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REVIEW
ΑΝΑΣΚΟΠΗΣΗ

Serum resistin, metabolic pathology and diseases in children and adolescents

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Επίπεδα ρεσιστίνης, διαταραχές του μεταβολισμού και νοσήματα σε παιδιά και εφήβους

Περίληψη στο τέλος του άρθρου

Resistin is a recently described adipokine which is expressed in low levels in human adipose tissue, pulmonary tissue and resting endothelial cells, and in high levels in mononuclear leukocytes, macrophages, and spleen and bone marrow cells. Serum levels of resistin have been found to be elevated in obese subjects and in subjects with insulin resistance and diabetes mellitus (DM). There is evidence that resistin is related to a variety of diseases, including rheumatoid arthritis, systemic lupus erythematous, sepsis, asthma and allergic rhinitis. A possible role of resistin has been documented in pathological metabolic conditions observed in children and adolescents, but the data are conflicting. This review summarizes the currently available data concerning the role of resistin in metabolic abnormalities and diseases in children and adolescents.

Key words

Children and adolescents
Insulin resistance
Metabolic syndrome
Obesity
Resistin
Type 2 diabetes mellitus

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1. INTRODUCTION

Resistin, a recently described adipokine, is a member of a family of proteins which are found in inflammatory zones.[1,2] Resistin is expressed in low levels in human adipose tissue, pulmonary tissue and resting endothelial cells and in high levels in mononuclear leukocytes, macrophages and spleen and bone marrow cells.[2] According to studies in animals, resistin represents the link between obesity and insulin resistance (IR).[2] There is evidence to suggest that resistin is related to a variety of disease states, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), asthma, sepsis and septic shock.[1–4] In addition, resistin appears to play a role in pathological conditions observed in infants and children. This review summarizes the currently available data concerning the role of resistin in metabolic abnormalities and disease in infancy, childhood and adolescence.

2. RESISTIN

Resistin was named for its initially observed association with insulin resistance (IR), and it is also known as adipose tissue-specific secretory factor.[1] Resistin is encoded by the *RETN* and *RSTN* genes situated on chromosome 19p13.3. It is formed of 108 amino acids (as pre-peptide) and has a low molecular weight (12.5 kDa) and it circulates in human blood as an omodimer of 92 amino acids the monomers of which are connected with cysteine at position 26.[4]

Resistin is member of a family of proteins which are found in inflammatory zones (FIZZ), also named resistin-related molecule (RELM). Each of these proteins has a distinctive distribution in tissues. FIZZ1/RELMa is found in allergic pulmonary inflammation in mice, although no human analog of FIZZ1 has yet been identified. FIZZ2/RELMb is expressed mainly in the small intestine and in the epithelial mucosal cells, while FIZZ3/resistin is expressed in the white adipose tissue in rodents as a dimer.[2] Human resistin shares a homology of about 59% with the murine form,

but has quite different tissue distribution and functions.[5]

The expression of the gene of resistin is induced by C/EBPa (an important factor of transcription for the regulation of adipocyte differentiation), and repressed by the peroxisome proliferator activated receptor-γ (PPAR-γ) through a direct binding of these transcription factors to the resistin promotor.[2] Its expression is modulated by a variety of endocrine factors. In the adipose cells of rodents, resistin expression is induced by corticosteroids, prolactin, testosterone and growth hormone, while insulin, epinephrine and somatotropin have an inhibitory effect.[2]

Correlation between serum resistin levels and inflammatory indicators, including interleukin 6 (IL-6), leptin, tumor necrosis factor-α (TNF-α) soluble receptor 2 and C-reactive protein (CRP) has been observed in patients with inflammation, obesity and type 2 diabetes mellitus (T2DM).[6] Resistin induces the production and release of TNF-α and IL-6 in peripheral human mononuclear cells and release of TNF-α and IL-12 in human macrophages. It induces vascular inflammation through the increased expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) in vascular endothelium.[3]

Although resistin signaling paths have not been widely described, it is presumed that the nuclear transcription factor NF-kB is implicated.[4] The dose-dependent resistin activity promotes the translocation of NF-kB from cytoplasm to nucleus. Both unit p65 and unit p50, complexes of NF-kB, have been found in the nuclear extracts of peripheral mononuclear cells stimulated by resistin.[2] NF-kB is a transcription factor that controls the expression of genes encoding immune responses, apoptosis and cellular cycle. Impaired regulation of NF-kB can give rise to inflammatory and autoimmune diseases, viral infection and cancer.[7]

In adipocyte cell cultures, resistin reduces glucose transport in response to insulin, while resistin antibody has the opposite effect, and resistin can inhibit the differentiation of adipocytes.[1–5] Absence of the resistin gene permits the activation of activated protein kinase (AMPK) and impedes the expression of the hepatic enzyme genes involved in gluconeogenesis.[1–5] Obese animals lacking the resistin gene were found to have lowered fasting glycemia, suggesting interaction between resistin, hyperglycemia and IR and obesity.[1–5] Other studies have indicated an inverse relationship between resistin, obesity and IR,[1–5] but further clarification is needed to establish the precise interaction between this adipokine and the metabolic diseases.

There is evidence that resistin may have pro-inflammatory properties.[1] It accumulates in the synovial liquid of patients with RA and *in vitro* resistin stimulation of human synovial fluid leucocytes has produced an increase in mRNA, IL-1β and IL-6.[2] Circulating levels of resistin are low in patients with RA, which suggests increased local production and or preferential accumulation of this molecule at the site of inflammation.[2]

A study in patients with SLE showed an association between resistin, inflammation and low levels of complement and high density lipoprotein cholesterol (HDL-C).[1] In this study, levels of serum resistin were associated inversely with kidney function and positively with glucocorticoid use, and participated in the regulation of bone metabolism by stimulating osteoblast and osteoclast differentiation.[1]

Resistin also has a role as an acute phase reactant in sepsis and septic shock; it is associated with the severity of sepsis and can be used as a prognostic marker.[4] A study comparing patients with and without sepsis showed that serum resistin levels were significantly raised in those with sepsis.[8] It has also been demonstrated that serum resistin levels could serve as an independent index of survival in critically ill patients without sepsis.[8]

La Rochelle et al found that serum resistin levels were significantly higher in patients with moderate to persistent asthma compared with patients without evidence of pulmonary or systemic inflammatory disease.[3] In addition, Korpela-Leivo et al showed that a high level of serum resistin can predict a favorable anti-inflammatory effect of inhaled glucocorticoids, suggesting that serum resistin level can act as an indicator of the steroid-sensitive phenotype in asthma.[9] Finally, in a study of patients suffering from persistent allergic rhinitis (AR), serum resistin levels were higher in patients with moderate-severe symptoms than in those with minor symptoms.[10]

3. RESISTIN IN OBESITY AND THE METABOLIC SYNDROME

A study in 236 children and adolescents (135 obese; 201 thin) demonstrated significant correlation between serum level of resistin and body mass index (BMI) in the obese group.[11] The relationship between serum resistin level and obesity was confirmed in a study of 3,508 children and adolescents (788 boys/1,720 girls) aged 6 to 18 years, which showed that obese children had a worse metabolic profile, with high resistin levels.[12] A recent investigation of the adipocytokine profile in obese children showed that serum levels of leptin, resistin and IL-6 were significantly higher, and adiponectin significantly lower in obese than in non-obese children. This study showed that resistin level

was positively correlated with the levels of leptin and IL-6.[13] A study of 67 obese and 62 lean children (mean age 10.9±2.8 years) showed that resistin was increased in the obese group independently of the quantity of the adipose tissue, and that a high level of resistin was related to inflammation and endothelial activation.[14]

In a study, conducted in Italy, in 47 obese children (19 boys/28 girls) the serum level of resistin was in inverse correlation with age, particularly in boys, and positive correlation with BMI. The study showed that serum resistin level showed close correlation with anthropometric parameters of child obesity, especially BMI.[15] Another recent study showed that school-based intervention designed to reduce BMI over a period of 12 months in Mexican-American children aged 12–14 years resulted in a reduction in the serum level of resistin of about 12% at 6 months.[16]

In a cross-sectional study of 73 boys and 77 girls in Saudi Arabia with varying BMI anthropometric measures and fasting serum levels of glucose, insulin, lipid profile, resistin, angiotensin II (ANG II) and PAI-1 were assessed. This study showed that resistin was positively correlated with hip and waist circumference and BMI. The association of resistin with the markers of obesity was significant in girls but not in boys.[17]

A study of 42 randomly selected obese male schoolchildren (BMI >95th percentile, mean age 15.7±1.5 years) showed no correlation between serum level of resistin and obesity, and the authors concluded that the metabolic abnormalities of IR seen in obese male patients are not related to resistin.[18] In accordance with this, a study investigating the effects of exercise training on plasma adipokines in 42 children (24 lean/18 obese) showed that serum resistin levels were similar in the two groups.[19] Another study, examining relationships between IR, weight loss, and resistin in 63 obese children and 36 lean children showed that serum levels of resistin did not differ significantly between obese and lean children. Resistin level was independent of age and pubertal stage, but girls demonstrated significantly higher levels of resistin than boys.[20]

Regarding the effect of metformin on the level of resistin and other markers of IR it was found in patients aged 4 to 17 years with glucose intolerance that metformin administration resulted in significant reduction in the serum level of resistin, independently of its effects on body weight.[21]

Resistin levels were examined in relation to obesity, IR and inflammation markers in 3,472 Asian children and adolescents aged 6–18 years (1,765 boys/1,707 girls). The level of resistin increased with central obesity in children of both sexes but not with simple adiposity in boys. Waist circumference, fat-mass percentage, waist-to-height ratio and BMI were positively correlated with resistin in children of both sexes. Blood lipids (triglycerides, non-esterified fatty acids [NEFA] and low-density lipoprotein [LDL] cholesterol), diastolic and systolic blood pressure (SBP) were all correlated positively with resistin in boys. NEFA and HDL-C were correlated negatively and inflammation markers (CRP and C3) positively with resistin in girls. In both boys and girls, resistin tended to decrease with age, but with girls having higher levels than boys.[22]

Evidence of the link between resistin levels and obesity is contradictory and the association between resistin and metabolic syndrome (MS) is not clear.[23] Studies in mice have defined the role of resistin in glucose metabolism and insulin sensitivity, but in humans the relation between resistin, body fat, and IR is indefinite and a stable relationship between resistin and MS cannot be demonstrated.[23] A possible explanation for the lack of association between resistin and MS could be the fact that human resistin is secreted mainly by macrophages and not by adipocytes.[23] The correlation between resistin and inflammation is supported by studies in humans that showed increased levels of resistin in the acute inflammatory state.[23] MS could be associated with low grade inflammation, which might be the reason why the relationship between MS and resistin is not clear.[23]

It is known that hepatic progenitor cells (HPCs) play a major role in liver repair and regeneration. In a study evaluating HPC involvement in pediatric nonalcoholic fatty liver disease (pNAFLD) liver biopsies from 30 consecutive children and adolescents with untreated NAFLD were examined (19 with nonalcoholic steatohepatitis [NASH] and 11 without NASH). Adiponectin expression in the HPCs of pNAFLD patients was down-regulated with respect to the healthy liver, and this expression was inversely correlated with NAS score and steatosis. Resistin expression in HPCs increased in pNAFLD and was related to degree of fibrosis.[24]

Another study evaluated the serum levels of leptin, adiponectin and resistin in obese children with NAFLD (44 consecutive obese children with suspected liver disease and in 24 lean control subjects). Serum leptin level was significantly higher and adiponectin level lower in the obese children with NAFLD compared to those in the control subjects. Only adiponectin was correlated with homeostasis model assessment of insulin resistance. Significant negative correlation was found between the ultrasonographic grades of liver steatosis and serum levels of adiponectin and resistin, which were lower in children with advanced

liver steatosis than in those with mild steatosis. These data suggest that adiponectin and resistin may be suitable serum markers for predicting advanced liver steatosis in children with NAFLD.[25]

In a study to investigate the relationship between serum levels of adiponectin and resistin and NAFLD in 113 obese children the adiponectin level of obese children was significantly lower than that of control subjects, while the resistin levels were no different. These results suggest that only adiponectin might be a protective factor for NAFLD occurrence in obese children.[26]

Another study aimed to clarify the usefulness of serum levels of adiponectin and resistin in 307 obese and overweight children aged 11–19 years of which 40 (13%) were classified as having MS. Although the median resistin level was higher in the obese than in the other children, the difference was not significant. The area under the curve (AUC) was not significant for adiponectin and resistin. In this study, adipokines had no predictive value in the diagnosis of MS.[27]

4. RESISTIN IN VARIOUS DISEASES

4.1. Resistin in asthma

A study by Arshi et al conducted in 21 patients with allergic asthma and 10 non allergic healthy individuals, aged 6 to 17.9 years, showed that in the patient group BMI and serum levels of leptin, IL-6 and resistin were correlated with IR.[28] Kim et al conducted a study in 149 children with asthma atopy, 37 with asthma but no atopy and 54 healthy control children.[29] According to the results of the study lower serum levels of resistin were found in children with asthmatic-atopy than in non-atopic and healthy children.[29]

A study by La Rochelle et al in adults aged 18 to 65 years, diagnosed with moderate to persistent asthma that were treated with inhaled glucocorticosteroids or other medications other than oral corticosteroids, showed that their serum levels of resistin were significantly elevated compared with a healthy control group.[3] This increase in serum resistin was independent of serum levels of CRP or glucose. In addition, serum resistin was consistently high in the patients with more frequent symptomatology.[3] These findings suggest that serum level of resistin is associated with inflammation of the airways in asthma and may reflect the state of severity of the disease.[3] Korpela-Leivo et al in a study of 35 asthmatic women with asthma not previously treated with corticosteroids, non-smokers, with median age of 34 years estimated lung function, expired NO, and serum levels of various adipokines (among them resistin) at the beginning of the study and after 8 weeks of treatment with fluticasone by aerosol.[9] The study demonstrated that a high level of serum resistin before treatment with inhaled corticosteroid could predict a favorable anti-inflammatory effect of the medication, suggesting that serum resistin can act as an indicator of the steroid-sensitive phenotype in asthma.[9]

4.2. Resistin in allergy

Few studies have been conducted to verify a correlation between serum level of resistin and allergic rhinitis (AR). A study was conducted to evaluate the serum level of resistin in 50 children with AR and its association with clinical disease severity, parameters of atopy and pro-/anti-inflammatory cytokines. The serum level of resistin was significantly higher in children with AR compared with that of 30 healthy control subjects. The serum level of resistin was associated with disease severity, being significantly higher in moderate-severe than mild persistent AR and positively correlated with nasal symptom scores and serum level of IL-6.[30]

Study of serum levels of resistin, apelin, and visfatin in 27 children with atopic dermatitis (AD) and in 46 healthy subjects showed that levels of resistin and apelin were significantly higher, and visfatin significantly lower in children with AD than in the healthy control subjects, although an increase in resistin levels was demonstrated exclusively in boys, and a significant increase in the level of apelin in girls. No relationship was found between the levels of adipokines and the degree of allergic sensitization.[31]

4.3. Resistin in other diseases

Resistin also plays an important role in juvenile idiopathic arthritis (JIA) and may be considered as a biomarker for disease activity especially in those cases with systemic onset. A study in 68 patients with JIA and 33 age- and sex-matched control children showed that the mean serum level of resistin was significantly higher in the patients with JIA, especially those with the systemic onset form. The level of resistin was significantly higher in those receiving steroids and those with positive antinuclear antibody testing. Of the patients with JIA 50 were females and 18 males and the serum level of resistin was slightly higher in females, but not to a significant degree.[32]

It is known that body fat is an important source of adipokines, not only in relation to the energy balance, but associated also with the inflammatory and immune

responses. For this reason the relationship between serum levels of adipokines and coronary artery aneurysm was explored in 165 patients with Kawasaki disease (KD). The study showed that serum levels of adiponectin and resistin were associated with the development of coronary aneurysm in children with KD. The up-regulation of resistin secreted from adipose tissue may be closely linked to the up-regulation of systemic pro-inflammatory markers in acute KD.[33]

A study in Chinese children, however, failed to show an association between coronary artery lesions and resistin gene (RETN) promoter polymorphism in KD children, and the serum level of resistin was significantly higher in patients with KD than in control subjects, regardless of the presence of coronary artery lesions.[34]

Resistin may have a key role as a diagnostic biomarker of serious bacterial infection in children. The results of a study of children in Malawi demonstrated that the addition of resistin protein measurement to procalcitonin significantly improved the diagnosis of serious bacterial infection in children, although further studies are needed in order to confirm this finding.[35]

In a study of 24 overweight children and adolescents and 40 control subjects of normal weight, cardiac structural and functional changes, such as increased left ventricular mass and diastolic dysfunction, were demonstrated. Although decreased serum level of adiponectin was not related to cardiac changes, it was shown that decreased levels of serum resistin in the obese subjects lead to left ventricular hypertrophy. A significant positive correlation was demonstrated between left ventricular mass, interventricular septum systolic diameter and resistin in the obese children.[36]

A study in 60 normal weight (BMI ≤75th percentile) and 60 overweight (BMI ≥95th percentile) adolescents aged 10–14 years showed, in multiple regression models controlling for puberty and ethnicity, that serum levels of adiponectin, resistin and IL-6 were associated with SBP.[37]

In a cross-sectional analysis of 319 children in the Chronic Kidney Disease (CKD) in Children cohort, a large cohort of children with stage II–IV CKD, serum level of resistin level was shown to increase with decline in glomelular filtration rate (GFR) and to be involved in the inflammatory milieu present in CKD.[38]

A study of 78 patients with either Graves' disease (29 girls/2 boys, aged 6–21 years) or Hashimoto's thyroiditis (30 girls/2 boys, aged 9–18 years) showed that patients with untreated Graves' disease had a higher serum level of adiponectin than the patients with hypothyroidism in Hashimoto's thyroiditis and in simple goiter, but a lower serum level of resistin than those with simple goiter and Hashimoto's thyroiditis. This study showed that the disturbances in thyroid hormones in thyroid diseases have affect the levels of adiponectin and resistin released by adipose tissue.[39]

5. CONCLUSIONS

The serum level of resistin might be useful as a diagnostic or prognostic marker in several metabolic disorders observed more often in childhood, such as obesity, IR and MS, which increase the risk of development of T2DM and cardiovascular disease in adult life. In addition, serum levels of resistin appear to have an important role in inflammatory diseases, although their correlation with metabolic disorders and inflammatory diseases is not always clear and the evidence is sometimes conflicting. For this reason the use of serum level of resistin as a diagnostic marker in daily clinical practice is not yet recommended. Further studies on the various effects of resistin need to be conducted.

ΠΕΡΙΛΗΨΗ

Επίπεδα ρεσιστίνης, διαταραχές του μεταβολισμού και νοσήματα σε παιδιά και εφήβους

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Η ρεσιστίνη είναι μια λιπονεκτίνη που ανακαλύφθηκε πρόσφατα και εκφράζεται σε χαμηλά επίπεδα στο λιπώδη ιστό, στο πνευμονικό παρέγχυμα και στα ενδοθηλιακά κύτταρα και σε υψηλά επίπεδα στα μονοκύτταρα και στα μακροφάγα του αίματος, στο σπλήνα και στο μυελό των οστών. Μελέτες έδειξαν ότι τα επίπεδα της ρεσιστίνης είναι υψηλά στα παχύσαρκα άτομα, καθώς και στα άτομα με αντίσταση στην ινσουλίνη και σακχαρώδη διαβήτη. Επίσης, υπάρχουν δεδομένα που δείχνουν τη σχέση της ρεσιστίνης με παθήσεις όπως η ρευματοειδής αρθρίτιδα, ο συστηματικός

ερυθηματώδης λύκος, η σήψη, το άσθμα και η αλλεργική ρινίτιδα. Πρόσφατα, μάλιστα, αποδείχθηκε ότι η ρεσιστίνη συμμετέχει στην παθογένεια των μεταβολικών διαταραχών σε παιδιά και εφήβους. Ωστόσο, η παραπάνω σχέση δεν έχει διευκρινιστεί πλήρως. Για το λόγο αυτό, σκοπός της παρούσας εργασίας ήταν η ανασκόπηση της υπάρχουσας βιβλιογραφίας σχετικά με το ρόλο της ρεσιστίνης στις διαταραχές του μεταβολισμού σε παιδιά και εφήβους.

Λέξεις ευρετηρίου: Αντίσταση στην ινσουλίνη, Μεταβολικό σύνδρομο, Παιδιά και έφηβοι, Παχυσαρκία, Ρεσιστίνη, Σακχαρώδης διαβήτης τύπου 2

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