrome, compared to healthy subjects [27]. Shabani et al. reported higher concentrations of CTRP1 in patients with non-alcoholic fatty liver disease associated with insulin resistance [23]. One study showed higher CTRP1 concentrations in the obese hyperglycaemic group, but the study was conducted in adolescents [41]. Higher CTRP1 concentrations have been reported in patients with type 2 diabetes compared to healthy controls [24–26, 42]. In the current study, patients with diabetes were excluded, which may explain our results. However, a significant positive correlation was observed between circulating CTRP1 and HOMA-IR. It is supposed that at the stage of reduced insulin sensitivity, before the development of type 2 diabetes, the differences in CTRP1 concentrations may not be as marked as in patients with diabetes. To date, the evidence seems insufficient to confirm higher CTRP1 concentrations in the group of patients with insulin resistance without diabetes. The role of CTRP1 as an early marker of insulin resistance needs further investigation.

**Limitations of the study.** Some limitations of the study should be highlighted. 1) The study group was relatively small in size; 2) the observed correlations do not imply causality, as the study is observational; 3) despite the high specificity of the WISP-1 and CTRP1 ELISA kits, cross-reactivity for analogs of these proteins cannot be fully ruled out; 4) the influence of dietary factors on the results of biochemical parameters cannot be excluded. Although most of the participants were on a regular, central European mixed diet, i.e. consisting of vegetables, bread and flour products, meat, fish, and fruits in balanced proportions, differences in their individual diets might have occurred, especially concerning their previous dietary history.

## CONCLUSIONS

Circulating WISP-1 correlated with total cholesterol and HDL-cholesterol, while serum CTRP1 correlated with fasting insulin, HOMA-IR, total cholesterol, HDL-, and LDL-cholesterol. Serum concentrations of WISP-1 and CTRP1 were significantly higher in females than in males. There was also a positive correlation between the serum concentrations of adipokines WISP-1 and CTRP1 in non-diabetic patients. The correlation was more substantial in the non-obese patients than in subjects with obesity. Therefore, the hypothesis could be assumed that non-disturbed positively correlated secretion of both WISP-1 and CTRP1 occurs in healthy and lean humans, and that this correlation weakens during the growth of body mass. Under these circumstances, the imbalance between WISP-1 and CTRP1 might be understood as one of the biochemical mechanisms involved in the pathogenesis of obesity. Confirmation of the mechanism explaining this association is needed.

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