

Association between resistin, adiponectin and leptin and cardiovascular risk factors in Japanese school children

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Abstract

Background

It is not clear whether resistin, adiponectin and leptin are as closely associated with cardiovascular disease risk in childhood as in adulthood.

Methods

A survey was performed on elementary school 4 th graders aged 9 to 10 years in Ina-machi, Saitama, Japan to investigate whether resistin, adiponectin and leptin in these children might be associated with cardiovascular risk factors (atherosclerosis index: AI, waist-to-height ratio: W/H ratio, body mass index: BMI), and how the presence of obesity might affect their association.

Results

A total of 204 boys and 176 girls participated in the survey. Leptin and the leptin-to-adiponectin ratio (L/A ratio) were significantly correlated with the cardiovascular risk factors except AI, and adiponectin was shown to be negatively correlated with all the cardiovascular risk factors examined in the entire study population. While the serum resistin concentration was not found to be significantly different among the boys and girls with or without obesity, the resistin-to-adiponectin ratio (R/A ratio) was found to be significantly different between the obese and non-obese boys but not between the obese and non-obese girls. Among the obese boys, there was a significant correlation between resistin and AI and between the R/A ratio and the cardiovascular risk factors, neither of which was noted among the entire boy population or the non-obese boys. Whereas the R/A ratio was significantly correlated with all the cardiovascular risk factors only in the obese boys. (AI: 0.426, $p < 0.05$, Waist Circumference: 0.545, $p < 0.01$, W/Hr: 0.562, $p < 0.01$, BMI: 0.401, $p < 0.05$)

Conclusions

Our study findings suggest that school children with high leptin and/or low adiponectin levels are placed at higher cardiovascular risk, regardless of gender. It was also suggested that among boys with obesity as a cardiovascular risk factor, cardiovascular risk was higher in those with high leptin and/or low adiponectin levels, regardless of gender. Furthermore, the findings suggest that resistin is elevated and adiponectin is decreased in obese boys who are placed at higher cardiovascular risk.

Background

Well into the 21st century, increases not only in adult but childhood obesity are drawing attention worldwide as a pressing issue calling for immediate action, with as many as one-tenth of all children in the world being reportedly overweight (1).

It has been reported by Freedman et al (2) and Guo et al (3) that childhood obesity is associated with its adult counterpart. In contrast, Funatogawa et al (4) reported in a study of Japanese schoolgirls that overweight children did not necessarily become overweight adults. While adult obesity is widely known to be a risk factor for arteriosclerosis and cardiovascular disease, it is suggested that childhood obesity is associated with increases in the prevalence of cardiovascular disease in early age (5,6) and that adolescent obesity increases the risk for the development of arteriosclerosis and cardiovascular disease in adulthood and later years (7).

Furthermore, more recently, Pliz et al (8) examined subcutaneous adipose tissue (SAT) thickness as a factor other than obesity that predicts the future risk of cardiovascular disease in infants for correlation with adiponectin in children with a mean age of 13 years, and found a negative correlation between these parameters. However, very few reports are available in Asia that relate to these findings.

Against this background, we performed a survey on elementary school 4th graders aged 9 to 10 years in Ina-machi, Saitama, to investigate whether adipocytokines are as closely associated with cardiovascular risk in childhood as in adulthood, and how the presence or absence of obesity may affect their association.

Methods

1) Study subjects

The study subjects comprised a total of 385 4th grader boys (n = 207) and girls (n = 178) aged 9 to 10 years who attended the 3 public elementary schools in Ina-machi, Saitama, Japan. The study was conducted at each of these schools during a 1 day period which formed part of the health checkup program implemented there in September, 2004.

2) Methods

Physical examinations performed included height, body weight and waist circumference. The waist circumference was measured at the umbilical level in each participant, with the next participant in line confirming that the tape measure was placed horizontally in measuring the waist circumference. Total cholesterol, HDL-cholesterol, leptin, adiponectin, and resistin were measured in hematological examinations. The total cholesterol and HDL-cholesterol levels were measured by using a commonly used method, while the leptin levels were measured by using an RIA kit (9,10), and the adiponectin and resistin levels were measured by using an ELISA kit (11–13). Atherosclerosis index (AI), waist-to-height ratio (W/H ratio) and body mass index (BMI) were employed to examine the subjects for cardiovascular risk. AI was calculated from total cholesterol and HDL-cholesterol values, and BMI was calculated from height and body weight measurements.

All data are represented as median (interquartile range). The median values for all parameters measured were compared between the boys and girls, and the boys and girls were divided into obese and non-obese

groups to investigate whether there were any differences in these parameters between these groups. In this study, the international criteria for obesity as proposed by Cole et al were used, in which BMI cut-off values have been determined by gender and age with that for obesity in those aged 18 years being 25 (BMI: 9-year-old boys, 19.10; 9-year-old girls, 19.07; 10-year-old boys, 19.84; 10-year-old girls, 19.86) (14).

Next, adipocytokines and cardiovascular risk were examined for association by gender and compared, and the subjects were divided into obese and non-obese groups to compare their association between these groups.

These measurements were made as an add-on to the school health checkup program which is in place as a lawfully mandatory measure in Japan, and informed consent was obtained from all participating children and their parents.

The study protocol was approved by the ethics committees of the Jikei University School of Medicine and Showa University School of Medicine.

3) Statistical analysis

In analyzing the data derived from the study, the leptin-to-adiponectin (L/A) and resistin-to-adiponectin (R/A) ratios were calculated, and the correlation functions were calculated by using both the ratio of each adipocytokine and the L/A and R/A ratios.

All differences in clinical and laboratory data were compared by using Mann-Whitney test, and Spearman's correlation coefficients were derived to examine each of the adipocytokines for comparative association with cardiovascular risk.

Results

1) Clinical characteristics of the participating school children

A total of 204 boys and 176 girls participated in the census with the participation rate being 98.5% and 98.87%, respectively, in the boys and girls. The median value for each of the parameters measured in the entire subjects was as follows: height (H), 135 cm; body weight, 30.2 kg; waist circumference (WC), 57.0; BMI, 16.4; W/H ratio, 0.422; total cholesterol, 170.9 mg/dL; HDL-cholesterol, 63.0 mg/dL; AI, 1.70; leptin, 3.10 ng/mL; adiponectin, 10.6 µg/mL; resistin, 6.30 ng/mL; L/A ratio, 0.29; and R/A ratio, 0.61 (**Table 1**). All parameters were compared for statistically significant difference between boys and girls, and BMI ($P = 0.032$), leptin ($P = 0.008$) and L/A ratio ($P = 0.03$) were found to be significantly different, with none of the other parameters found to be significantly different.

2) Adipocytokine status in the presence/absence of obesity

The subjects were divided by gender and examined for adipocytokine status between the obese and non-obese groups as classified by using the above-mentioned international criteria for obesity. As a result, 26 and 178 boys were diagnosed as obese and non-obese, respectively, with the rate of obesity among the boys being 12.7%, whereas 11 and 165 girls were diagnosed as obese and non-obese, respectively, with the rate of obesity among the girls being 6.2%.

Of the adipocytokines examined, leptin and adiponectin were found to be significantly different between the obese and non-obese children, regardless of gender. While leptin was significantly higher in the obese children regardless of gender ($P < 0.001$ in either gender group), adiponectin was significantly higher in the non-obese children regardless of gender ($P = 0.001$ in boys; $P = 0.004$ in girls). On the other hand, while the serum resistin concentration was not found to be significantly different among the boys and girls with or without obesity, it tended to be slightly lower among the girls. Furthermore, the L/A ratio was found to be significantly different between the obese and non-obese children, regardless of gender, whereas the R/A ratio was found to be significantly different between the obese and non-obese boys but not between the obese and non-obese girls (**Table 2**).

3) Association between adipocytokines and cardiovascular risk factors

We examined the children for association between the adipocytokine parameters and cardiovascular risk factors, and found that leptin and the L/A ratio were significantly strongly correlated with the cardiovascular risk factors except AI, which suggested a strong correlation between the adipocytokines and cardiovascular risk factors. Again, adiponectin showed a negative correlation with all the cardiovascular risk factors, with this correlation shown to be significantly stronger among the girls than the boys (**Table 3**).

Next, we compared correlation coefficients for association between the adipocytokine parameters and cardiovascular risk factors in the presence or absence of obesity among the boys and girls (**Tables 4, 5**).

Among the non-obese boys, as shown among all the boys, leptin and the L/A ratio were significantly strongly correlated with the cardiovascular risk factors except AI, with this correlation being the strongest between leptin and BMI ($r = 0.697$). However, adiponectin and resistin were not found to be significantly correlated with the cardiovascular risk factors among these boys.

Among the obese boys, however, leptin was shown to have a stronger correlation with the W/H ratio than with BMI, unlike among the non-obese boys. In addition, adiponectin was found to be significantly negatively correlated with the cardiovascular risk factors except AI. Furthermore, among the obese boys, there was a significant correlation between resistin and AI and between the R/A ratio and the cardiovascular risk factors, neither of which was noted among the entire boy population or the non-obese boys.

Among the non-obese girls, as among all the girls, leptin and the L/A ratio were found to be significantly strongly correlated with the cardiovascular risk factors other than AI. Again, adiponectin was found to be significantly negatively correlated with all the cardiovascular risk factors examined, quite unlike the findings observed among the non-obese boys. While resistin was not shown to be significantly correlated with the cardiovascular risk factors, the R/A ratio was found to be significantly correlated with the cardiovascular risk factors.

In contrast, among the obese girls, only the L/A ratio and the W/H ratio were found to be significantly strongly correlated ($r = 0.767$), and the other adipocytokine parameters were not found to be significantly correlated with the cardiovascular risk factors. The absolute values of the correlation coefficients for the obese girls tended to be larger than those for the entire girl population or the non-obese girls, a finding not observed among the obese boys when compared to the entire boy population or the non-obese boys.

Discussion

In 1994, the “Ina-machi Lifestyle-related Diseases Screening Program for School Children” was started to promote health among the school children residing in Ina-machi, Saitama Prefecture, Japan. Ina-machi is a town with a population of some 35,000 inhabitants, and is located approximately 30 km north of Tokyo, the capital of Japan. Traditionally, Ina-machi used to be prosperous in agriculture, such as fruit growing; however, it has developed in recent years into a bedroom suburb for commuters to the Tokyo area.

The activities that are currently being implemented to promote health in this town constitute an in-depth health program that consists of height, body weight, and waist circumference measurements, blood tests, and intervention in terms of lifestyle modification in those in whom such intervention is deemed necessary based on screening results. These activities are being implemented as an add-on program to the annual health checkup program which is in place as a lawfully mandatory measure in Japan.

In this study, we investigated which of the adipocytokines examined (leptin, adiponectin and resistin) might predict the future development of atherosclerotic disease among all the elementary school 4th graders in this town by examining these adipocytokines for correlation with the cardiovascular risk factors, i.e., AI, which is a minimally invasive and convenient test, waist circumference, W/H ratio, and BMI.

Furthermore, we investigated whether any association between the adipocytokines and cardiovascular risk factors examined might be altered in the subjects with obesity, a risk factor for atherosclerosis, and if so, which adipocytokine might be closely associated with the cardiovascular risk factors.

As shown in a study of adult obese patients with type 2 diabetes by Satoh et al (15) that the L/A ratio is better correlated with Pulse Wave Velocity (PWV) as an index for atherosclerosis, than leptin or adiponectin, not only leptin and adiponectin but L/A ratio were used in this study. Again, as resistin, adiponectin and R/A ratio have been reported to be differently associated with cardiovascular risk factors, resistin, adiponectin, and R/A ratio were also examined in the subjects for association with

cardiovascular risk factors. Furthermore, as the W/H ratio has been reported in a study of Japanese school children by Hara et al (16) to be the best predictive factor among the cardiovascular risk factors including BMI, percent body fat, waist-to-hip ratio, and waist circumference, the W/H ratio was included among the cardiovascular risk factors to be examined, in addition to BMI and AI.

Clinical characteristics of the school children

There was a significant gender difference in BMI, leptin and the L/A ratio between the pre-pubertal boys and girls aged 9 to 10 years, with the leptin level particularly shown to be higher in the girls at 3.55 ng/mL than in the boys at 2.80 ng/mL (Table 1).

While leptin is generally known to vary greatly in serum concentration depending on the presence or absence of obesity, leptin is also reported to be positively correlated with subcutaneous fat mass (17,18). However, as shown in Table 1, BMI as an index for obesity was shown to be greater in the boys than in the girls, and waist circumference as an index for subcutaneous fat mass was not significantly different between the boys and girls, which made it difficult to account for the significantly higher leptin level in the girls compared to the boys. However, when the subjects were grouped by gender into obese and non-obese individuals (Table 2), the leptin level was shown to be significantly higher and the adiponectin level was shown to be significantly lower in the obese individuals, suggesting that these adipocytokines are significantly different between those with obesity and those without.

The leptin level was shown to be significantly different between the genders, regardless of the presence of obesity or of the subcutaneous fat mass present (Table 1), suggesting that the gender difference accounted for the difference in the leptin level between the genders, rather than obesity or subcutaneous fat mass. While sex hormones were thought less likely to affect the leptin values in these subjects, given their age of 9 to 10 years which suggested that the majority was pre-pubertal, they may not have an influence on the leptin level in the subjects. While there are several interesting findings reported on the association between leptin or adiponectin and testosterone (19–22), unfortunately, this study was performed as part of the health checkup programs implemented in accordance with the Japanese School Health Law, which included no sex hormone measures, and did not allow us to validate these findings in the literature. In the years to come, if estradiol and testosterone are to be included among the hematological examinations in school children, insight will be gained into the influence of these hormones on adipocytokines, as well as the association between adipocytokines, cardiovascular risk factors, and these sex hormones, to make it possible to screen those children at high cardiovascular risk with greater precision.

Association between the adipocytokines and cardiovascular risk factors

1) Analysis of association by gender

There was no significant difference by gender in the association between the adipocytokines and cardiovascular risk factors. In the entire study population, there was a positive correlation between leptin

and the cardiovascular risk factors as well as a negative correlation between adiponectin and the cardiovascular risk factors, regardless of gender. Of the adipocytokines examined, only resistin showed no association with any of the cardiovascular risk factors studied, and analyses using the R/A ratio demonstrated no association with the cardiovascular risk factors.

2) Analysis of association by the presence or absence of obesity

There was a marked difference between the boys and girls in the association between the adipocytokines and cardiovascular risk factors when they were divided into obese and non-obese groups.

As the association between the adipocytokines and cardiovascular risk factors in the obese boys showed a similar pattern to that in the entire boy population, the obese boys may have consisted of individuals with high- and low-risk cardiovascular risk. However, given the greater correlation coefficients found for association between leptin or adiponectin and the cardiovascular risk factors among the obese boys, it was likely that those at higher cardiovascular risk concentrated in the obese boys. Therefore, of the obese boys examined, those showing high leptin and/or low adiponectin values are likely to be at higher cardiovascular risk. Furthermore, there was a strong correlation between the R/A ratio and the cardiovascular risk factors in the obese boys, suggesting that resistin is elevated and adiponectin is decreased in obese boys who are placed at higher cardiovascular risk.

In contrast, results were different for the obese girls than for the obese boys. The obese girls differed from their non-obese counterparts in terms of association between the adipocytokines and cardiovascular risk factors, and this association was found to be significant only between the L/A and W/H ratios, with nearly all significant associations found in the entire girl population disappearing in these girls. However, the association between the adipocytokines and cardiovascular risk factors in the non-obese girls was found to be similar to that in the entire girl population. These findings suggested that these obese girls constituted a homogeneous group in terms of cardiovascular risk, while the reason that the R/A ratio was significantly correlated with all the cardiovascular risk factors among the non-obese girls, because the non-obese girls consisted of individuals with both high and low cardiovascular risk. Therefore, it was not possible to identify any predictive factor from among the adipocytokines examined that might assist in detecting obese girls at even higher risk from among all the obese girl population, a population reported to be already at high risk in the literature.

These study findings suggest that the use of the international BMI-based criteria for obesity could not only lead to obese boys at low cardiovascular risk being included in the obese population which is associated with high risk, but also to non-obese girls with high cardiovascular risk being included in the non-obese population which is associated with low cardiovascular risk. While Japanese children appear to be not as different in physique from their Western counterparts as Japanese adults are from their Western counterparts, our findings suggest that it may not necessarily be appropriate to use the international criteria for obesity in Japanese children without reservation. And the difference among individuals of sex hormones in pre-pubertal may have an influence on adipocytokine levels.

In this study, we investigated whether or not adipocytokines might be used to predict the future development of atherosclerosis, as well as cardiovascular disease which is further downstream. Our study findings demonstrate that school children with high leptin and/or low adiponectin levels are placed at higher cardiovascular risk, regardless of gender. Furthermore, it was suggested that among even those with obesity as a cardiovascular risk factor, cardiovascular risk was found to be higher in individuals with high leptin and/or low adiponectin levels, regardless of gender, while this risk was found to be significant only in the obese boys. In addition, our study findings suggested that the definition of obesity might call for revision in regard to its BMI cut-off values and other factors. Further follow-up of the study subjects is required to confirm the usefulness of these adipocytokines in children as risk factors for the future progression of atherosclerosis as well as for the future development of cardiovascular disease.

Abbreviations

SAT

subcutaneous adipose tissue,

AI

atherosclerosis index,

W/H ratio

waist-to-height ratio,

BMI

body mass index,

L/A

leptin-to-adiponectin,

R/A

resistin-to-adiponectin,

WC

waist circumference.

Declarations

1) Ethics approval and consent to participate

The informed consent of this study was obtained from all participating children and their parents. The study protocol was approved by the ethics committees of the Jikei University School of Medicine and Showa University School of Medicine.

2) Availability of data and material

Data used in the current study are not publicly available as they contain personal information.

3) Competing interests

The authors declare that they have no competing interests.

4) Funding

Not applicable

5) Authors' contributions

Not applicable

6) Acknowledgements

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Tables

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