# Effect of Weight Loss on Puberty Onset in Overweight Children

Thomas Reinehr, PhD[1], Christina Bosse, MD[1], Nina Lass, MD[1], Juliane Rothermel, MD[1], Caroline Knop, MD[1], and Christian Ludwig Roth, MD[2,3]

**Objective** To assess the impact of weight changes on the onset of puberty in overweight children.

**Study design** We evaluated the timing of puberty onset in 160 prepubertal overweight children (aged 11.2 ± 1.0 years) depending on the changes of their weight status in a 1-year lifestyle intervention. We determined body mass index (BMI), pubertal stage, luteinizing hormone (LH), follicle-stimulating hormone, insulin-like growth factor (IGF)-1, insulin-like growth factor binding protein-3, insulin resistance index homeostatic model assessment, and serum gonadotropins at baseline and 1 year later.

**Results** Puberty onset during the 1-year follow-up was significantly ($P = .014$) more frequent in girls without BMI-SDS reduction (75.0%) compared with girls with BMI-SDS reduction (45.7%). The start of puberty was significantly ($P = .024$) more frequent in boys with BMI-SDS reduction (76.9%) compared with boys without BMI-SDS reduction (53.6%). In logistic regression analyses adjusted for baseline age and BMI-SDS, BMI-SDS reduction was associated with a decreased likelihood for puberty onset in girls (OR 0.24; 95% CI 0.07-0.85) and an increased likelihood in boys (OR 3.77; 95% CI 1.34-10.52). Central onset of puberty was confirmed by an increase of LH concentration and LH/follicle-stimulating hormone ratio in both boys and girls. Homeostatic model assessment, IGF-1, and IGF-1/insulin-like growth factor binding protein-3 ratio as marker for free IGF-1 at baseline or their changes were not associated with the onset of puberty.

**Conclusions** BMI-SDS reduction in overweight children was associated with earlier gonadotropin-dependent onset of puberty in boys and later onset of puberty in girls, suggesting earlier puberty in obese girls and later puberty in obese boys. We found no evidence that insulin resistance or IGF-1 have an impact on the start of puberty in obese children. *(J Pediatr 2017;184:143-50).*

**Trial registration** ClinicalTrials.gov: NCT00435734.

Multiple studies have noted a relationship between obesity and an earlier timing of pubertal onset in girls,[1-10] although the situation in obese boys is less clear. Some groups reported that boys with greater body mass index (BMI) or fat mass entered puberty earlier,[1,9,11] whereas other studies did not note a consistent relationship between BMI and timing of puberty,[5,7,12-16] or they reported that boys with greater BMI entered puberty later.[3,5,6,16-18] Lee et al[19] reported earlier puberty in overweight compared with normal-weight boys and later puberty for obese boys. Most of these studies were cross-sectional analyses and therefore prone to confounding.[1,4-6,11-13,16,18-20] The few longitudinal studies only reported data from girls, demonstrating that BMI z scores at age of 3 or 5 years of age are associated with earlier breast development as well as earlier age of menarche.[21,22]

The observed association between obesity and early puberty leads to the speculation that there are mechanisms by which obesity leads to early puberty. One is through the direct action of adipokines, in particular the key metabolic peptide leptin, signaling energy reserves as well as having other direct metabolic effects.[1] In addition, insulin-like growth factor (IGF)-1 and insulin resistance have been hypothesized to be associated with earlier onset of puberty.[1,23,24] Furthermore, adipose tissue has aromatase action, which increases androgen conversion to estrogens.[1,25] The greater estrogen concentrations could promote earlier onset of breast development and menarche in girls independently of gonadotropins. Another mechanism for gonadotropin-independent earlier onset of breast development in obesity may occur through endocrine-disrupting chemicals (EDCs) acting on adipocytes or on other hormonally responsive tissues.[1,26,27]

As the result of these controversial findings concerning the onset of puberty in overweight children, we performed a longitudinal study to assess whether weight changes are associated with pubertal development. If obesity is directly linked to

| | |
|---|---|
| BMI | Body mass index |
| EDC | Endocrine-disrupting chemical |
| FSH | Follicle-stimulating hormone |
| HOMA | Homeostatic model assessment |
| IGF | Insulin-like growth factor |
| IGFBP | Insulin-like growth factor binding protein |
| LH | Luteinizing hormone |

earlier onset of puberty, one would expect that overweight children with weight loss would enter puberty later as compared with overweight children without overweight reduction.

## Methods

Written informed consent was obtained from children and their parents. The study was approved by the local ethics committee of the University of Witten/Herdecke in Germany and was registered at ClinicalTrials.gov (NCT00435734).

We examined 160 overweight and obese prepubertal white children from our obesity cohort (for details, see Reinehr et al[28]). Girls were chosen in the age range 9-11 years and boys in the age range 11-13 years since (1) puberty onset occurs in healthy German girls at the age of 10 years and in German boys at the age of 12 years[16] and (2) the onset of puberty in obesity was reported a few months earlier in overweight compared with normal-weight girls[1-8] and a few months earlier or later in overweight white boys.[1,5,6,9,11,16,18] None of the children in the current study suffered from endocrine disorders, premature adrenarche, or syndromal obesity (for details, see Reinehr et al[28]).

### Interventions

All overweight children participated in the 1-year lifestyle intervention "Obeldicks." The intervention has been described in detail elsewhere.[29,30] This intervention has to follow a published training manual, and all personnel attend a 1-week training seminar.[30] To summarize, this outpatient intervention program is based on physical activity, nutrition education, and behavior therapy including individual psychological care of the child and his or her family. An interdisciplinary team of pediatricians, nutrition counselors, psychologists, and exercise physiologists is responsible for the training.

### Measurements

We analyzed anthropometrics, pubertal stage, IGF-1, insulin-like growth factor binding protein (IGFBP)-3, insulin resistance index (ie, homeostatic model assessment [HOMA]), and gonadotropins in all children at baseline and 1 year later.

### Clinical Measures

Height was measured to the nearest centimeter with a rigid stadiometer. Weight was measured with the subject unclothed to the nearest 0.1 kg with a calibrated balance scale. BMI was calculated as weight in kilograms divided by the square of height in meters. The degree of overweight was quantified with the Cole least mean square method, which normalized the BMI skewed distribution and expressed BMI as a SDS (BMI-SDS).[31] Reference data for German children were used.[32] Children with BMI >90th percentile were defined as overweight and children with BMI >97th percentile were defined as obese according to the definition of the International Obesity Task Force.[33] The pubertal developmental stage was determined according to Marshall and Tanner. Pubertal developmental stage was categorized into 2 groups based on breast and genital stages (prepubertal: boys with genital stage I, girls with breast stage I; pubertal: boys with genital stage ≥II, girls with breast stage ≥II). Breasts were palpated in girls and testicular volume assessed in boys by palpation, with the use of an orchidometer. These examinations were performed in a standardized way by a pediatric endocrinologist or by well-trained pediatricians in subspecialty training for pediatric endocrinology, who are all experienced in performing these examinations. For this study, pubic hair development was not included because pubic hair also could be attributed to premature adrenarche, which is a known complication of obesity.[34]

### Biochemical Measures

Blood sampling was performed in the fasting state at 8 a.m. After clotting, blood samples were centrifuged for 10 minutes at 5376 g. Serum was stored at −81°C for later determination of insulin. All samples were thawed only once.

Insulin concentrations were measured by microparticle enhanced immunometric assay (MEIA; Abbott, Wiesbaden, Germany). Glucose concentrations were determined by colorimetric test with the use of a Vitros analyzer (Ortho Clinical Diagnostics, Neckargmuend, Germany). HOMA was used to detect the degree of insulin resistance using the formula: resistance (HOMA) = (insulin [mU/L] × glucose [mmol/L])/22.5.[35] Concentrations of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) were determined by high-specific chemiluminescence-immunoassays (ADVIA [Siemens Healthcare Diagnostics, Erlangen, Germany], IMMULITE [Siemens Healthcare Diagnostics], intra- and interassay coefficient of variation <5%, sensitivity 0.1 IU/L). LH > 0.3 IU/L is typical for the development of central pubertal.[36] IGF-1 and IGFBP-3 concentrations were measured with high specific chemiluminescence-immunoassays (IGF-1, IGFBP-3 IMMULITE 2000; Siemens Healthcare Diagnostics) without any cross reactions to proinsulin, insulin, and IGF-2. Intra- and interassay coefficient of variations were <6%. SDS for serum concentrations were calculated by the formula $(X − x)/SDS$, where X is the value of the serum concentration for a given chronological or bone age and x and SDS are, respectively, the mean and SD.[37] The ratio of IGF-1 and IGFBP-3 served as an indirect measurement of free IGF-1 concentrations.

### Statistical Analyses

Statistical analyses were performed with the Winstat software package (R. Fitch Software, Bad Krozingen, Germany). The children were divided in children with overweight reduction (defined by decrease of BMI-SDS) and children without overweight reduction (defined by stable or increase of BMI-SDS) during the 1-year observation period. Normal distribution was tested by the Kolmogorov-Smirnov test. To compare variables, the Fisher exact test and Student t test were used for unpaired and paired observations, and Mann Whitney U test and Wilcoxon test were used as appropriate. Multiple logistic regression was calculated with onset of puberty as the dependent variable and BMI-SDS at baseline, age, and decrease of BMI-SDS (0 = none, 1 = yes) as independent variables in boys and girls separately. LH was correlated to pubertal stage (0 = prepubertal, 1 = pubertal) by Spearman correlation.