Onset of Puberty and Cardiovascular Risk Factors in Untreated Obese Children and Adolescents

A 1-Year Follow-up Study

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Objective: To determine the course of obesity-associated nonalcoholic fatty liver disease (NAFLD) and the cardiovascular risk factors of hypertension, dyslipidemia, and disturbed glucose metabolism in untreated obese children.

Design: Obese children were examined prospectively at baseline and 1 year later.

Setting: Obesity clinic.

Participants: A total of 287 untreated obese children; 53.3% were girls, the mean age was 11.4 years, and the mean body mass index (calculated as weight in kilograms divided by height in meters squared) was 28.2.

Main Outcome Measures: Homeostasis model assessment of insulin resistance (HOMA-IR) values and prevalence of hypertension, dyslipidemia, impaired fasting glucose level, and NAFLD.

Results: At baseline, 20.6% of obese children had hypertension, 22.3% had dyslipidemia, 4.9% had impaired fasting glucose levels, and 29.3% had NAFLD. These prevalences, as well as weight status, remained stable at the 1-year follow-up visit. Increases (SDs) in prevalence of hypertension (16.1% [51.8%]), hypertriglyceridemia (9.7% [59.3%]), and impaired fasting glucose level (8.1% [32.9%]), as well as mean HOMA-IR value (0.42 [1.22]), were observed in 62 children entering puberty. In contrast, mean decreases (SDs) in hypertension (−16.1% [51.8%]), hypertriglyceridemia (−12.5% [53.1%]), impaired fasting glucose level (−6.3% [38.1%]), and NAFLD prevalence (−18.8% [44.5%]), as well as mean HOMA-IR value (−0.83 [2.56]), were observed in 50 children entering late puberty (P < .01 for change of pubertal status in the multivariate model). Changes in HOMA-IR values were only weakly related to changes in prevalence of cardiovascular risk factors or transaminase levels (r < 0.2).

Conclusions: Cardiovascular risk factors worsened at onset of puberty and improved in late puberty in obese children whose weight status did not change. The weak correlation between HOMA-IR value and cardiovascular risk factors suggests that other characteristics may affect these disorders.

Arch Pediatr Adolesc Med. 2009;163(8):709-715

The increasing prevalence of obesity in childhood and adolescence poses an overwhelming problem. In addition, cardiovascular risk factors and comorbidities such as hypertension, dyslipidemia, disturbed glucose metabolism, and nonalcoholic fatty liver disease (NAFLD) are commonly present in obese children and adolescents. Reduction of obesity is recommended because several studies have demonstrated an improvement in cardiovascular risk factors and NAFLD after lifestyle intervention–induced weight loss. However, most obese children and adolescents do not participate in lifestyle interventions, the long-term effects of which remain controversial. Furthermore, the natural courses of hypertension, dyslipidemia, disturbed glucose metabolism, and NAFLD are largely unknown in obese children who do not lose weight. In addition, to our knowledge, studies addressing the onset of these disorders in obese children are scarce. In a previous study of obese children participating in a lifestyle intervention, a change in weight status did not predict changes in blood pressure (BP) or lipid and glucose levels.

Because such data are limited, we prospectively evaluated a large sample of obese children and adolescents at baseline and 1 year later based on the guidelines of the American, European, and German pediatric obesity associations. We analyzed the prevalences of hypertension, dyslipidemia, disturbed glucose metabolism, and NAFLD. In addition, we analyzed the association between change of pubertal stage...
and change in insulin resistance and its relationship to the frequency of comorbidities of obesity. We hypothesized that stage of puberty is associated with the onset and course of hypertension, dyslipidemia, disturbed glucose metabolism, and NAFLD because insulin resistance is one of the postulated underlying mechanisms of these disorders.8,12,13

**METHODS**

The local ethics committee of Witten/Herdecke University approved this study. Written informed consent was obtained from all participants and their parents.

At an outpatient center specializing in pediatric obesity and endocrinology, we prospectively examined all obese children and adolescents aged 4 to 16 years without endocrine or syndromal disorders following a standardized diagnostic procedure based on the guidelines of the American, European, and German pediatric obesity associations.4,6 All children were screened for degree of overweight, hypertension, dyslipidemia, disturbed glucose metabolism, and NAFLD. They were invited to participate in the lifestyle intervention program Obeldicks, which has been described previously.1 If children and/or parents did not want to participate in the intervention owing to lack of time, lack of transportation, lack of motivation, or other reasons, we recommended drug treatment for the comorbid disorders, according to the guidelines of the American, European, and German pediatric obesity associations. Furthermore, we recommended that all children, irrespective of participation in the intervention, attend a follow-up examination after 1 year to evaluate changes in weight status, hypertension, dyslipidemia, disturbed glucose metabolism, and NAFLD.

From January 1, 1999, to December 21, 2007, a total of 1042 obese children were examined in our obesity clinic, and 688 participated in the lifestyle intervention. The positive effect of this lifestyle intervention on cardiovascular risk factors has previously been reported.1 Fifty-seven obese children not participating in the lifestyle intervention were unavailable for follow-up. Ten children were excluded before analysis because of drug treatment in the lifestyle intervention were unavailable for follow-up. Twenty-eight untreated children not participating in the intervention who visited the clinic at baseline and 1 year later were included in the analysis. These children did not differ in the distribution of age, sex, pubertal stage, degree of overweight (body mass index [BMI] standard deviation score), and prevalence of hypertension, dyslipidemia, impaired fasting glucose level, or NAFLD at baseline compared with the 57 children unavailable for follow-up. Furthermore, there were no significant differences with regard to age, sex, pubertal stage, degree of overweight, and prevalence of hypertension, dyslipidemia, impaired fasting glucose level, and NAFLD at baseline between children who did and did not participate in the lifestyle intervention.

Degree of overweight was derived from BMI (measured as weight in kilograms divided by height in meters squared). Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured, with children wearing underwear, to the nearest 0.1 kg using a calibrated balance scale. Obesity was defined by a BMI above the 97th percentile for German children, according to the International Task Force for childhood obesity.14,15 We used Box-Cox transformation to calculate the BMI standard deviation score as a measure for degree of overweight, owing to the skewness of the BMI distribution.16

Pubertal stage was determined by trained physicians, according to the criteria of Marshall and Tanner. Pubertal developmental stage was categorized into 3 groups based on breast and genital stages (prepubertal: boys with genital stage I, girls with breast stage I; pubertal: boys with genital stage II or III, girls with breast stage II or III; late pubertal: boys with genital stage >III, girls with breast stage >III).

Blood pressure was measured using a validated protocol.17 Systolic and diastolic BP were measured in the right arm twice after a 10-minute rest in the supine position by using a calibrated sphygmomanometer, and the mean of both measurements was calculated. The cuff size was based on the length and circumference of the upper arm and was as large as possible without having the elbow skin crease obstructing the stethoscope.17 The intraoperator and interoperator variability was less than 5% for both systolic and diastolic BP. Hypertension was defined by BP above the 95th percentile for height, age, and sex.17

Blood sampling was performed in the fasting state. Commercially available tests were used to measure serum triglyceride, high-density lipoprotein cholesterol (HDL-C), aspartate transaminase, alanine transaminase, and insulin, and glucose concentrations were measured using commercially available test kits (HDL-C Plus and Cobas Integra 400, Roche Diagnostics, Mannheim, Germany; Vitros analyzer, Ortho Clinical Diagnostics, Neckargemünd, Germany; and MEIA, Abbott, Wiesbaden, Germany). Insulin concentrations were measured by microparticle enhanced immunometric assay. Intra-assay and interassay variations for the concentrations of these variables were less than 5%. Homeostasis model assessment of insulin resistance (HOMA-IR) values were calculated as follows18: resistance=(insulin [microinternational units per liter] x glucose [millimoles per liter]) / 22.5.

Cutoff points above the 95th percentile for healthy German children were used to define dyslipidemia.6 These cutoff points were 40 mg/dL for HDL-C and 150 mg/dL for triglycerides. Impaired fasting glucose was defined as a value greater than 100 mg/dL.19 (To convert HDL-C to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; and to convert glucose to millimoles per liter, multiply by 0.0555.)

Cases of NAFLD were diagnosed as described previously,8 and according to the American Gastroenterological Association Medical Position Statement,20 by standardized liver ultrasonography criteria measurements, as well as absence of alcohol abuse. The liver ultrasonography procedures were read by a radiologist who was blinded to the laboratory data and BP values, and quantification of fatty liver was performed according to the criteria of Saverymuttu et al.21 Differential diagnoses were excluded in all children with suspected NAFLD by measuring serum creatine phosphokinase, antinuclear antibodies, liver autoantibodies (smooth muscle antigen, liver kidney microsome, and soluble liver antigen), copper, ceruloplasmin, 24-hour urinary copper, α1-antitrypsin, Epstein-Barr Virus antibody, hepatitis A virus antibody, hepatitis B virus antibody, and hepatitis C virus antibody levels, according to international recommendations.22

Statistical analyses were carried out using Winstat for Excel (Microsoft Corp, Redmond, Washington); R statistical software, version 2.6.1; and SAS statistical software, version 9.1.3 (SAS Institute Inc, Cary, North Carolina). Changes in hypertension, hyperglycemia, low HDL-C levels, and high triglyceride levels and corresponding 95% confidence intervals were calculated. To assess the impact of the change in pubertal stage on these cardiovascular risk factors, we calculated generalized linear models a priori also considering sex, age, difference in height, pubertal status at baseline, and an interaction term between change in pubertal status and pubertal status at baseline. To assess whether the effects of pubertal stage change are associated with insulin resistance, we additionally adjusted for the HOMA-IR value difference and compared the P values for the change in pubertal status effect of these 2 models against each other. Agreement between the change in HOMA-IR value
RESULTS

Five children with hypertension, 2 with dyslipidemia, and 3 with type 2 diabetes mellitus were excluded before the analysis because of drug treatment. A total of 287 children, 153 girls (53.3%) and 134 boys (46.7%), were included in the study. The mean (SD) age was 11.4 (2.3) years. Table 1 shows additional baseline characteristics. At baseline, 118 children (41.1%) were prepubertal, 110 (38.3%) were pubertal, and 59 (20.6%) were late pubertal. Stratification by pubertal stage and change of pubertal stage yielded 5 groups: children remaining in the prepubertal phase during the study period (n=56); children entering puberty (n=62); children remaining in puberty (n=60); children entering late puberty (n=50); and children remaining in late puberty (n=59).

At baseline, 59 children (20.6%) had hypertension, 64 (22.3%) had dyslipidemia, 14 (4.9%) had impaired fasting glucose, none had type 2 diabetes, and 84 (29.3%) had NAFLD. In our study sample, the degree of overweight (Table 1) and the unadjusted proportion of children with hypertension, hyperglycemia, low HDL-C levels, or high triglyceride levels remained virtually unchanged from baseline to the 1-year follow-up visit. The differences (SDs) between baseline and follow-up were 1.4% (54.8%) for hypertension, 0.4% (30.9%) for hyperglycemia, 1.1% (45.6%) for HDL-C levels of less than 40 mg/dL, and 0.0% (49.0%) for triglyceride levels of more than 150 mg/dL. None of these differences were significant. Furthermore, the prevalence of NAFLD did not differ between baseline and the 1-year follow-up visit (29.0% vs 28.5%). In addition, BP, HOMA-IR value, and transaminase, triglyceride, HDL-C, and glucose levels did not change significantly (Table 1).

Prevalence of cardiovascular risk factors or NAFLD was unchanged among children remaining in the prepubertal, pubertal, or late pubertal stages, whereas cardiovascular risk factors increased significantly among children entering puberty. In contrast, prevalence of cardiovascular risk factors and NAFLD decreased significantly among children entering late puberty (Figure). Accordingly, BP worsened significantly among children entering puberty, but improved significantly among children entering late puberty, and remained stable among all children whose pubertal stage did not change during the study period (Table 2). Weight status did not change significantly, independent of pubertal stage or change in pubertal stage (Table 2).

The mean (SD) increase in the HOMA-IR value was 0.27 (1.83) units among prepubertal children, 0.42 (1.22) units among children entering puberty, and 0.16 (1.98) units among children remaining in puberty. In contrast, the mean (SD) HOMA-IR value decreased by −0.83 (2.56) units among children entering late puberty and by −0.99 (2.59) units among children in late puberty during the 12-month study period. Changes in HOMA-IR values were weakly correlated (P < .05) with changes in triglyceride (r = 0.14) and glucose (r = 0.20) levels, whereas there was no correlation with changes in systolic BP (r = 0.01), diastolic BP (r = 0.08), HDL-C level (r = −0.01), aspartate transaminase level (r = 0.03), or alanine transaminase level (r = 0.08).

In the multivariate linear regression model for repeated measurements, the change of pubertal status was significantly associated with changes in systolic and diastolic BP, aspartate transaminase, alanine transaminase, triglyceride, HDL-C, and glucose levels; and HOMA-IR value after adjustment for sex, age, change in height, and pubertal status at baseline (P < .01). An interaction term between change in pubertal status and pubertal status at baseline was not significant (P = .30). Considering HOMA-IR as a confounder rather than a response variable only marginally altered the effect of change of pubertal stage on cardiovascular risk factors, which was still significant (P = .01). The change in HOMA-IR values explained less than 1% of the variance in different models of cardiovascular risk factors (data not shown).

Table 1. Characteristics at Baseline and the 1-Year Follow-up Visit in 287 Untreated Obese Children and Adolescents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>1-y Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, mean (SD)</td>
<td>28.2 (3.8)</td>
<td>29.5 (4.1)</td>
</tr>
<tr>
<td>BMI-SDS, mean (SD)</td>
<td>2.38 (0.37)</td>
<td>2.41 (0.43)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>111 (110-122)</td>
<td>112 (110-122)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>60 (32-65)</td>
<td>61 (35-70)</td>
</tr>
<tr>
<td>HDL-C level, mean (SD), mg/dL</td>
<td>50 (10)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>Triglyceride level, mg/dL</td>
<td>106 (72-145)</td>
<td>102 (72-147)</td>
</tr>
<tr>
<td>AST level, µU/L</td>
<td>24 (20-28)</td>
<td>24 (20-28)</td>
</tr>
<tr>
<td>ALT level, µU/L</td>
<td>25 (17-33)</td>
<td>25 (19-33)</td>
</tr>
<tr>
<td>Glucose level, mean (SD), mg/dL</td>
<td>87 (7)</td>
<td>87 (7)</td>
</tr>
<tr>
<td>Insulin level, µIU/L</td>
<td>17 (12-24)</td>
<td>18 (14-24)</td>
</tr>
<tr>
<td>HOMA-IR value</td>
<td>3.5 (2.5-4.8)</td>
<td>3.6 (2.5-4.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BMI-SDS, BMI standard deviation score; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure.

COMMENT

To our knowledge, this is the first large observational study analyzing the changes in cardiovascular risk factors and NAFLD prevalence among untreated obese children by pubertal stage. The observed prevalences of hypertension, dyslipidemia, and NAFLD underline the necessity of screening for these disorders because most are asymptomatic but related to later cardiovascular diseases.

PUBERTY AS AN APPARENT CARDIOVASCULAR RISK FACTOR

Entering puberty was associated with deteriorations in BP, as well as lipid and glucose levels, and an increase in


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HOMA-IR values, whereas changing from middle to late puberty was associated with improvement in these factors and a decrease in NAFLD prevalence. These findings suggest a relationship between cardiovascular risk factors, NAFLD, and insulin resistance.8,12,13 However, the relationship between changes in cardiovascular risk factors, transaminase levels, and HOMA-IR values were weak or not significant, suggesting that there may be other contributing factors. The concentration of sex hormones and adipocytokines changes dramatically during pubertal development. For example, adiponectin levels have been negatively correlated with many cardiovascular risk factors.

Figure. Prevalence of cardiovascular risk factors and nonalcoholic fatty liver disease (NAFLD) by pubertal group and pubertal status change in 287 untreated obese children and adolescents. A, Entire study group (N=287). B, Children remaining prepubertal during the study period (n=56). C, Children changing from prepubertal at baseline to pubertal during the study period (n=62). D, Children remaining pubertal during the study period (n=60). E, Children changing from prepubertal to late-pubertal during the study period (n=50). F, Children who were late-pubertal at baseline and at the end of the study period (n=59). P values are for the baseline vs follow-up comparison. HDL-C indicates high-density lipoprotein cholesterol. To convert glucose to millimoles per liter, multiply by 0.0555; to convert HDL-C to millimoles per liter, multiply by 0.0259; and to convert triglycerides to millimoles per liter, multiply by 0.0113.
tors and decrease with onset of puberty in boys. Of interest, the prevalences of hypertension, hypertriglyceridemia, and NAFLD were lower in late-pubertal children compared with prepubertal children. The reasons for these differences remain unclear. However, one limitation was that participants were compared with other groups rather than comparing different pubertal stages for the same group.

SCREENING FOR CARDIOVASCULAR RISK FACTORS

Lipid, glucose, and transaminase levels, as well as BP, did not change among children whose pubertal stage did not change, which raises questions about the necessity of repeated screenings among children with stable weight status. However, obese children should be screened repeatedly for these parameters at puberty onset because of its association with changes of cardiovascular risk factors.

TREATMENT OF CARDIOVASCULAR RISK FACTORS AND COMORBITIES

Because cardiovascular risk factors and transaminase levels improved from middle to late puberty, the question arises whether drug treatment of present cardiovascular risk factors and NAFLD is necessary in pubertal obese children. In contrast, cardiovascular risk factors worsened after entering puberty and remained stable during all other pubertal stages. Hypertension, dyslipidemia, impaired glucose metabolism, and NAFLD in childhood are associated with early cardiovascular changes as measured by an increase of intima-media thickness of the common carotid artery, as well as later arteriosclerosis, suggesting the necessity of treatment of comorbidities in obese children. Although a specific therapy for NAFLD, other than lifestyle intervention, is not available, hypertension and dyslipidemia can effectively be treated by drug therapy. However, most of our children with hypertension and dyslipidemia were not treated with drugs by their general practitioners as recommended: only 7.8% of children with hypertension and 3.0% of children with dyslipidemia at initial screening were taking antihypertensive or lipid-lowering drugs during the 1-year follow-up period. This is in line with other findings regarding dyslipidemia or hypertension among obese children with type 2 diabetes mellitus. Patient compliance with drug treatment in childhood and pediatricians’ awareness about treatment of mild hypertension or dyslipidemia in obese children might be limited. Furthermore, families with obese children, as well as general practitioners, might hope that weight loss itself will improve these risk factors. However, without an intervention, change of weight status and improvement of cardiovascular risk factors and NAFLD seem to be unlikely, as was observed in our study.

STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this study are its longitudinal and prospective design and large study sample. However, some potential limitations have to be considered. First, BMI percentiles were used to classify children as overweight. Although BMI is a good measure for overweight, it is an indirect measurement of fat mass. Second, the HOMA-IR model is only an assessment of insulin resistance, and clamp studies are the criterion standard to analyze insulin resistance. Because the HOMA-IR model has been correlated with clamp studies, it seems to be a
suitable method for measuring insulin resistance in field studies. Third, we did not measure sex hormone and adipocytokine levels, which might be related more directly to changes in cardiovascular risk factors during puberty compared with insulin resistance. Fourth, this is a clinic-based observational study and not a population-based study, which may lead to overestimation of the prevalence of cardiovascular risk factors and NAFLD in obese children. Furthermore, only children followed up for 1 year after baseline were included in the analysis, possibly leading to a further overestimation. However, obese children primarily sought treatment at our clinic for their obesity and not for their comorbidities or cardiovascular risk factors. The overall frequency of hypertension, dyslipidemia, impaired fasting glucose, and NAFLD at baseline and 1 year’s follow-up was similar to previous reports. Fifth, diagnosis of NAFLD was not confirmed by analysis of liver biopsy specimens. In a large study cohort such as ours, liver biopsies are difficult to perform, not least for ethical reasons, because no specific therapy follows a histological diagnosis of NAFLD apart from recommending reduction of overweight, which is generally advised for all obese children. Sixth, the definition of dyslipidemia was based on cutoff points that do not consider age or sex in children, although it is well known that lipid levels change with age or sex, particularly during puberty. Finally, children with cardiovascular risk factors who were treated with drugs were excluded from this study. They likely have the most unfavorable risk factor profile, which probably led to understimation of the changes in cardiovascular risk factors in this study. However, only a small number of children were excluded.

CONCLUSIONS

An improvement in weight status, hypertension, dyslipidemia, impaired glucose metabolism, and NAFLD cannot be expected among untreated obese children and adolescents. The frequency of these cardiovascular risk factors is high among obese children. Cardiovascular risk factors worsened at the onset of puberty among obese children, and insulin resistance increased. The change from middle to late puberty was associated with an improvement in cardiovascular risk factors, prevalence of NAFLD, and insulin resistance. These findings indicate relationships between cardiovascular risk factors, NAFLD, and insulin resistance. However, less than 1% of the variance in cardiovascular risk factors was explained by insulin resistance, suggesting that there are further operating factors. Repeated screening for cardiovascular risk factors and transaminase levels seems to be necessary, particularly at the onset of puberty. However, without changes in pubertal stage, no changes in cardiovascular risk factors or transaminase levels are to be expected among children with stable weight.

Accepted for Publication: December 18, 2008.

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Author Contributions: Both authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Reinehr. Acquisition of data: Reinehr. Analysis and interpretation of data: Reinehr and Toschke. Drafting of the manuscript: Reinehr. Critical revision of the manuscript for important intellectual content: Reinehr and Toschke. Statistical analysis: Reinehr and Toschke.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grant 01 GI0839 from the German Competence Net Obesity program, which is supported by the German Federal Ministry of Education and Research, and by Ferring Pharmaceuticals, Kiel, Germany.

Additional Contributions: Gideon de Sousa, MD, provided a critical review of the manuscript.

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Announcement

2010 Certifying Examination in Adolescent Medicine Examination date: March 22, 2010.
The final month of registration requires payment of a late fee.
All applicants must complete applications online during the registration periods. The requirements for online applications are found on the American Board of Pediatrics Web site: http://www.abp.org. Additional information including eligibility requirements is found on the American Board of Pediatrics Web site. Each application will be considered individually and must be acceptable to the American Board of Pediatrics.
Correspondence: American Board of Pediatrics, 111 Silver Cedar Ct, Chapel Hill, NC 27514-1513 (http://www.abp.org).