

Assessment of serum levels resistin in girls with anorexia nervosa.

Part I. Relationship between resistin and body mass index

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Abstract

OBJECTIVES: There are only few studies available on blood resistin (RES) levels in patients with anorexia nervosa (AN), which revealed scarce results, however it has been demonstrated that RES mRNA expression in adipose tissue of these patients is increased. The aim of this study is: 1) the evaluation of serum resistin levels in girls with AN and determination a threshold value differentiating these patients from healthy subjects; 2) analysis of the relationship between serum resistin levels and BMI in examined subjects.

DESIGN AND SETTING: Serum RES concentration has been assayed using ELISA kit in 195 adolescent girls: 87 with restrictive AN (mean BMI-SDS: -2.65 ± 0.2), 17 with not otherwise specified eating disorders (NOS) (mean BMI-SDS: -1.4 ± 0.68), 30 with simple obesity (OB) (mean BMI-SDS: 6.91 ± 1.23) and 61 healthy (mean BMI-SDS: -0.18 ± 0.54).

RESULTS: Mean serum RES concentration in AN (2.8 ± 0.6 ng/ml) and NOS (3.1 ± 0.9 ng/ml) were significantly lower ($p < 0.0001$) than in OB and H groups (4.8 ± 0.5 and 4.1 ± 0.4 ng/ml respectively). After corrected for BMI, RES values in AN were similar as in H subjects, but significantly higher ($p < 0.005$) in comparison to OB group. ROC curve analysis revealed that 3.87 ng/ml is the threshold value of RES serum concentration differentiating AN from H girls (specificity 100%, sensitivity 80%). No significant correlations between BMI and serum resistin concentration are found in AN group, although a significant positive correlation has been established for all examined subjects.

CONCLUSION: Additional adaptive mechanisms may be involved in regulation of RES levels in adolescent girls with AN.

INTRODUCTION

Resistin (RES – *resistin*; ADSF – *adipocyte-specific secretory factor*; FIZZ3 – *found in inflammatory zone family*), identified in 2001 as a transcript overexpressed in pre-adipocytes (precursors of fat cells) differentiating into adipocytes, down-regulated *in vitro* by thiazolidinediones, has been described by several groups of researchers as a new, so far unknown factor secreted by adipose tissue and a protein which is homological to proteins secreted during inflammatory processes (Banerjee & Lazar 2003; Holcomb *et al.* 2000; Kim *et al.* 2001; Koerner *et al.* 2005; Steppan *et al.* 2001).

The relationship between RES and weight disorders is unclear, although RES is known to be involved in regulation of energy homeostasis in rodents (Banerjee & Lazar 2003; Steppan *et al.* 2001). In experimental trials in *ob/ob* and *db/db* mice and in mice with diet-induced obesity, high blood RES levels were observed (Steppan *et al.* 2001). Other authors (Way *et al.* 2001) observed low blood RES levels in other obese rodent models or increased blood RES levels (Koerner *et al.* 2005) only in case of obesity accompanied by insulin resistance.

There are few studies available on blood RES levels in patients with *anorexia nervosa* (AN). These studies were conducted in small groups of female patients. Some authors (Dostalová *et al.* 2007; Křížová *et al.* 2008) observed significantly lower blood RES concentrations in female patients with AN as compared to healthy controls; whereas the others (Dolezalova *et al.* 2007) failed to demonstrate any differences, however they observed increased RES mRNA expression in biopsy samples of adipose tissue in patients with AN.

The purpose of this study is: 1) the evaluation of serum resistin levels in girls with AN and determination a threshold value differentiating these patients from healthy subjects; 2) analysis of the relationship between serum resistin levels and BMI in examined subjects.

MATERIAL AND METHODS

The study was conducted in 195 girls aged 11 to 19 years included into four groups: the group of anorectic girls (AN), as well as the following control groups: NOS (not otherwise specified eating disorders), OB (simple obesity) and H (healthy) (Table 1).

BMI (Body Mass Index: BMI = (weight [kg]/height [m]²) and BMI-SDS (body mass index standard deviation score) using the following formula: BMI-SDS = (current patient's BMI [kg/m²] – BMI at 50th percentile [kg/m²]) / (½ x BMI at 50th percentile [kg/m²] – BMI at 3rd percentile [kg/m²]) were calculated in all study subjects. The assessment was performed using sex- and age-specific BMI percentile charts, currently valid for the Polish population (Palczewska & Niedźwiecka 2001).

The AN group consisted of 87 girls (mean age: 15.2 ± 0.3 years) with the restrictive subtype of *anorexia nervosa* and the NOS group included 17 girls (mean age: 16.4 ± 0.9 years), who failed to meet all the criteria for AN. The diagnosis of AN was established based on the DSM-IV diagnostic criteria (American Psychiatric Association DSM IV, 1994). Mean weight in patients with AN was 38.46 ± 1.2 kg, mean BMI: 14.67 ± 0.33 kg/m², mean BMI-SDS: –2.65 ± 0.2 (Table 1). Mean weight in the NOS group was 47.5 ± 2.9 kg, mean BMI: 17.86 ± 1.04 kg/m², mean BMI-SDS: –1.4 ± 0.68. The OB group consisted of 30 girls with simple obesity (mean age: 14.6 ± 0.8 years; BMI > 97th centile; BMI-SDS > 2 SD). No binge eating disorder was observed in any patient. Mean weight was 85.87 ± 7.58 kg, mean BMI: 31.86 ± 2.19 kg/m², mean BMI-SDS: 6.91 ± 1.23. Sixty one female volunteers were included in the H group (mean age: 15.4 ± 0.8 years). None of the healthy subjects used any weight loss diets or other slimming methods within the last three months before the study. Mean weight in the H group was 52.26 ± 3.66 kg, mean BMI: 19.75 ± 1.12 kg/m², mean BMI-SDS: –0.18 ± 0.54 (Table 1).

Tab. 1. Characteristics of examined groups of girls.

	AN (n = 87)	NOS (n = 17)	OB (n = 30)	H (n = 61)
	mean ± 1.96 SE (range)			
Age [years]	15.18±0.32 (11.3–18.5)	16.35±0.85* (11.9–18.9)	14.62±0.84* (11–18.3)	15.36±0.8 (11.7–17.9)
Body weight [kg]	38.46±1.2 (26.7–51.6)	47.5±2.9** (39.2–60.7)	85.87±7.58*** (57.7–134.0)	52.26±3.66*** (31.5–71.7)
Height [cm]	162.0±1.49 (143.5–175.0)	163.40±4.50 (146.5–178.0)	163.57±3.51 (145.0–186.5)	162.60±3.49 (138.0–183.0)
BMI [kg/m ²]	14.67±0.33 (10.85–17.85)	17.86±1.04** (14.34–21.85)	31.86±2.19*** (25.5–52.0)	19.75±1.12*** (15.29–23.93)
BMI-SDS	–2.65±0.2 (–5.21–1.08)	–1.42±0.68* (–3.23–1.41)	6.91±1.23*** (3.23–17.83)	–0.18±0.54*** (–2.11–1.89)

H – healthy group; AN – anorexia nervosa group; NOS – not otherwise specified eating disorders group; OB – simple obesity group; SE – standard error; BMI-SDS – body mass index standard deviation score
p*<0.05 - NOS vs OB; *p*<0.05 - NOS vs AN; ****p*<0.00001 - OB and H vs AN

In all study subjects the development of secondary sexual characteristics according to the Tanner scale (Tanner, 1962) was consistent with the chronological age. In all patients with AN primary (14 girls) or secondary (73 girls) amenorrhea was observed. One girl in the NOS group was premenarcheal, and 13 others had secondary amenorrhea. All other study subjects had regular menstruations.

The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (Register No. KNW-6501-62/08). Informed consent for participation in the study was obtained from all study subjects and their parents or legal guardians.

Blood samples for analyses were collected in the morning (7⁰⁰–8³⁰) from patients in the fasting state. After centrifugation at 1000 × g for 15 min at +4 °C, the obtained plasma and serum were divided into Eppendorf tubes and frozen at –70 °C until assays were performed.

Serum RES levels were determined in all study subjects by the ELISA method (enzyme-linked immunosorbent assay) using commercial assay kits of BioVendor LLC (USA). The lowest RES concentration determined was 0.1 ng/ml, intra-assay error was 3.4%, and inter-assay was 6.8%.

The results were analyzed using a licensed version of Statistica v. 3.0 software. In statistical analysis, the distribution of results was tested for consistency with normal distribution using the Shapiro-Wilk test. Significance of differences in mean values was assessed using the analysis of variance (ANOVA) and the homogeneity of variance was evaluated using the Levene's test. As the Shapiro-Wilk test demonstrated that study variable distributions are significantly different from normal distribution, and the Levene's test indicated lack of homogeneity of variance, the non-parametric Kruskal-Wallis test and the median test were used in the final

assessment. To verify differences between mean values, the HSD (Honestly Significant Difference) Tukey's multiple comparison test was used for different sample sizes. Accuracy of diagnostic hormone measurement tests was assessed using the ROC (Receiver Operation Characteristic) curve analysis. A threshold value of resistin levels was calculated, which corresponds to the maximum effectiveness of the test at the points where sensitivity and specificity are equal. Correlations were tested using the Spearman test.

RESULTS

The mean age of girls in the AN group was similar compared to girls in the NOS, the OB and the H group (Table 1).

Mean body weight and BMI in the AN group were statistically significantly lower compared to the NOS ($p < 0.05$) as well as the OB and the H groups ($p < 0.00001$) (Table 1). BMI-SDS in the AN group was significantly lower compared to BMI-SDS in the OB and the H groups ($p < 0.00001$). BMI-SDS of the NOS patients was significantly lower ($p < 0.05$) compared to the OB group (Table 1).

Mean serum resistin levels in the AN group (2.8 ± 0.6 ng/ml) was similar to these established in the NOS group (3.1 ± 0.9 ng/ml). The observed values of RES concentration in the AN and the NOS groups were significantly lower ($p < 0.0001$) compared to mean values obtained in the group of obese (4.8 ± 0.5 ng/ml) and healthy patients (4.1 ± 0.4 ng/ml) (Figure 1).

On the other hand, BMI-corrected mean resistin levels (in the contrast to mean absolute values) were statistically significantly higher ($p < 0.005$) in the AN group as compared to the OB group, and they did not differ from the values observed in the H group (Figure 2).

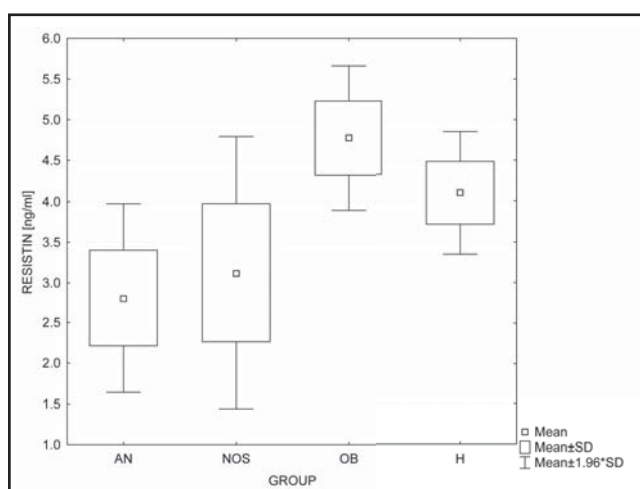


Fig. 1. Mean serum resistin concentration (ng/ml) in examined groups. H – healthy group; AN – anorexia nervosa group; NOS – not otherwise specified eating disorders group; OB – simple obesity group; * $p < 0.0001$ AN vs OB and H

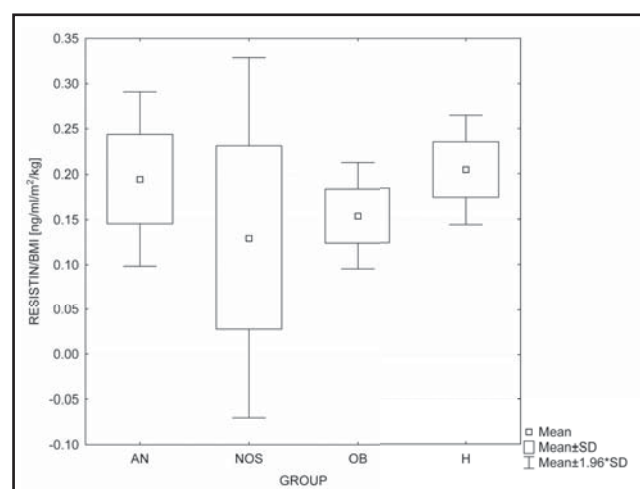


Fig. 2. Mean serum resistin concentration per BMI (ng/ml/m²/kg) in examined groups. H – healthy group; AN – anorexia nervosa group; NOS – not otherwise specified eating disorders group; OB – simple obesity group; * $p < 0.05$ AN vs OB

Comparison of resistin concentrations in the AN group with these obtained in the healthy group and the construction of the so-called ROC curves helped to determine the cut-off point, i.e. the hormone level which differentiates the AN group from the H group. The serum RES level differentiating the AN group from the H group was 3.87 ng/ml, with 80% sensitivity and 100% specificity (Figure 3), which means that serum RES levels below 3.87 ng/ml are typical for AN, whereas the values above 3.87 ng/ml are observed in healthy individuals.

In all study subjects analyzed together, a statistically significant, positive correlation between BMI and blood RES levels was noted ($r = 0.66$; $p < 0.0001$), whereas no such correlation was observed in the AN group (Figure 4).

DISCUSSION

The range of serum RES levels has not been characterized, yet. The difficulty in comparison of our results with these obtained by other authors may result from different methods for the determination of blood RES used by various researchers (Körner *et al.* 2005). Some authors (Anderlová *et al.* 2006; Housová *et al.* 2005; Křížová *et al.* 2008; Li *et al.* 2006) determined blood RES levels using the ELISA method, as we did. Dostalova *et al.* (2006) used the RIA method. In studies conducted to date (Kulik-Rechberger & Rechberger 2003; Lewandowski *et al.* 2005) a wide range of serum RES values were obtained, probably due to evaluation different RES molecular isoforms (Gerber *et al.* 2005).

Very few reports evaluating the RES expression in adipose tissue and its blood levels in patients with eating disorders have been published, yet (Dolezalova *et al.* 2007; Dostalová *et al.* 2007; Housová *et al.* 2005; Křížová *et al.* 2008). Some authors (Dostalová *et al.* 2007; Křížová *et al.* 2008) observed lower blood RES

levels in patients with AN compared to healthy volunteers, whereas others (Dolezalova *et al.* 2007; Housová *et al.* 2005) failed to demonstrate any significant differences. Studies comparing blood RES levels in patients with AN and in obese patients are also rare (Křížová *et al.* 2008).

Our study has demonstrated that mean blood RES levels in girls with AN (2.8 ng/ml) were almost twice lower than in healthy (4.1 ng/ml) and obese (4.8 ng/ml) girls. In all study subjects analyzed together, RES levels demonstrated a positive correlation with BMI. Similarly to our research, Křížová *et al.* (2008), comparing blood RES levels in 28 women with AN to those in a group of 77 obese women, observed significantly lower blood RES levels in patients with *anorexia nervosa* (3.99 ± 0.33 ng/ml) as compared to obese (8.11 ± 0.60 ng/ml; $p < 0.001$) and healthy women (6.27 ± 0.50 ng/ml; $p < 0.05$).

Dolezalova *et al.* (2007) noted no differences in blood RES levels in 12 women with the restrictive subtype of AN in comparison with a group of healthy women. However, they demonstrated significantly higher resistin mRNA expression in subcutaneous adipose tissue in anorectic patients as compared to healthy controls. These authors concluded that local changes in RES mRNA expression in adipose tissue did not reflect the levels of this hormone in the blood of patients with AN. Other authors (Gerstmayer *et al.* 2003; Rea & Donnelly, 2004) consider resistin a hormone which constitutes a “bridge” linking the adipose tissue with the immune system, as the principal source of RES in humans seem to be macrophages rather than adipose cells. Furthermore, RES takes part in regulating the body’s response to generalized inflammatory processes (Savage *et al.* 2001).

The increased production of RES in subcutaneous adipose tissue (Dostalova *et al.* 2006) as well as its mRNA expression (Dolezalova *et al.* 2007) in this tissue in patients with AN seems an interesting observation,

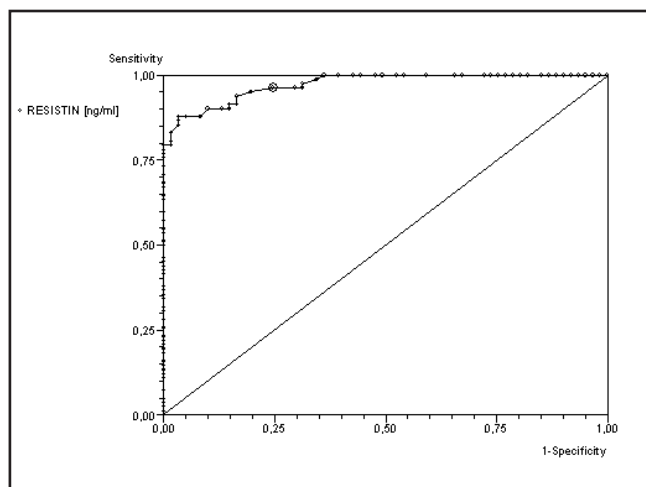


Fig. 3. ROC curve for resistin. Cut-off value 3.87 ng/ml; Efficiency 0.9016; Sensitivity 0.8033; Specificity 1.0; Negative likelihood ratio 5.0833.

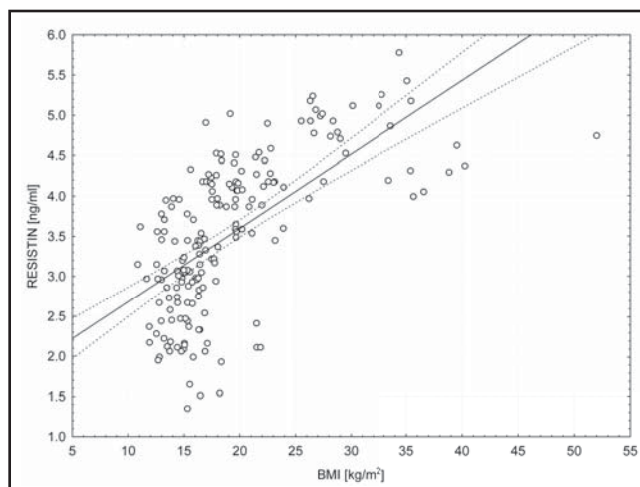


Fig. 4. Correlation between BMI (kg/m²) and serum resistin concentration (ng/ml) in all examined subjects ($r = 0.66$; $p < 0.0001$).

since the increased RES expression has so far been demonstrated in rodents mainly in visceral rather than subcutaneous adipose tissue (Banerjee & Lazar 2003).

Housova *et al.* (2005) found no significant differences between mean blood RES levels in patients with the restrictive (3.44 ng/ml) or the binge-purge subtype of AN (5.12 ng/ml), or in women with *bulimia nervosa* (4.36 ng/ml), as compared to healthy subjects (4.38 ng/ml). No correlation between blood RES levels and BMI and adipose tissue content was observed in any of the study groups. Therefore, Housova *et al.* (2005) concluded that blood RES levels are not associated with the nutritional status.

However, other authors (Yannakoulia *et al.* 2003) demonstrated a positive correlation between blood RES levels and the amount of adipose tissue and BMI in healthy individuals. Our study demonstrated a positive correlation between blood RES levels and BMI in all study subjects analyzed together ($r = 0.66$; $p < 0.0001$); however, no correlation was observed in individual groups. Similarly as in the study by Housova *et al.* (2005), it might have been associated with a small range of RES concentration values and BMI values within individual groups.

Dostalova *et al.* (2006) demonstrated decreased blood RES concentrations in women with AN, which were accompanied by an increase in RES levels in extracellular space of adipose tissue. Blood RES levels in *anorexia nervosa* and healthy study subjects were not dependent on RES concentrations in adipose tissue, BMI, or body fat percentage.

A decrease in blood RES levels may not only result from malnutrition, but also from reduced RES production in the bone marrow, increased RES clearance (Patel *et al.* 2003) or mononuclear cell/macrophage dysfunction and impaired production of cytokines (Brichard *et al.* 2003; Dostalova *et al.* 2006), such as TNF- α and IL-6, which enhance RES expression in macrophages (Lehrke *et al.* 2004).

Our study showed that BMI-corrected RES concentration values in girls with AN were higher than those noted in obese patients (in contrast to the absolute values), but were similar to values obtained in healthy controls. The elimination of the effect of body weight on blood RES concentration values, obtained by correcting blood RES levels for BMI, indicates that the amount of this hormone in the blood in girls with AN is comparable to that observed in healthy individuals, but markedly higher than in obese patients. This may possibly result from compensatory higher RES production in other than adipose tissue structures in patients with AN.

The ROC curves we had constructed demonstrated usefulness of determining blood resistin levels. It helped to determine the cut-off point, i.e. the value of the hormone concentration which differentiates the AN group from the healthy controls, with very high sensitivity and specificity. Evaluation of large groups of girls with

AN and healthy controls contributed to obtaining such results. To our knowledge it is the first trial of establishing such value. There are only some data according to serum leptin concentration in course of AN treatment, above which LH and FSH levels returned to normal (1.85 $\mu\text{g/l}$ and 1.2 $\mu\text{g/l}$, respectively) and menstruation reappeared (Hebebrand *et al.* 2007; Köpp *et al.* 1999) as it has long been postulated (Frisch & Revelle 1990) that the so-called critical body weight is necessary to initiate menstruation.

We conclude that although serum resistin concentrations in girls with *anorexia nervosa* are significantly lower compared to healthy and obese subjects, there may be adaptive mechanisms including increased RES expression in adipose tissue and/or its higher extraadiposal production in anorectic patients.

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