Adiposity Rebound and the Development of Metabolic Syndrome

WHAT’S KNOWN ON THIS SUBJECT: Early adiposity rebound is associated with future obesity and an increased risk of development of type 2 diabetes and coronary heart disease in adult life.

WHAT THIS STUDY ADDS: This study shows that early adiposity rebound is associated with future obesity and metabolic consequences of higher triglycerides, atherogenic index, apolipoprotein B, and blood pressure and lower high-density lipoprotein cholesterol at 12 years of age.

abstract

OBJECTIVE: The age of adiposity rebound (AR) is defined as the time at which BMI starts to rise after infancy and is thought to be a marker of later obesity. To determine whether this age is related to future occurrence of metabolic syndrome, we investigated the relationship of the timing of AR with metabolic consequences at 12 years of age.

METHODS: A total of 271 children (147 boys and 124 girls) born in 1995 and 1996 were enrolled in the study. Serial measurements of BMI were conducted at the ages of 4 and 8 months and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 years, based on which age of AR was calculated. Plasma lipids and blood pressure were measured at 12 years of age.

RESULTS: An earlier AR (<4 years of age) was associated with a higher BMI (≥20) and a lipoprotein phenotype representative of insulin resistance. This phenotype consists of elevated triglycerides, apolipoprotein B, and atherogenic index and decreased high-density lipoprotein cholesterol in boys and elevated apolipoprotein B in girls at 12 years of age. The earlier AR was also related to elevated blood pressure in boys.

CONCLUSIONS: This longitudinal population-based study indicates that children who exhibit AR at a younger age are predisposed to future development of metabolic syndrome. Therefore, monitoring of AR may be an effective method for the early identification of children at risk for metabolic syndrome. Pediatrics 2014;133:e114–e119

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KEY WORDS
adiposity rebound, BMI, metabolic syndrome, obesity

ABBREVIATIONS
AI—atherogenic index
ApoB—apolipoprotein B
AR—adiposity rebound
DBP—diastolic blood pressure
HDL-C—high-density lipoprotein cholesterol
LDL-C—low-density lipoprotein cholesterol
SBP—systolic blood pressure
TC—total cholesterol
TG—triglycerides

Dr Koyama collected, analyzed, and interpreted data, generated figures, and drafted the initial manuscript; Drs Ichikawa, Kojima, and Shimura collected and analyzed data and reviewed the manuscript; Dr Sairenchi analyzed and interpreted data, generated figures, and reviewed the manuscript; Dr Arisaka conceived and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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The prevalence of obesity in children in Japan was increasing until the early 2000s due to westernization of lifestyle after World War II and large economic growth between the late 1980s and early 1990s but has gradually decreased since this time.1 Obesity currently affects 10% to 19% of schoolchildren worldwide.2-4 BMI is widely used internationally as a definition of obesity,5 and a rapid increase in BMI generally occurs during the first year of life. BMI subsequently declines and reaches a nadir at ~6 years of age, and then increases again throughout childhood. This second rise in BMI after the last minimum BMI (nadir) is referred to as the adiposity rebound (AR).6 The timing of this rebound is thought to have predictive value for obesity in adulthood.7 The adverse health consequences of obesity in childhood include dyslipidemia, hypertension, and insulin resistance. Clustering of these atherogenic risk factors in early life is believed to play a critical role in the development of atherosclerosis during childhood.8,9 Metabolic syndrome, components of which include hypertension, glucose intolerance, hypertriglyceridemia, decreased high-density lipoprotein cholesterol (HDL-C) levels, and central abdominal obesity, confers an excessively high risk of atherogenic cardiovascular disease, with an increased prevalence in overweight children.10-12 Evidence suggests that stunted fetal growth or early infant weight gain may be a predisposition for development of obesity and metabolic syndrome in later life.13,14 Eriksson et al15 found that early AR is associated with a high mean BMI at 12 years of age and an increased risk of developing type 2 diabetes in adult life. Baker et al16 also suggested that higher BMI during childhood is associated with an increased risk of coronary heart disease in adulthood. These reports imply that children who exhibit weight gain in early life are at significantly higher risk for development of metabolic syndrome and subsequent diabetes or cardiovascular disease in adulthood. These metabolic changes may have started in childhood. Therefore, in the current study, we investigated whether the early origin of obesity is related to the future occurrence of metabolic syndrome, with a specific focus on the relationship between the timing of AR and the levels of plasma lipids and blood pressure at 12 years of age.

METHODS

Subjects

All 296 children (157 boys and 139 girls) born in the town of Fujioka in Tochigi prefecture in Japan between 1995 and 1996 were enrolled in the study. The population of this town is 18 000, with one-half of the people working as farmers and one-half commuting to nearby large cities. The town has 4 elementary schools and 2 junior high schools. All of the children in the study were followed up with infant health checks at a health center during the preschool period, and data were stored at a regional health center. During the school-age period, children underwent an annual physical examination at school, and the resulting data were also kept at the regional health center. At 12 years of age, all the children underwent a blood examination. We excluded 25 children (10 boys and 15 girls) from the study due to missing BMI data from 1 to 8 years of age that prevented determination of the age of AR. These data were missing because some children did not attend all health checks and physical examinations. About 90% of the children underwent each health check and physical examination. The study analysis included 271 children (147 boys and 124 girls).

Written informed consent was obtained from the guardian for the physical examination. The study was approved by the ethics committee of Dokkyo Medical University.

Identification of the Age of AR Based on BMI

Standard anthropometric measurements of length or height and weight, with the use of strict protocols, were conducted by a small group of trained staff when the children were 4 and 8 months and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 years of age. The anthropometric data at age ≤5 years is more accurate than that after age 6 years because the assessment was performed close to the child's birthday ≤5 years but was performed at school on 1 date each year for all children. For example, data at 6 years of age were collected between 6 and 6.9 years of age. All subjects underwent a total of 15 measurements. Length and height were measured to the nearest 0.1 cm by using a digital infant table (M-5000K, Nakamura Medical Industry Co., Ltd., Tokyo, Japan) at birth and at follow-up <2 years of age, and thereafter by using a digital height and weight scale (AD-6224A, A & D company, Ltd, Tokyo, Japan). Weight was assessed to the nearest 100 g by using the digital infant table at birth and <2 years of age, and the Yamato digital weight scale (DP-7100W, Yamato Weighing & Information Technology, Hyogo, Japan) thereafter. At each follow-up visit, BMI was calculated from the measured height and weight (by using the formula weight [in kilograms]/height [in meters squared]). At visits <2 years of age, a proxy for BMI was used (weight [in kilograms]/length [in meters squared]).17,18 We defined the age of AR as the age between 1 and 12 years at which the lowest BMI occurred before the second BMI rise. When the BMI curve showed repeating minor increases and decreases or had a plateau, we defined the age of AR as that at which the lowest BMI occurred. No subjects showed the__END__
same values of BMI at 2 points in the curve when their BMI curve had a plateau. The children were then divided into 6 groups according to the age of AR: group 1, AR ≤2 years; group 2, AR 3 years; group 3, AR 4 years; group 4, AR 5 years; group 5, AR 6 to 6.9 years; and group 6, AR ≥7 years.

Measurement of Lipoproteins and Blood Pressure

Blood sampling and measurement of plasma lipids and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were performed at 12 years of age. Levels of total cholesterol (TC) (Cholestest CH0, Daiichi Pure Chemicals Co. Ltd., Tokyo, Japan) and triglycerides (TG) (Aqua-auto TG-II, Kainos Laboratories, Inc., Tokyo, Japan) were determined by using enzymatic methods. HDL-C was measured by precipitation of other lipoproteins with the direct method (Cholestest N HD, Daiichi Pure Chemicals Co. Ltd.). Low-density lipoprotein cholesterol (LDL-C) was calculated by using the Friedewald formula. Apolipoprotein B (ApoB) was quantified by turbidimetric immunoassay (ApoB auto N, Daiichi Pure Chemicals Co. Ltd.). The atherogenic index (AI) was calculated as follows: $\text{AI} = \frac{\text{TC} - \text{HDL-C}}{\text{HDL-C}}.$

Statistical Analysis

Statistical tests for trends and the associations of the age at AR with BMI, blood pressure, and biochemical parameters (TC, LDL-C, HDL-C, TG, and ApoB) at 12 years of age were examined using simple linear regression analysis. BMI, TC, LDL-C, HDL-C, TG, AI, ApoB, SBP, and DBP were log-transformed because the normal distribution of these variables was questionable (Shapiro-Wilk test, $P < .10$). The log-transformed BMI, TC, LDL-C, HDL-C, TG, AI, ApoB, SBP, and DBP were used separately as the dependent variable, and the age at AR was used as the independent variable in simple regression analysis. The $P$ for a trend was defined as the $P$ value for the regression coefficient for the age at AR. $P < .05$ was considered to be statistically significant.

RESULTS

Geometric means of height, weight, BMI, and other biochemical parameters at 12 years of age in boys and girls are shown in Table 1. The mean age of AR was 4.8 ± 1.4 (mean ± 2 SDs) years in boys and 4.7 ± 1.5 years in girls. The serial changes of BMI between 4 months and 12 years of age in the 6 groups formed based on the age of AR are shown in Figs 1 and 2 for boys and girls, respectively. BMI at 12 years of age was highest in the group with an AR age ≤2 years and lowest in the group with an AR age ≥7 years in both boys and girls. BMI at 12 years of age was much higher in the group with an earlier age of AR, but BMI before AR was not higher in the group with an age of AR ≤2 years compared with the other groups in boys and girls. BMI at 1 year of age was lower than that at 8 months in all 6 groups, and BMI at 8 months was lower than that at 4 months in almost all of the groups. Thus, in this study, the peak BMI value in infancy occurred between 4 and 8 months.

Relationships of the age of AR with BMI and biochemical parameters in boys and girls are shown in Table 2. An earlier AR resulted in higher BMI ($P < .001$), TG ($P < .001$), AI ($P = .001$), ApoB ($P < .001$), SBP ($P = .05$), and DBP ($P = .03$) in boys at 12 years of age. An inverse relationship was found between the timing of AR and HDL-C levels ($P < .001$). Relationships of the age of AR with BMI and biochemical parameters in girls are shown in Table 3. As with boys, earlier AR was related to higher BMI ($P < .001$) and ApoB ($P = .004$) in girls at 12 years of age, but there was no significant relationship of the timing of AR with HDL-C ($P = .25$), TG ($P = .77$), AI ($P = .48$), SBP ($P = .49$), and DBP ($P = .47$) in girls.

DISCUSSION

To the best of our knowledge, this is the first report to show a relationship between the timing of AR and the levels of plasma lipids and blood pressure at 12 years of age. An earlier AR was related to higher TG, AI, ApoB, and blood pressure and lower HDL-C levels in boys at 12 years of age. In girls, earlier AR was related only to higher ApoB at 12 years of age. These variables were within the normal range, and we did not investigate the consequences in later life. However, Juhola et al. found that childhood blood pressure, serum lipid levels, and BMI correlate strongly with values measured in middle age and that these associations seem to be stronger with increased age at measurement. Thus, although the variables at 12 years of age were within the normal range in our study, there may be an increasing risk for future development of insulin resistance in subjects with earlier AR.

The timing of AR has been related to obesity in adulthood, and early AR has been associated with a high mean BMI at 12 years of age and in adolescence. Our data also showed that BMI at 12 years of age was highest in children with an age of AR ≤2 years and lowest in those with an age of AR
The peak BMI in infancy has been shown to be ~1 year old.\textsuperscript{25} In our study, BMI at 1 year in all groups was not higher than that at 8 months, and BMI at 8 months in some groups was a little higher than that at 4 months. Thus, the peak BMI in our subjects occurred between 4 and 8 months, which is somewhat earlier than in previous reports. We speculate that this may be due to more rapid growth in height because of improvement of nutritional status.\textsuperscript{23,24}

Associations of the age of AR with serum lipids, lipoproteins, AI, SBP, and DBP, with an earlier AR related to appearance of more atherogenic variables at 12 years of age, was apparent in boys in the current study; only Apo B showed a significant association with AR age in girls. The underlying mechanism of these sexually dimorphic differences may involve sex hormone levels and the androgen/estrogen balance. Sex hormones are important regulators of plasma lipid kinetics and are responsible for sexual dimorphism in plasma lipid and lipoprotein profiles.\textsuperscript{25,26} Gender differences in serum adiponectin levels that appear at entry into puberty may also be related to sexually dimorphic association of the age of AR and blood pressure at 12 years of age.\textsuperscript{27,28} The mean age of entering puberty is ~9.5 years in girls and 11.5 years in boys in Japan.\textsuperscript{29,30} In the current study, we did not examine the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;2 y (n = 11)</th>
<th>3 y (n = 13)</th>
<th>4 y (n = 40)</th>
<th>5 y (n = 39)</th>
<th>6 to 6.9 y (n = 18)</th>
<th>≥7 y (n = 26)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>23.7 ± 1.3</td>
<td>21.2 ± 1.2</td>
<td>20.6 ± 1.2</td>
<td>19.1 ± 1.2</td>
<td>19.5 ± 1.2</td>
<td>16.9 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>166.6 ± 1.2</td>
<td>155.1 ± 1.1</td>
<td>162.4 ± 1.2</td>
<td>160.7 ± 1.2</td>
<td>162.5 ± 1.2</td>
<td>168.2 ± 1.2</td>
<td>.78</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>93.8 ± 1.3</td>
<td>84.2 ± 1.2</td>
<td>88.9 ± 1.3</td>
<td>85.1 ± 1.2</td>
<td>89.3 ± 1.3</td>
<td>88.8 ± 1.3</td>
<td>.46</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>59.9 ± 1.2</td>
<td>58.9 ± 1.2</td>
<td>61.3 ± 1.2</td>
<td>62.2 ± 1.2</td>
<td>64.0 ± 1.2</td>
<td>71.5 ± 1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>74.1 ± 1.5</td>
<td>59.0 ± 1.5</td>
<td>59.2 ± 1.5</td>
<td>60.6 ± 1.6</td>
<td>52.0 ± 1.4</td>
<td>46.7 ± 1.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AI</td>
<td>1.8 ± 1.4</td>
<td>1.6 ± 1.3</td>
<td>1.6 ± 1.5</td>
<td>1.4 ± 1.3</td>
<td>1.5 ± 1.4</td>
<td>1.3 ± 1.4</td>
<td>.001</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>80.5 ± 1.2</td>
<td>79.1 ± 1.1</td>
<td>86.6 ± 1.2</td>
<td>82.2 ± 1.2</td>
<td>73.1 ± 1.3</td>
<td>65.0 ± 1.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>114.1 ± 1.1</td>
<td>108.1 ± 1.1</td>
<td>109.5 ± 1.1</td>
<td>104.8 ± 1.1</td>
<td>106.4 ± 1.1</td>
<td>103.8 ± 1.1</td>
<td>.05</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>63.8 ± 1.2</td>
<td>60.6 ± 1.2</td>
<td>60.5 ± 1.1</td>
<td>58.9 ± 1.1</td>
<td>57.4 ± 1.1</td>
<td>59.0 ± 1.1</td>
<td>.03</td>
</tr>
</tbody>
</table>

Data are presented as geometric means ± SD. The P for a trend was defined as the P value for the regression coefficient for the age at AR. P values < .05 were considered significant.
puberty status, but almost all the girls and some of the boys would have been in puberty at 12 years of age. This pubertal timing may be a bias in this study because an earlier AR will lead to a higher BMI, which will result in earlier pubertal timing that may in turn influence metabolic markers. This finding is also why an earlier AR is related to appearance of more atherogenic variables at 12 years of age.

Early AR and a higher BMI during childhood have been associated with an increased risk of developing type 2 diabetes and coronary heart disease in adulthood.\(^\text{15,16,31,32}\) We were unable to investigate the levels of blood glucose and insulin in the current study, but our data indicate that children who exhibit early AR are predisposed to future development of insulin resistance due to higher BMI, TG, AI, ApoB, and blood pressure and lower HDL-C in boys and higher ApoB in girls. The mechanism through which early AR is associated with higher adverse lipoprotein profiles is unclear, but we speculate that metabolic programming leading to future insulin resistance may occur during the early increase of BMI. This period may involve programming of a future adaptation response of metabolism to adverse environmental factors, such as overnutrition or reduced physical activity in later life. Thus, early AR seems to result in increased susceptibility to development of metabolic syndrome. The timing of AR is difficult to identify at the time of occurrence, but recognition of AR may be key to improvement of lifestyles and obesity avoidance in infancy and early childhood. In Japan, all children receive health checks at 1.5 and 3 years old, and a higher BMI at 3 years compared with 1.5 years of age indicates that AR has occurred. We propose that early AR should be considered as a basis for prevention of future metabolic syndrome.

CONCLUSIONS

Our longitudinal population-based cohort study indicates that children who exhibit early AR are predisposed to future development of metabolic syndrome. Therefore, detection of early AR may permit identification of young children at risk for developing later metabolic syndrome and provide an opportunity for preventive intervention.

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