Peptides 49 (2013) 49–52

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Resistin levels are related to fat mass, but not to body mass index in children

Lorena Ortega [a], Pía Riestra [a], Pilar Navarro [a], Teresa Gavela-Pérez [b], Leandro Soriano-Guillén [b], Carmen Garcés [a,*]

[a] Lipid Research Laboratory, IIS-Fundación Jiménez Díaz, 28040 Madrid, Spain
[b] Department of Pediatrics, IIS-Fundación Jiménez Díaz, 28040 Madrid, Spain

ARTICLE INFO

Article history:
Received 7 August 2013
Received in revised form 22 August 2013
Accepted 22 August 2013
Available online xxx

Dedicated to the late Prof. Manuel de Oya, as the warmest homage to his memory.

Keywords:
Body mass index
Children
Fat mass
Resistin levels

ABSTRACT

The relationship of resistin levels with obesity remains unclear. The aim of this study was to determine resistin levels in prepubertal children and adolescents and evaluate their association with anthropometric parameters and body composition. The study population included 420 randomly selected 6–8-year-old children and 712 children aged 12–16 years. Anthropometric data were measured and body mass index (BMI) and waist-to-hip and waist-to-height ratios were calculated. Body composition was assessed using an impedance body composition analyzer. Serum resistin levels were determined using a multiplexed bead immunoassay. Resistin levels were not significantly different between sexes. No significant differences in serum resistin concentrations were found between obese, overweight, and normal weight children at any age, and no significant correlations were observed between resistin concentrations and weight or BMI. However, resistin levels showed a significant positive correlation with fat mass in 12–16-year-old children, particularly in girls. In addition to describing serum resistin levels in prepubertal children and adolescents, our study suggests that resistin is related to body fat rather than to BMI in adolescents.

1. Introduction

Obesity is the consequence of an excess of adipose tissue, resulting from an imbalance between food intake and energy expenditure [6]. In the last years, the view of adipose tissue has changed from that of an "inert" storage tissue to an endocrine organ that secretes several proteins, adipokines, which play an important physiological role in controlling energy homeostasis and have important endocrine functions [2,9,11]. Resistin is one of those adipocyte-secreted peptide hormones that have been linked to obesity and obesity-associated alterations, although its role in metabolic disorders is under debate [13,25]. In humans, resistin is secreted by adipocytes and by macrophages in adipose tissue and the liver [26]. Some studies in humans have reported significantly higher serum resistin levels in obese than in lean subjects [1,5,20], or have positively related resistin concentrations with body fat mass [27,28]. However, these associations have not been confirmed in other studies [10,12,24,29].

The association of this cytokine with obesity has also been analyzed in children, producing, likewise, discordant results. Although resistin levels have been linked with obesity in different populations of children and adolescents [8,15,22], and significant correlations between serum resistin concentrations and BMI and waist circumference have been reported [14], other studies do not support a relationship between resistin and weight status in childhood [21] or suggest a weak association [7]. In general, the results of these studies are not derived from population-based samples, but rather from either relatively small population samples or studies including a broad range of age groups. Only the study by Li et al. [14] reported data from a cross-sectional survey in Chinese children, and, to the best of our knowledge, observational studies in Caucasian pubertal children have largely failed to test for the relationship between resistin levels and body composition. Our study examines resistin levels in pre-pubertal Spanish children and adolescents between the ages of 12 and 16, and analyzes their relationship with anthropometric measurements and body composition in a population-based cohort of healthy children.

2. Materials and methods

2.1. Subjects

The study population included two population-based samples comprising 420 (207 boys and 213 girls) 6–8-year-olds, and 712

Abbreviations: BMI, body mass index; OW, overweight; NW, normal-weight.

* Corresponding author at: Lipid Research Laboratory, IIS-Fundación Jiménez Díaz, Avda. Reyes Católicos, 2, 28040 Madrid, Spain. Tel.: +34 91 5432880; fax: +34 91 5432880.
E-mail address: cgarces@fjd.es (C. Garcés).

0196-9781/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.peptides.2013.08.019

(347 boys and 365 girls) 12–16-year-olds. Children were participants in a cross-sectional study designed to analyze cardiovascular risk factors in Spanish schoolchildren. Children were selected by means of random cluster-sampling in schools, and stratified by sex. Sampling was carried out in two stages: first, schools were selected from lists made available by the Regional Educational Authorities; and second, class rooms and pupils were selected. The study was formally presented to the Board of each of the schools participating. Following this, a letter was circulated to the parents of all the children invited to join the study, outlining the study goals and procedures. Parents were required to provide written consent for their children to participate in the study. All children reported by their parents to be suffering from metabolic syndrome, endocrine, liver or kidney disorders or taking any medication were excluded from the study so as to rule out any possible alteration in the values of the variables of interest.

Precocious puberty cases among 6–8-year-old children were also excluded. The study protocol complied with the Helsinki Declaration guidelines and Spanish legal provisions governing clinical research on humans, and was approved by the Clinical Research Ethics Committee of the Fundación Jiménez Díaz in Madrid.

2.2. Anthropometric variables

Measurements were taken with children wearing light clothing and barefoot. Weight was determined to the nearest 0.1 kg using a standardized digital scale and height was measured to the nearest 0.1 cm using a portable stadiometer. Body mass index (BMI; weight in kilograms/height in meters squared) was calculated and *z*-score BMI was calculated according to the reference population [3]. In a subgroup of 12–16-year-old children, waist and hip circumferences and body composition were recorded. Waist circumference was measured at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. Hip circumference was measured at the widest point of the hips with the subject standing with both feet together. Body composition (expressed as fat mass (kg), lean mass (kg), and percent of body fat) were assessed using a Tanita (Arlington Heights, IL, USA) TBF-300MA impedance body composition analyzer. We considered children to be overweight (OW) or obese if their BMI exceeded the age- and sex-specific cut-off points proposed for children by Cole et al. [4] in a synthesis of international studies.

2.3. Biochemical data

Fasting (12 h) venous blood samples were obtained by venipuncture and collected in Vacutainer tubes. Serum resistin levels were quantified using multiplex assay kits that utilize fluorescent microbead technology, allowing simultaneous quantification of several target proteins within a single serum sample. A customized panel from BioRad was used (Bio-Plex Pro™ Human Diabetes Standard 10-Plex; Bio-Rad, Hercules, CA, USA) in the platform Luminex 200 System (Luminex corporation, Invitrogen; Caramillo, CA, USA). Assay working ranges were 2.3–4739 pg/mL.

2.4. Statistical analysis

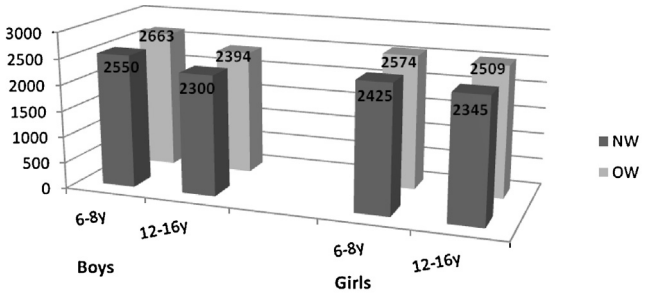
Statistical analyses were performed using the SPSS software package, version 9.0 (SPSS, Inc., Chicago, IL). The results are expressed as mean (95% confidence interval). The Kolmogorov–Smirnov test was used to check whether the variable under study was normally distributed; accordingly to the results, differences in resistin levels between gender and age groups were assessed using a *t*-test. Differences in variables by weight category in boys and girls were evaluated by one-factor ANOVA. According to the parametric or non-parametric distribution of the variables, Pearson or Spearman correlation analyses were performed to evaluate the relationships between resistin levels and both anthropometric variables and body composition.

3. Results

Serum resistin levels in prepubertal children and adolescents according to weight category (normal-weight (NW) and overweight or obese children (OW)) by gender are shown in Fig. 1. We have analyzed overweight and obese children together due to the small number of obese children in our samples: 9 obese boys and 15 obese girls in the 6–8-year-old group and 26 obese boys and 13 obese girls among 12–16-year-old children. Resistin levels were not significantly different between NW 6–8-year-old girls (2425 pg/mL) and NW 12–16-year-old girls (2345 pg/mL) or between OW 6–8-year-old girls (2574 pg/mL) and their OW 12–16-year-old counterparts (2509 pg/mL). Slight differences were observed between NW 6–8-year-old boys (2550 pg/mL) and NW 12–16-year-old boys (2300 pg/mL). No differences were found between OW 6–8-year-old boys (2663 pg/mL) and OW 12–16-year-old boys (2394 pg/mL) (Fig. 1).

No significant differences in resistin concentrations were found between genders at any age. Even though overweight/obese boys and girls tend to have higher resistin levels than their NW counterparts in both age groups, the differences were not statically significant.

Correlation analysis showed no significant correlations of resistin levels with weight or BMI in any gender in any age group (Table 1). In 12–16-year-old children, we did observe a significant correlation between resistin levels and waist circumference in girls but not in boys, and did not find any significant correlation with waist to hip or waist to height ratios (Table 2). Resistin levels correlated significantly with total fat mass and percentage of fat mass, with the correlations being more important in girls (Table 2).



	6-8 years	
	Normal-weight (NW)	Overweight (OW)
Boys (117 NW/ 29 OW)	2550 (2384-2715)	2663 (2337-2990)
Girls (108 NW/ 45 OW)	2425 (2256-2594)	2574 (2315-2833)
	12-16 years	
	Normal-weight (NW)	Overweight (OW)
Boys (236 NW/ 110 OW)	2300 (2192-2409)	2394 (2231-2556)
Girls (288 NW/ 77 OW)	2345 (2240-2450)	2509 (2318-2700)

Fig. 1. Serum resistin levels (pg/mL) in prepubertal children and adolescents according to weight category by gender.

Table 1
Correlation analysis between resistin levels and anthropometric data in 6–8 year-olds and 12–16 year-old boys and girls.

	6–8 year-olds		12–16 year-olds	
	Boys (n = 154)	Girls (n = 163)	Boys (n = 347)	Girls (n = 365)
Weight (kg)	137	006	074	087
BMI (kg/m^2)	078	−016	084	067
z-Score BMI	068	048	063	063

Table 2
Correlation analysis of resistin levels with anthropometric indices and body composition in 12–16 year-old boys and girls.

	Boys (n = 134)	Girls (n = 143)
Waist circumference (cm)	098	173[a]
Waist/hip ratio	041	−046
Waist/height ratio	083	131
Fat mass (kg)	161	200[a]
Fat-mass (%)	166[a]	174[a]

[a] $p < 0.05$.

4. Discussion

Data on resistin levels in healthy populations are scarce and contradictory, mainly because of methodological difficulties. In our study we have described resistin levels in Spanish children using a multiplexed bead immunoassay, which appears to be a promising method for measurement of adipokines [17]. To the best of our knowledge, this is the first study to presents data on resistin levels from a large population of Caucasian children.

Even though some studies have reported that resistin levels are age-dependent in both boys and girls and that a correlation exists between resistin concentration and pubertal stage [7], in our study we have observed no differences in resistin levels between prepubertal and adolescents in girls, and only small differences in boys. Although higher average resistin levels were reported in prepubertal than in pubertal children in both genders in the study by Li et al. in Chinese children [14], the association is less evident when analyzing the association of resistin with Tanner stage development, and is not present in normal weight children, excluding of the analysis those with central obesity [14]. A previous study in healthy Spanish children showed no differences from prepubertal stage to mid-puberty, showing higher resistin levels after puberty was completed, suggesting a possible link between resistin levels and changes in body fat content in adult females [16]. Contrary to what has been observed in other populations [7,14,21], and similar to data described in Spanish children [16], resistin concentrations in our population were not different between boys and girls at any age.

In addition to examining the relationship of resistin levels with anthropometric variables, an additional strength of our study is that we analyzed the association between these levels and percentage of fat mass, an aspect seldom addressed in Caucasian children. Contrary to results previously reported in some child populations [8,15,22] but in agreement with results from other studies [7,21], we not only failed to find significant correlations of resistin with weight or BMI, but also did not find significant differences between mean resistin levels in normal-weight and overweight/obese children. Conventionally, waist circumference is used in both clinical practice and biomedical research as a marker of abdominal obesity. A significant correlation of resistin levels with waist circumference has been observed in girls, although no correlation with waist-to-hip ratio or waist-to-height ratio was found. Gerber et al. [7] described a significant correlation of resistin levels with waist circumference in females, failing to find any association with waist-to-hip ratio. On the contrary, Li et al. [14] found a significant correlation of resistin concentrations with the markers of abdominal obesity analyzed: waist circumference and waist-to-weight ratio. Furthermore, it has been suggested that is the amount of body fat which is related to resistin levels in humans; however, while some cross-sectional studies in adults have related resistin concentrations to fat mass [5,27,28], others have failed to find any association with percent of body fat [12,24]. In our study we have found an association of resistin levels with total fat mass and percentage of body fat mass, particularly in girls. The study by Li et al. [14] in Chinese children also found a positive correlation between fat-mass percentage and resistin levels in both genders. No studies in Caucasian children have included in their analyses an evaluation of the association between resistin levels and body fat composition. Our results, showing significant correlations of resistin with fat mass but not with BMI in adolescents, suggest that, more than BMI itself, the amount of fat mass appears to be related to resistin concentrations in our population. High levels of resistin mRNA expression associated to abdominal fat have been described [18]. However, it has been reported that, although resistin expression in adipose tissue from morbidly obese patients is significantly higher than in lean subjects, there is no correlation between BMI and resistin expression [23].

Resistin seems to act in peripheral tissues to influence sensitivity to insulin and it is assumed that has a proinflammatory action [19]. The association of body fat mass with resistin levels already in children has an important significance regarding the link between adipose tissue and insulin resistance and inflammatory processes later in life.

5. Conclusion

Besides describing resistin levels in healthy pre-pubertal children and adolescents between the ages of 12 and 16, our study supports the hypothesis of a relationship between resistin levels and fat body composition in 12–16-year-old children, particularly in girls.

Conflict of interest

None declared.

Acknowledgements

The article is dedicated to the late Prof. Manuel de Oya as the warmest homage to his memory. Prof. de Oya designed the Four Province Study and the ideas reflected in our work can be traced back to his.

This work was supported by a grant from the Fondo de Investigación Sanitaria (FIS 11/00344) and Biobank grant FEDER RD09/0076/00101. The contract of C Garcés is co-financed by the Fondo de Investigación Sanitaria. Lorena Ortega is a fellow of the Conchita Rábago Foundation. We thank Oliver Shaw for his revision of our manuscript.

References

[1] Azuma K, Katsukawa F, Oguchi S, Murata M, Yamazaki H, Shimada A, et al. Correlation between serum resistin level and adiposity in obese individuals. Obes Res 2003;11:997–1001.
[2] Badman MK, Flier JS. The adipocyte as an active participant in energy balance and metabolism. Gastroenterology 2004;132:2103–15.
[3] Carrascosa A, Fernández JM, Fernández C, Ferrández A, López-Siguero JP, Sánchez E, Sobradillo E, et al. Spanish cross-sectional growth study 2008. Part II. Height, weight and body mass index values from birth to adulthood. An Pediatr (Barc) 2008;68:552–9.
[4] Cole TJ, Bellizi CB, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–3.

[5] Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R, et al. Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metab 2003;88:5452–5.
[6] Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. Cell 2004;116:337–50.
[7] Gerber M, Boettner A, Seidel B, Lammert A, Bär J, Schuster E, et al. Serum resistin levels of obese and lean children and adolescents: biochemical analysis and clinical relevance. J Clin Endocrinol Metab 2005;90:4503–9.
[8] Gherlan I, Vladoiu S, Alexiu F, Giurcaneanu M, Oros S, Brehar A, et al. Adipocytokine profile and insulin resistance in childhood obesity. Maedica (Buchar) 2012;7:205–13.
[9] Gnacinska M, Malgorzewicz S, Stojek M, Lysiak-Szydlowska W, Sworczak K. Role of adipokines in complications related to obesity: a review. Adv Med Sci 2009;2:150–7.
[10] Heilbron LK, Rood J, Janderova L, Albu JB, Kelley DE, Ravussin E. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. J Clin Endocrinol Metab 2004;89:1844–8.
[11] Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;6:2548–56.
[12] Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, et al. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. J Clin Endocrinol Metab 2003;88:4848–56.
[13] Lee S, Kim HS. Human resistin in cardiovascular disease. J Smooth Muscle Res 2012;48:27–35.
[14] Li M, Fisette A, Zhao XY, Deng JY, Mi J, Cianflone K. Serum resistin correlates with central obesity but weakly with insulin resistance in Chinese children and adolescents. Int J Obes 2009;33:424–9.
[15] Maggio AB, Wacker J, Montecucco F, Galan K, Pelli G, Mach F, et al. Serum resistin and inflammatory and endothelial activation markers in obese adolescents. J Pediatr 2012;161:1022–7.
[16] Martos-Moreno GA, Barrios V, Argente J. Normative data for adiponectin, resistin, interleukin 6, and leptin/receptor ratio in a healthy Spanish pediatric population: relationship with sex steroids. Eur J Endocrinol 2006;155:429–34.
[17] Martos-Moreno GA, Burgos-Ramos E, Canelles S, Argente J, Barrios V. Evaluation of a multiplex assay for adipokine concentrations in obese children. Clin Chem Lab Med 2010;48:1439–46.
[18] McTernan CL, McTernabn PG, Harte AL, Levick PL, Barnett AH, Kumar S. Resistin, central obesity and type 2 diabetes. Lancet 2002;359:46–7.
[19] McTernan PG, Kusminski CM, Kumar S. Resistin. Curr Opin Lipidol 2006;17:170–5.
[20] Piestrzeniewicz K, Łuczak K, Komorowski J, Maciejewski M, Wika JJ, Goch JH. Resistin increases with obesity and atherosclerotic risk factors in patients with myocardial infarction. Metabolism 2008;57:488–93.
[21] Reinehr T, Roth CL, Menke T, Andler W. Resistin concentrations before and after weight loss in obese children. Int J Obes 2006;30:297–301.
[22] Roth CL, Kratz M, Ralston MM, Reinehr T. Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. Metabolism 2011;60:445–52.
[23] Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, et al. Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator–activated receptor-γ action in Humans. Diabetes 2001;50:2199–202.
[24] Silha JV, Krsek M, Skrha JV, Sucharda P, Nyomba BL, Murphy LJ. Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. Eur J Endocrinol 2003;149:331–5.
[25] Steppan CM, Lazar MA. The current biology of resistin. J Intern Med 2004;255:439–47.
[26] Szalowska E, Elferink MGL, Hoek A, Groothuis GMM, Vonk RJ. Resistin is more abundant in liver tan adipose tissue and is not up-regulated by lipopolysaccharide. J Clin Endocrinol Metab 2009;94:3051–7.
[27] Volarova de Courten B, Degawa-Yamauchi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. Diabetes 2004;53:1279–84.
[28] Yannakoulia M, Yiannakouris N, Blüher S, Matalas AL, Klimis-Zacas D, Mantzoros CS. Body fat mass and macronutrient intake in relation to circulating soluble leptin receptor, free leptin index, adiponectin, and resistin concentrations in healthy humans. J Clin Endocrinol Metab 2003;88:1730–6.
[29] Youn BS, Yu KY, Park HJ, Lee NS, Min SS, Joun MY, et al. Plasma resistin concentrations measured by enzyme-linked immunosorbent assay using a newly developed monoclonal antibody are elevated in individuals with type 2 diabetes mellitus. J Clin Endocrinol Metab 2004;89:150–6.