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Original Article

Association of resistin and hs-CRP with liver enzymes and components of the metabolic syndrome in Iranian adolescents with excess weight: the CASPIAN-III Study

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ABSTRACT

Backgroun & Objectives: High-sensitivity C-reactive protein (*hs-CRP*) and the *adipokine resistin are* suggested as predictive factors for chronic diseases; however their association with liver enzymes and cardiometabolic risk factors in overweight children remain to be determined.

This study aimed to determine the association of resistin and hs-CRP with liver enzymes and cardiometabolic risk factors in a nationally-representative sample of Iranian obese children and adolescents.

Methodology: This cross-sectional multi-center study was performed on 100 overweight and or obese adolescents. It was performed as a sub-study of a nationwide survey entitled CASPIAN-III Study, conducted among 5570 students living in 27 provinces in Iran. Participants were randomly selected from students with age- and gender-specific body mass index (BMI) of >+1 z-score.

Results: Data from 96 participants (49 boys) were complete and are included in the statistical analysis. The mean (SD) age of participants was 15.01 (2.4) years. Resistin had significant correlations with indexes of generalized and abdominal obesity, as well as with serum alanine aminotransaminase, aspartate aminotransaminase, fasting blood glucose, and triglycerides. It had inverse association with serum HDL-C concentration, and marginally significant correlations with total- and LDL-cholesterol. Hs-CRP had significant correlation with indexes of abdominal obesity, inverse marginal association with HDL-C, and marginally significant association with BMI and triglycerides. Multiple regression analysis, adjusted for age and gender, revealed nearly similar associations.

Conclusions: Our findings suggest that resistin seems to have a contributory role in childhood obesity and its metabolic consequences as fatty liver and metabolic syndrome. The common significant association of resistin and hs-CRP with other variables was mainly their correlation with abdominal obesity. Further studies should be considered for the underlying pathophysiological process of resistin, as well as for the clinical implications of the current findings.

KEY WORDS: Liver enzymes, Adipokines, Resistin, C-reactive protein, Obesity, Adolescence.

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INTRODUCTION

Obesity is accompanied with a series of cardiometabolic risk factors and non-alcoholic fatty liver disease (NAFLD). Affecting and being affected by various metabolic pathways, fat tissue has a reciprocal relation with metabolism.[1-5] Adipose tissue secrets hormones and different cytokines called adipokines as leptin, interleukins, tumor necrotizing factor, adiponectin, and

resistin.[6-11] A variety number of autocrine, paracrine and endocrine pathways are affected by these substances.[12-15]

Resistin is a newly discovered cysteine-rich protein; many previous studies have been conducted to evaluate its probable association with obesity and MetS.[15-20] The role of resistin in the pathogenesis of MetS and NAFLD seems to be unclear. Adiponectin has anti-inflammatory effects, whereas resistin is pro-inflammatory, thus their imbalance may result in low grade inflammation.[21]

Yet, the pathophysiologic role of resistin in human beings remains to be determined.[16,17] A number of studies have demonstrated higher level of resistin in obese patients, while others reported inconsistent results.[18-20] A study documented that serum resistin level does not differ among obese and normal-weight persons, and that it remains unchanged even after weight loss.[22]

Some studies have shown a potential role for resistin in insulin tolerance and diabetes[22], whereas some others have demonstrated its role in coronary artery disease, hypertension and type II diabetes.[23] Obesity and its co-morbidities as MetS and NAFLD are considered as pre -inflammatory states for which measuring the inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) can be used to predict the outcome of such disorders and the incidence of chronic diseases.[24-27] However, the role of resistin in co-morbidities of obesity is still unknown, thus evaluating the relationship of resistin with pediatric MetS and NAFLD may be useful to have a better understanding of the metabolic pathways and the comorbidities of excess weight from early life.

MetS and NAFLD are considered as inter-related disorders even in the pediatric age group, and have common predisposing factors. Some studies have documented the impact of ethnic and life style differences as well as cultural habits and environmental diversities on pediatric MetS and NAFLD.[28,29]

This study aimed to determine the association of resisitin and hs-CRP with components of MetS and liver enzymes in a nationally-representative sample of Iranian obese adolescents.

METHODOLOGY

This cross-sectional multi-center study was performed on 100 overweight and or obese adolescents. It was conducted as a sub-study of the third survey of the national school-based surveillance system entitled **C**hildhood and **A**dolescence **S**urveillance and Prevention of **A**dult **N**on-communicable disease (CASPIAN-III) (Caspian is the name of the world's largest lake, located in Northern, Iran) study in Iran. Details of data collection and sampling are explained previously[30], and here we present it in brief.

The main study was conducted as a school-based nationwide health survey among 5570 students aged 10-18 years, who were recruited by multistage random cluster sampling from urban and rural areas of 27 provincial counties in Iran. Those students with history of any acute or chronic diseases and any medication use were not included to the study. The survey was performed in accordance with the ethical standards of the Helsinki Declaration. The main study approved by the institutional review boards at national and provincial level, and the current sub-study was approved by the Ethics Committee of the Research Department of Isfahan University of Medical Sciences.

A trained team of health professionals conducted the physical examination under standard protocols by using calibrated instruments. Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2). We used the growth curves of the World Health Organization (WHO) to define BMI categories, i.e. overweight as sex-specific BMI for age of >+1 z-score , and obesity as sex-specific BMI for >+2 z-score.[31]

This study comprised 100 overweight and or obese adolescents selected by random sampling from participants with age- and gender-specific BMI of >+1 z-score living in different provinces in Iran.

For blood sampling, students were invited to the nearest health center to the school. Fasting venous blood samples were centrifuged, and fresh sera were analyzed for blood glucose, lipid profile, and aminotransaminases by using Pars Azmoon reagents kit (Tehran, Iran). For the current sub-study, the serum resistin level was measured by Biovendore kit and hs-CRP was measured with the use of auto-analyzer.

Statistical analysis: Data were analyzed by statistical software SPSS (SPSS, Inc., Chicago, Illinois) version 18.0. The normality of the distribution of variables with a Kolmogorov–Smirnov test was verified and found to have no significant deviation from normality. Analyses were initially stratified by gender, but as the differences were not significant, results are presented for girls and boys combined. Quantitative data are presented as mean and standard deviation (SD).

Table-I: Characteristics* of participants.

Variables	*Mean (SD)*	*Interquartile range*
Body mass index(kg/m2)	27 (2.3)	27 [25-29]
Waist-to-height-ratio	0.57 (0.06)	0.56 [0.48-0.60]
Systolic blood pressure(mmHg)	109.1(12)	110.2 [100.5-120.7]
Diastolic blood pressure(mmHg)	70.1 (10.9)	70.5[60.2-80.7]
Resistin (ng/mL)	4.4 (1.2)	3.9[3.7-5.4]
Hs-CRP (mg/L)	1.9(0.07)	1.7[1.5-2.4]
Alanine aminotransaminase (U/L)	29.1(4.7)	25.7[24.8-34.6]
Aspartate aminotransaminase(U/L)	27.1(4.5)	24.6[23.1-32.6]
Fasting blood glucose(mg/dL)	83.2(11.4)	83[76.2-91.4]
Total cholesterol (mg/dL)	170.4(10.1)	170.1 [160.1-180.5]
LDL-C (mg/dL)	92.4(11.8)	92.1 [81.7-105.2]
HDL-C (mg/dL)	40.1(7.4)	39.2[32.5-48.1]
Triglycerides (mg/dL)	109.1(26.4)	107.1[81.4-130.1]

*: mean (standard deviation)

Pearson's correlation test and multiple regression analysis was adjusted for age and gender. The level of statistical significance was set at $P < 0.05$.

RESULTS

Data from 96 participants (49boys) were complete and are included in the statistical analysis. The mean (SD) age of participants was 15.01 (2.4) years. Table-I shows the mean (SD) value and interquartile range of measured variables. As presented in Table-II, resistin had significant correlations with indexes of generalized and abdominal obesity, as well as with FBG, TG, ALT, and AST. It had inverse association with serum HDL-C concentration, and marginally significant correlations with total- and LDL-cholesterol. Hs-CRP had significant correlation with indexes of abdominal obesity, inverse marginal association with HDL-C, and marginally significant association with BMI and TG. Multiple regression analysis, adjusted for age and gender, was used to assess predictive coefficients for variables studied, and revealed nearly similar associations (Table-III).

DISCUSSION

This study revealed some significant associations of serum resistin concentration with liver enzymes and some cardiometabolic risk factors, notably components of MetS, among overweight and obese children and adolescents.

Limited experience exists on the association of resistin with NAFLD and liver enzymes in the pediatric age group. The association of resistin with liver enzymes is reported in children with acute hepatitis[32]; however the role of resistin in pediatric NAFLD remains to be determined. We documented significant age- and gender-adjusted correlations of resistin with ALT and AST. Studies in adults suggested that hyperresistinemia might be involved in the development of NAFLD[33], whereas inconsistent results exist on the association of resistin with liver enzymes in the pediatric age group. While some studies did not document such correlation[34,35], a study confirmed this association among prebuscent children, and not among adolescents.[36]

A study on 113 obese children, divided to three groups of those without any liver abnormality were compared with those having fatty infiltration in the liver sonography, and those with liver function abnormality, with 37 non-obese controls. Serum resistin levels were not different between groups studied.[35]

The correlation of resistin with the grade of liver steatosis remains controversial; while some studies revealed negative correlation.[34,37] Some evidence exists on the association of low serum resistin level with excessive ectopic fat in the liver of insulin resistant individuals.[38] Other evidence suggests that hepatic progenitor cells express resistin, and

Table-II: Correlation of resistin and hs-CRP with variables studied.

	BMI	*WC*	*WHtR*	*FBG*	*TC*	*LDL-C*	*HDL-C*	*TG*	*ALT*	*AST*	*SBP*	*DBP*
Resistin												
r	0.4	0.6	0.6	0.4	0.2	0.3	-0.4	0.5	0.6	0.6	0.2	0.2
P	0.04	0.02	0.01	0.04	0.05	0.05	0.02	0.04	0.01	0.02	0.07	0.1
Hs-CRP												
r	0.3	0.5	0.6	0.2	0.3	0.3	-0.3	0.3	0.3	0.3	0.1	0.1
P	0.05	0.04	0.03	0.08	0.06	0.09	0.05	0.05	0.06	0.07	0.09	0.07

Hs-CRP: High-sensitive C-reactive protein; BMI: body mass index; WC: waist circumference;
FBG: fasting blood glucose; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol;
HDL-C: high density lipoprotein-cholesterol; ALT: alanine aminotransaminase;
AST: aspartate aminotransaminase; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table-III: Regression analysis* of resistin and hs-CRP with variables studied.

	Correlation coefficient with resistin	*P*	*Correlation coefficient with CRP*	*P*
BMI(kg/m2)	0.3	0.02	0.2	0.07
WC(cm)	0.5	0.03	0.4	0.04
WHtR	0.6	0.03	0.2	0.08
SBP (mmHg)	0.2	0.1	0.2	0.09
DBP(mmHg)	0.2	0.1	0.2	0.07
ALT (U/L)	0.6	0.02	0.2	0.1
AST(U/L)	0.5	0.04	0.2	0.09
FBG(mg/dL)	0.4	0.04	0.1	0.07
TC (mg/dL)	0.3	0.05	0.2	0.1
LDL-C (mg/dL)	0.3	0.05	0.2	0.1
HDL-C (mg/dL)	-0.3	0.04	-0.2	0.09
TG (mg/dL)	0.5	0.03	0.3	0.06

*: adjusted for age and gender
Hs-CRP: High-sensitive C-reactive protein;
BMI: body mass index; WC: waist circumference;
FBG: fasting blood glucose; TC: total cholesterol;
LDL-C: low density lipoprotein-cholesterol;
HDL-C: high density lipoprotein-cholesterol;
ALT: alanine aminotransaminase;
AST: aspartate aminotransaminase; SBP: systolic blood pressure; DBP: diastolic blood pressure.

are significantly associated with the severity of pediatric NAFLD.[39]

We found significant associations of resistin with obesity, notably with abdominal obesity. Findings of various studies are conflicting about the association of resistin level with childhood obesity. A study on 79 obese children with mean age of 14.3(1.9) years and 35 controls showed higher serum resistin level among obese children than controls.[40]

In a large study on 3472 children aged 6-18 years, waist circumference, fat-mass percentage, waist-to-height ratio, and BMI had positive correlation with resistin in both genders. Resistin increased with abdominal obesity in both genders, but not with simple adiposity among boys.[41]

In a study on 42 obese boys, aged 15.7(1.5) years, and 38 age-and sex-matched controls, serum resistin level was not significantly different between groups, and was not correlated with BMI.[43] In a study comparing 79 obese children aged 10-15 years with 35 normal-weight controls; resistin level was higher in obese participants than controls.[40]

Another study compared the level of resistin in 42 obese boys (mean age of 15.7 years) with 38 age- and sex-matched controls. This study revealed no difference in the resistin level of both groups, and no correlation of resistin level with BMI.[42]

In a study on 317 overweight and obese children, with mean age of 14.2 (1.8) years, the median resistin values were higher in obese than in overweight children, but this difference was not statistically significant.[44] Consistent with our previous study[46], the correlation of hs-CRP was stronger with abdominal- than with generalized obesity.

Contradicting results are reported regarding the association of resistin concentration and MetS. Most studies did not document any association of serum resistin level and MetS in the pediatric age group.[40-43,6,47]

However, the largest study in this field revealed associations of serum resistin level with cardiometabolic risk factors. Among boys, resistin had positive correlation with TG, LDL-C, and systolic BP; whereas among girls it had negative correlation with HDL-C and positive correlation with hs-CRP.[42] Consistent with the latter study, we found significant age- and gender-adjusted association of resistin with components of MetS as WC and TG, and inverse association with HDL-C. We did not find significant association for resistin and hs-CRP with BP. A previous study among adolescents documented an inverse association of resistin and SBP.[48]

Given the controversies regarding the association of resistin with liver enzymes and cardiometabolic risk factors, an experimental study assessed whether inflammation may induce expression of resistin in human liver and adipose tissues, as organs regulating total body energy metabolism. This study found significantly higher resistin gene and protein expression in liver than in the adipose tissue. In liver, resistin co-localized with markers for Kupffer cells, as well as for a subgroup of endothelial and fibroblast-like cells. This study suggested that resistin should not be considered only as an adipokine in humans. As inflammation induced by lipopolysaccharide did not affect resistin protein synthesis in human liver and adipose tissues, this study implied that elevated serum resistin levels are not indicative for inflammation of adipose tissue or liver in a way similar to known inflammatory markers as interleukins or TNFalpha.[49]

Although resistin is considered as an adipokine correlated with inflammatory markers and is suggested as a predictive for chronic diseases, its role in NAFLD, insulin resistance and type 2 diabetes mellitus remains to be determined. The controversial findings of different studies may be because of its measurement with diverse assay systems. It is also suggested that resistin may

circulate in dissimilar molecular isoforms, and this may raise problems for the comparison of its levels measured in different studies.[50]

Study limitations and strengths: The main limitation of this study is its cross-sectional nature, so the associations of different variables should be considered with caution. The study strengths are the novelty of studying the association of resistin with liver enzymes in the pediatric age group, and using data of a nationally-representative group of children, which would increase the generalizability of the study findings.

CONCLUSIONS

As a whole, our findings suggest that resistin seems to have a contributory role in childhood obesity, and its metabolic consequences as NAFLD and MetS. In our study, the common significant association of resistin and hs-CRP with other variables was mainly their correlation with abdominal obesity. Further studies should be considered for the underlying pathophysiological process of resistin, as well as for the clinical implications of the current findings.

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Conflict of interest: None to declare.

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