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ROLE OF INSULIN RESISTANCE IN NON-OBESE ADOLESCENTS

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ABSTRACT

Insulin resistance in the obese is closely related with cardiovascular diseases and their risk factors not only in adults but also in children and adolescents. We aimed to elucidate whether insulin resistance in non-obese adolescents is related with these conditions. A total of 74 non-obese high-school students (38 boys and 36 girls) were recruited. Anthropometry, blood pressure, fasting serum chemistry and insulin activity were measured. Subjects with a homeostasis model assessment-insulin resistance (HOMA-IR) level greater than the 75th percentile (> 2.25 for boys and > 2.89 for girls) were defined as insulin resistant. Non-obese boys with impaired insulin sensitivity had higher systolic blood pressure, lower HDL-cholesterol concentration, and fewer hours of vigorous exercise during weekdays, while non-obese girls with impaired insulin sensitivity had higher systolic blood pressure than their peers with normal insulin sensitivity. By multiple stepwise regression analysis, systolic blood pressure ($p<0.001$) and the hours of vigorous exercise during weekdays ($p<0.03$) were independently associated with HOMA-IR in boys, while systolic blood pressure ($p<0.0001$) and serum concentrations of HDL-cholesterol ($p<0.01$) were found in girls. In non-obese adolescents, insulin sensitivity is related with cardiovascular risk factors.

Key Words: Insulin resistance, Adolescents, Obesity, Metabolic syndrome, Hypertension

INTRODUCTION

The prevalence of childhood obesity and metabolic syndrome are increasing in western countries[1,2] as well as in Asia.[3-5] The prevalence of metabolic syndrome increases with the severity of obesity, reaching 50 percent in severely obese children and adolescents.[6] However, since the generally accepted and unifying hypothesis to describe the pathology of metabolic syndrome is insulin resistance and not obesity itself, metabolic syndrome patients can also be of normal weight.[7] Indeed, a study using a Japanese population has revealed the emergence of cardiovascular risk factors even in mildly obese children.[8] Therefore, this study aimed to investigate whether insulin sensitivity in non-obese adolescents is related with cardiovascular risk factors.

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METHODS

Study subjects and measurements

We recruited a total of 77 non-obese students (40 boys and 37 girls) admitted to Aichi prefectural public high schools in the year 2008. Although none of the subjects fell into the internationally acceptable definition of childhood obesity,[9] we excluded overweight subjects (two boys and a girl) with a body mass index of more than 25 kg/m^2. Thus, data of the remaining 38 boys and 36 girls were included and finally used for the analyses. The characteristics of the subjects are summarized in Table 1. The study subjects and their guardians gave written informed consent to participate in the study, which was approved by our institutional review board.

Data was collected at school entry in April 2008. Experienced nurses measured each subject's body weight to the nearest 0.1 kg and height and waist circumference to the nearest 0.1 cm. We calculated the body mass index (BMI), which was defined by body weight (kg) divided by the square of height (m). Blood pressure was measured with an automatic oscillometric sphygmomanometer after the student had been seated in a chair for more than 5 min. A second measurement was performed 2 min later, and the average of the two measurements was used in the analysis. The sphygmomanometer we used (BP-103iII, Colin, Nagoya, Japan) was based on the oscillometric method and met the specifications of the 1992 Association for the Advancement of Medical Instrumentation standards for electronic or automated sphygmomanometers. The validity and reliability of the device had been confirmed and reported, i.e. in adult subjects, the mean difference and standard deviation of the differences between the oscillometric and auscultatory methods were 2.81 +/– 5.35 mm Hg (mean +/– SD) for systolic blood pressure and 0.04 +/– 4.90 mm Hg for diastolic blood pressure as defined by phase V Korotkoff's sounds.[10] We used appropriately sized cuffs and calibrated the sphygmomanometer before the study session. The resting HR (beats per minute, bpm) was calculated as 60/mean heart periods (seconds) during the blood pressure recordings.

After an overnight fast, blood samples (6 ml) were drawn from the peripheral veins for measurements of the plasma concentrations of glucose, triglyceride, and high- and low-density lipoprotein cholesterol (Hitachi 917 Biochemical Analyzer, Tokyo, Japan). Insulin concentrations were measurd by means of a chemiluminescence immunological assay (Chemilumi Insulin; Kyowa Medics, Tokyo, Japan). Insulin sensitivity was calculated by the homeostasis model assessment method (HOMA-IR), which was calculated by multiplying fasting insulin (mUI/mL) by fasting glucose (mmol/L) and dividing by 22.5.[11] Subjects with a HOMA-IR level above the highest quartile of the present study population (> 2.25 for boys and > 2.89 for girls) were defined as having insulin resistance. Prior to the check-up, all students had been handed an interview sheet containing questions regarding the hours of vigorous exercise and of television watching

Table 1 Characteristics of study subjects

	Boys (n=38)		Girls (n=36)	
	Mean ± SD	Range	Mean ± SD	Range
Age (years)	15.5 ± 0.3	15.0 – 15.9	15.5 ± 0.3	15.0 – 15.9
Height (cm)	169.6 ± 5.9	155.7 – 184.6	159.1 ± 5.2	148.5 – 171.0
Body weight (kg)	57.3 ± 6.9	43.9 – 77.8	51.7 ± 5.3	42.5 – 62.2
WC (cm)	69.9 ± 4.5	62.1 – 80.0	71.3 ± 4.7	61.5 – 78.3
BMI (kg/m^2)	19.9 ± 2.1	16.1 – 23.8	20.4 ± 1.9	16.2 – 23.9
WC/height ratio	0.41 ± 0.03	0.37 – 0.49	0.45 ± 0.03	0.38 – 0.51

Abbreviations: BMI = body mass index (kg/m^2); WC = waist cicumference (cm)

during weekdays.

Complete sets of measurements and answers to the questionnaires were obtained on 38 boys and 36 girls, and subsequently used for the analysis.

Statistics

A probability value of $p<0.05$ was considered statistically significant. Comparisons of the measurements of normal and impaired insulin sensitivity were analysed with a Mann-Whitney's U-test. Since HOMA-IR may be influenced by several factors, a stepwise multiple regression analysis was performed using HOMA-IR as the dependent variable and, as independent variables, height, body weight, waist circumference, body mass index, waist circumference/height ratio, systolic and diastolic blood pressures, heart rate at rest, serum levels of triglyceride as well as high- and low-density lipoprotein cholesterol, and hours of vigorous exercise and television watching during weekdays. All statistical analyses were performed using the Japanese edition of SPSS version 15.0 (Tokyo, Japan).

RESULTS

None of the study subjects met the criteria for Japanese childhood metabolic syndrome.[12] Comparisons of the variables of the subjects with impaired and normal insulin sensitivities are summarized in Table 2. In brief, non-obese boys with impaired insulin sensitivity had higher systolic blood pressure, lower HDL-cholesterol concentration, and fewer hours of vigorous

Table 2 Comparisons of body composition. Hemodynamic, metabolic and lifestyle parameters of non-obese adolescents with and without insulin resistance

Variables	Boys			Girls		
	Impaired IR (n=9)	Normal IR (n=29)	p value	Impaired IR (n=9)	Normal IR (n=27)	p value
Height (cm)	168.1 ± 7.0	170.0 ± 5.7	0.42	159.2 ± 2.4	159.1 ±5.9	0.76
Body weight (kg)	56.8 ± 3.2	57.5 ± 7.7	0.98	50.1 ± 4.6	52.3 ± 5.4	0.32
WC (cm)	70.5 ± 3.4	69.7 ± 4.8	0.63	70.0 ± 5.3	71.7 ± 4.6	0.18
BMI (kg/m^2)	20.2 ± 2.0	19.8 ± 2.1	0.74	19.8 ± 2.1	20.6 ± 1.9	0.18
WC/height	0.42 ± 0.03	0.41 ± 0.03	0.95	0.44 ± 0.03	0.45 ± 0.03	0.17
SBP (mmHg)	127 ± 10	115 ± 16	0.03	120 ± 6	110 ± 9	0.01
DBP (mmHg)	67 ± 9	63 ± 9	0.33	67 ± 7	65 ± 7	0.81
RHR (beats/min)	75 ± 12	66 ± 13	0.12	75 ± 17	68 ± 10	0.32
TG (mg/dl)	69 ± 9	47 ± 13	0.19	59 ± 24	60 ± 17	0.79
HDL-C (mg/dl)	59 ± 9	67 ± 13	0.04	73 ± 12	67 ± 11	0.22
LDL-C (mg/dl)	95 ± 17	98± 21	0.54	99 ± 17	107 ± 21	0.29
Vig-ex (hours)	1.3 ± 0.6	2.4 ± 1.2	0.01	1.1 ± 0.7	1.1 ± 0.9	0.76
Video-hr (hours)	1.9 ± 0.8	1.5 ± 1.1	0.57	1.2 ± 0.8	1.4 ± 1.0	0.66

Insulin resistance was calculated by the homeostasis model assessment method (HOMA-IR). Subjects with A HOMA-IR levesl above the highest quartile (> 2.25 for boys and > 2.89 for girls) were defined as having insulin resistance. Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; vig-ex = hours of vigorous exercise during weekdays; HDL-C = serum high-density cholesterol concentration; HR = resting heart rate; IR = insulin resistance; LDL-C = serum low-density cholesterol concentration; SBP = systolic blood pressure; TG = serum triglyceride concentration; Video-hr = hours of television watched during weekdays; WC = waist circumference

exercise during weekdays, while non-obese girls with impaired insulin sensitivity had higher systolic blood pressure in comparison with girls with normal insulin sensitivity. Interestigly, anthropometric measurements (body weight, waist circumference, and waist circumference to height ratio and body mass index) did not differ between those with and those without insulin resistance. By multiple stepwise regression analysis, systolic blood pressure (β=0.63, $p<0.001$) and the hours of vigorous exercise during weekdays (β=–0.30, $p<0.03$) were independently associated with HOMA-IR in non-obese boys, while systolic blood pressure (β=0.62, $p<0.0001$) and serum HDL-cholesterol concentration (β=–0.37, $p=0.01$) were similarly associated in non-obese girls.

DISCUSSION

In the present study of non-obese Japanese adolescents, we found that: 1) HOMA-IR is related with systolic blood pressure and hours of vigorous exercise during weekdays in boys, and with systolic blood pressure and serum HDL-cholesterol level in girls, though without anthropometric measurements; and 2) boys with impaired insulin sensitivity had higher systolic blood pressure, lower serum HDL-cholesterol levesl and fewer hours of vigorous exercise during weekdays, while girls with insulin resistance had higher systolic blood pressure in comparison with those without insulin resistance. These findings show that insulin resistance is associated with cardiovascular risk factors even in non-obese adolescents, which supports the hypothesis that insulin resistance, not obesity per se, plays a key role in the development of metabolic syndrome. These findings confirm the study by Sinaiko et al. who found that thin, insulin-sensitive individuals have more favorable HDL-cholesterol, lower triglyceride concentration and lower BP than thin, insulin-resistant individuals.[13)]

In obese children and adolescents, as well as in adults, insulin resistance is known to be associated with abnormal lipid profiles and hyperdynamic circulation, including hypertension and resting tachycardia.[14-16)] It is also well known that the incidence of metabolic syndrome is related with the severity of childhood obesity.[6)] However, it has thus been unclear whether insulin resistance is related with cardiovascular risk factors in non-obese adolescents. The present study, to our knowledge, is the first to demonstrate that even in non-obese Japanese adolescents insulin resistance is indeed related with cardiovascular risk factors.

Our findins that there are some adolescents who are insulin resistant but non-obese indicate the need to promote a healthy lifestyle among youngsters, including non-obese adolescents, although multiple regression analyses show that the hours of vigorous exercise during weekdays are independently associated with HOMA-IR only in non-obese boys, but not in girls. Such insulin-resistant but non-obese adolescents may benefit from lifestyle interventions that can prevent them from developing real metabolic syndrome later in life. A recent study by Monzavi et al. showed an improvement in risk factors for metabolic syndrome and insulin resistance in overweight youth by lifestyle interventions.[17)] Therefore, intervening early in life (e.g., during the transition from adolescence to adulthood) may prove a fruitful area for the prevention of metabolic syndrome.[17,18)]

We used cut-off levels of HOMA-IR (above 75th percentiles of the study subjects, i.e. > 2.25 for boys and > 2.89 for girls) that are lower than those previously reported. Tresaco *et al.*[19)] and Keshin *et al.*[20)] reported cut-off values for adolescents of 3 and 3.16, respectively. Results of the present study show that adolescents with HOMA-IR levels lower than those previously reported cut-off values have even exhibited relatively impaired lipid metabolism and hyperdynamic circulation. However, the issue of whether or not such adolescents with normal weight and "abnormally" high HOMA-IR levels are actually at high risk for developing cardiovascular or

metabolic diseases must await further study, e.g. one using a receiver operating curve.

There is a limitation in the present study. Since the correlation of HOMA-IR and total glucose disposal rate is smaller in subjects with lower BMIs. HOMA-IR in non-obese adolescents may not reflect their actual insulin resistance. This issue awaits further investigation.

In conclusion, the present study shows the associations of insulin resistance with lipid metabolism and hyperdynamic circulation in non-obese adolescents. Therefore, there is now a valid reason to intervene with adolescents who have cardiovascular risk factors, irrespective of their obesity level.

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