

Childhood Obesity and Pubertal Development

Shin Hye Kim, M.D. and Mi Jung Park, M.D., Ph.D.

Department of Pediatrics, Inje University Sanggye Paik Hospital, Seoul, Korea

During the past decades, advancement in pubertal maturation in children has been noticed worldwide. Growing evidence indicates that increasing prevalence of obesity in children is a major factor for the secular trend of earlier puberty. In girls, several epidemiologic studies suggest that earlier pubertal onset and earlier menarche might be caused by obesity. On the other hand, in boys, few research reported an association between obesity and pubertal development, and the results are inconsistent; Some studies found a link between obesity and delayed puberty, but others reported a causal relationship between obesity and early puberty. To date, mechanisms linking childhood obesity and earlier puberty remain unclear. In this review, we presented the potential impact of obesity on puberty-related hormones and summarized human studies on potential relationship of childhood adiposity and pubertal development. (**Pediatr Gastroenterol Hepatol Nutr** 2012; **15**: 151 ~ 159)

Key Words: Obesity, Puberty, Sexual maturation

INTRODUCTION

Puberty is a complex process during which children attain secondary sexual characteristics and reproductive capability. Normal puberty is initiated by reactivation of the hypothalamic secretion of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH), in turn, FSH and LH stimulates the gonadal development and sex steroid production. The first sign of pubertal onset is an increase in testicular volume above 4 mL (Tanner G2 stage) in boys and the first appearance of breast buds

(Tanner B2 stage) in girls [1]. A number of factors including ethnicity, inheritance, stress, body fat and nutrition are known to be involved in the timing and tempo of pubertal development.

During the past decades, advancement in the age of pubertal development in girls has been reported all around the world. The age at thelarche has advanced about one year since mid-1980s and early 1990s among US white girls [2,3] and Danish girls [4]. With regards to menarche, trend toward earlier menarche is continuing in China [5] and Korea [6] since 1980s, meanwhile decrease in menarcheal age appears to be slowed down in developed nations such as US [7] Japan [8] and some European countries [9,10]. Also

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Corresponding author: Mi Jung Park, M.D., Ph.D., Department of Pediatrics, Inje University Sanggye Paik Hospital, 1342, Dongil-ro, Nowon-gu, Seoul 139-707, Korea. Tel: +82-2-950-1130, Fax: +82-2-951-1246, E-mail: PMJ@paik.ac.kr

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in boys, secular trend of earlier pubertal onset has been noted in US [11], Denmark [12], Korea [13], and China [14]. Interestingly, these secular trends of puberty have coincided with the worldwide increase in childhood obesity prevalence. A rapid increase of obesity prevalence in children has been noted in many countries including US [15], UK [16], Germany [17], France [17], Australia [18], Brazil [19], China [19], and Japan [20]. In Korea, the prevalence of childhood obesity increased from 5.8% in 1997 to 9.7% in 2005 [21], and now it has reached 10-20% and among high schoolers [22]. Several epidemiologic studies have demonstrated that girls with greater body mass index (BMI) enter thelarche [5,23,24] or menarche [25] earlier than girls with normal BMI, leading to a suggestion that excess adiposity influence the onset and progression of puberty.

In this paper, we reviewed the possible mechanism by which obesity may influence pubertal maturation in children and summarized human studies showing impact of childhood obesity on the pubertal timing.

POSSIBLE MECHANISMS LINKING OBESITY AND PUBERTAL DEVELOPMENT

Leptin and puberty

In 1970, Frisch and Revelle [26] proposed a hypothesis that a weight of 48 kg is required to achieve menarche, suggesting that the critical weight causes a change in metabolic rate, in turn, affects hypothalamus-ovarian feedback. This hypothesis has been supported by the discovery of leptin, a hormone secreted by adipocytes. Leptin informs hypothalamus of amount of body fat mass, and suppresses appetite and stimulates energy expenditure [27]. Also, leptin play a role in pubertal development [27]. Leptin deficient mice have obese phenotype and fail to achieve puberty and fertility due to hypogonadotropic hypogonadism [28], and their infertility is reversed by the administration of leptin [29]. Similarly, human individuals with mutations in the leptin or leptin receptor gene have hypogonadotropic hypogonadism

[30,31], and these individuals gain LH pulsatility of puberty following leptin administration [32,33]. However, several evidences indicate that leptin is a permissive factor for pubertal onset but is not a trigger factor for timing of puberty. For instance, leptin administration to normal prepubertal mice does not induce precocious puberty [34], and serum leptin levels in rodents remain relatively constant during the prepubertal and postpubertal stages [35]. Longitudinal human studies showed that serum leptin levels increase gradually during peripubertal period, rather than surging at the pubertal onset [36,37]. Mechanism of leptin action on pubertal onset is explained as an activation of GnRH-gonadotropin axis. Leptin receptors have been identified in the anterior pituitary [38] and leptin directly stimulates the release of LH and FSH [39]. Leptin receptors are also expressed in ventral premammillary neurons (PMV) which expresses the excitatory neurotransmitter glutamate [40]. Leptin stimulates PMV to release glutamate, which, in turn, activates GnRH neurons (Fig. 1) [41].

Hyperinsulinemia and puberty

During puberty, increased growth hormone induces insulin resistance and physiological hyperinsulinemia [42]. Increased insulin facilitates pubertal weight gain, vise versa, obesity exacerbates the pubertal insulin resistance [43]. Obesity induced hyperinsulinemia may exaggerate pubertal maturation

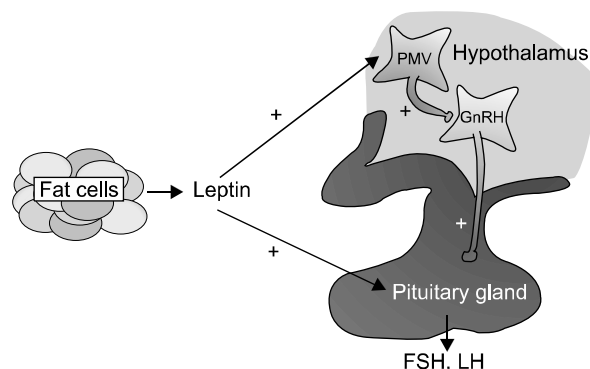


Fig. 1. Effect of leptin as a permissive factor for pubertal onset. GnRH: gonadotropin releasing hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, PMV: ventral premammillary neurons.

via various endocrine pathways. First, hyperinsulinemia in obesity may stimulate adrenal androgen secretion and precocious pubarche [44,45]. Low birth weight and rapid postnatal weight gain has been demonstrated to increase subsequent obesity risk [46] and linked to precocious pubarche and subsequent early puberty [47,48]. Studies reporting insulin sensitizing treatment (with metformin) prevents early menarche in girls with precocious pubarche [49,50] suggests important role of hyperinsulinemia in pubertal maturation. Second, hyperinsulinemia can reduce sex hormone binding globulin (SHBG) production from liver [51], increasing sex steroid bioavailability. Third, insulin stimulates ovarian growth and steroidogenesis via insulin receptors in ovary, increasing production of estrogens and androgens [52]. Fourth, aromatase activity is increased in obese children, possibly by increased insulin, resulting in increased conversion of androgens to estrogens [43]. Increased sex steroid levels by insulin effects on multiple organs could induce gonadotropin-independent or gonadotropin-dependent precocious puberty [53] (Fig. 2).

RELATIONSHIP OF OBESITY AND PUBERTY IN GIRLS

A number of evidences have demonstrated an associations between adiposity and early puberty in girls (Table 1). In 1997, Pediatric Research in Office Settings (PROS) study demonstrated that girls aged 6-9 years with breast development had higher BMI z-scores compared with prepubertal girls at each age [23]. Similarly, a study on pubertal development in black girls aged 8-10 years reported that increasing stages of breast development were related to increased BMI, waist circumference and fat mass [54]. A nationally representative study based on the data from the National Health Examination Survey (NHES 1963-1970) and National Health And Nutrition Examination Survey III (NHANES 1988-1994) was examined the trend of menarcheal age during the 25 year period [55]. The authors reported that menarcheal age advanced from 12.7 to 12.5 years and prevalence of overweight increased from 16% to 27% during the study period. And they also demonstrated that the average menarcheal age in 1988-1994 could be predictable based on the secular changes in distributions of BMI z-score, race, and age, suggesting causality exists between increasing obesity and ad-

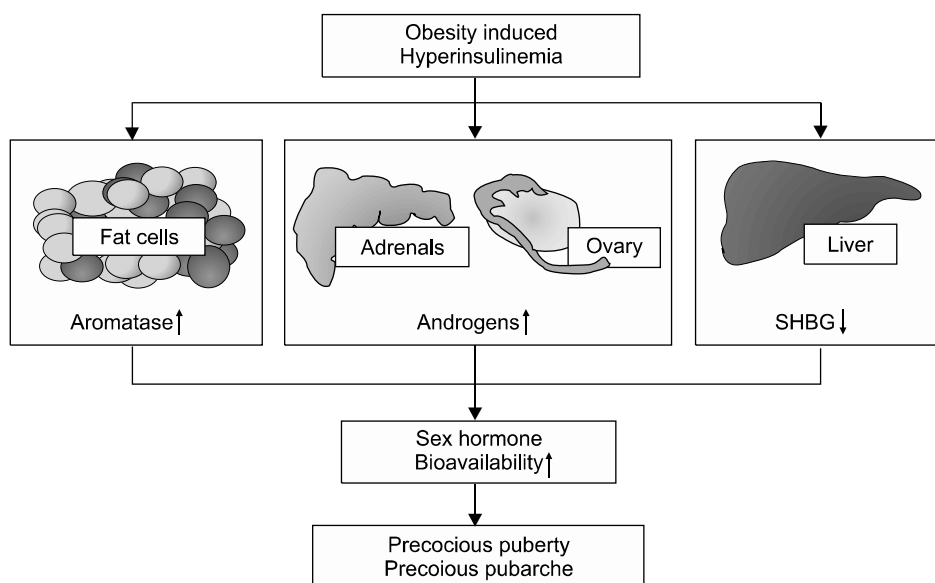


Fig. 2. Role of hyperinsulinemia in obesity on early pubertal maturation. SHBG: sex hormone binding globulin.

Table 1. Studies on Relationship between Body Composition and Timing of Puberty in Girls

Study population (sample size)	Method	Findings	Reference
US girls aged 6-9 yr (total 17,077)	Cross-sectional study Assessment of breast bud and pubic hair	Higher BMI z-scores in girls with breast budding or premature pubarche compared with prepubertal girls	Kaplowitz et al. [23]
African-American girls aged 8-10 yr (total 147)	Cross-sectional study Assessment of Tanner stages	Positive association between breast stage and BMI, WC and fat mass No association with pubic hair stage	Himes et al. [54]
US girls aged 10-15 yr (1,076 girls from NHES, 1,326 girls from NHANES)	Cross-sectional study Assessment of menarcheal age	Advanced menarcheal age (about 2.5 months) during the 25 yr study period was strongly associated with increased BMI z-score in the population	Anderson et al. [55]
US girls age 8-14 yr (total 1,501)	Cross-sectional study Assessment of breast bud	The prevalence of obesity and overweight is higher in girls with early puberty than in control	Wang [24]
US girls aged 8-18 yr (total 2,065)	Cross-sectional study Assessment of Tanner stages and menarcheal age	Early puberty and early menarche are more prevalent in overweight girls than in normal weight girls	Rosenfield et al. [56]
US, 2,058 girls Baseline age: 5-9 yr Follow up age: 10-17 yr	Cohort study Assessment of menarcheal age	Higher BMI and triceps skin fold thickness at baseline correlates with earlier menarcheal age	Freedman et al. [25]
Australia, 1,391 women	Retrospective cohort study Assessed pubertal ages	Overweight at age 5 yr is predictor for more advanced pubertal stages at age 14 yr	Mamun et al. [57]
Germany, 107 girls	Cohort study Assessment of age at PHV and menarcheal age	Higher BMI and fat mass are associated with shorter duration of puberty and earlier menarcheal age	Buyken et al. [58]
Afro-Caribbean girls (total 140)	Cohort study Assessment of Tanner stages and menarcheal age	Fat mass at age 8 yr is associated with advanced pubertal stage at age 11 yr; BMI at age 11 yr is associated with earlier menarcheal age	Boyne et al. [59]
UK, 347 girls	Cohort study Assessment of serum adrenal androgen levels	Low birth weight and catch-up growth are associated with higher adrenal androgen levels at age 8 yr	Ong et al. [48]
Belgian girls with PP (total 187)	Cohort study Assessment of menarcheal age	Pubertal onset and menarche occurs earlier in PP girls with low birth weight than in PP girls with normal birth weight	Ibáñez et al. [49]
Korean girls aged 7-10 yr (total 252)	Case-control study Assessment of HPG axis by GnRH stimulation test	Adiposity and central obesity is severer in girls with PPP than in girls with CPP	Yoon et al. [60]

BMI: body mass index, WC: waist circumference, NHES: National Health Examination Survey, NHANES: National Health And Nutrition Examination Survey, PHV: peak height velocity, PP: precocious pubarche, PPP: peripheral precocious puberty, CPP: central precocious puberty.

vanced menarcheal age [55]. Other studies using NHANES III data demonstrated that prevalence of obesity and overweight is significantly higher in girls with early puberty than in control [24], *vis versa*, early puberty and early menarche are more prevalent in overweight girls than in normal weight girls [56]. Besides cross-sectional studies, there are some longitudinal studies that investigated the association of body composition and pubertal timing in girls. The

Bolgalusa Heart study, which examined the relations between menarche and prepubertal adiposity, found that increased BMI z-score measured at aged of 5-9.9 years correlates earlier age (<11.0 years) at menarche [25]. A cohort study in Australia reported that overweight at age 5 years is a predictor for more advanced pubertal stages at age 14 years [57]. In a prospective study in Germany, higher prepubertal BMI was associated with earlier pubertal progression and

shorter puberty duration, resulting earlier attainment of menarche [58]. Likewise, a recent prospective study demonstrated that fat mass at age 8 years was associated with advanced pubertal stage at age 11 years and BMI at age 11 years had negative association with the age of menarche [59]. As discussed earlier, small size at birth and childhood catch-up growth have been associated with increased risk of premature pubarche and early menarche, resulting from insulin resistance [48,49]. Although a large number of studies evaluated the association between adiposity and pubertal stage on physical examination, the relationship between adiposity and precocious puberty diagnosed with hormonal assay has been rarely discussed. Recently, we demonstrated that girls with precocious puberty has higher adiposity than control, and adiposity and central obesity is severer in girls with gonadotropin-independent precocious puberty than in girls with gonadotropin-dependent precocious puberty [60]. This supports that obesity is a contributing factor for early puberty especially in girls with gonadotropin-in-

dependent precocious puberty.

RELATIONSHIP OF OBESITY AND PUBERTY IN BOYS

There are fewer studies on a relationship between obesity and pubertal maturation in boys (Table 2). Contrary to the study results reporting significant associations between obesity and earlier puberty in girls, the relationship is mixed in boys according to the population studied. In a cross-sectional study in Italy, the obese boys tended to have delayed pubertal maturation [61]. Similarly, a large scaled US study based on NHANES III data, pubertal development was delayed in obese boys [24]. A more recent prospective study in US showed that boys in the highest BMI trajectory had a higher risk of later pubertal onset [62]. Putative mechanism of delayed puberty in obese boys was explained as increased circulating estrogens by increased aromatase activity in fat tissue. Increased estrogens, in turn, may inhibit gonadotropin secretion in negative feedback mechanism

Table 2. Studies on Relationship between Body Composition and Timing of Puberty in Boys

Study population (sample size)	Method	Findings	Reference
Italian boys aged 6-16 yr (total 141)	Cross-sectional study Assessment of Tanner stages	Obese boys tends to have delayed pubertal maturation	Vignolo et al. [61]
US boys aged 8-14 yr (total 1,520)	Cross-sectional study Assessment of Tanner stages	Obese boys has a decreased risk of early puberty	Wang [24]
US, 401 boys	Prospective study Assessment of Tanner stages	Boys in the highest BMI trajectory has a higher risk of being prepubertal compared with boys in the lowest BMI trajectory	Lee et al. [62]
Spanish boys aged 10-15 yr (total 299)	Prospective study Assessment of Tanner stages	A positive relation between the age of pubertal onset and BMI	Vizmanos and Martí-Henneberg [64]
Australia, 1,506 men	Retrospective cohort study Assessed pubertal ages	Overweight at age 5 yr is predictor for more advanced pubertal stages at age 14 yr	Mamun et al. [57]
Swedish 2,065 boys	Cohort study Assessment of Tanner stages	Higher childhood BMI is related to an earlier puberty and reduced height gain during puberty	He and Karlberg [65]
UK, 423 boys	Cohort study Assessment of serum adrenal androgen levels	Low birth weight and catch-up growth are associated with higher adrenal androgen levels at age 8 yr	Ong et al. [48]
Danish boys aged 6-19 yr (total 1,528)	Prospective study Assessment of Tanner stages, gonadotropin, testosterone	Advanced pubertal onset was directly impacted from increased BMI between 1991-1993 and 2006-2008	Sørensen et al. [12]

BMI: body mass index.

[63]. However, some longitudinal studies have demonstrated a positive relationships between pubertal onset and obesity in boys. A Spanish study [64] and an Australian study [57] reported a negative relation between the age of pubertal onset and prepubertal BMI in boys. A Swedish population-based study [65] also demonstrated similar impact of childhood BMI on early pubertal onset and reduced height gain during puberty. A UK cohort study [48] showed low birth weight and catch-up growth increased the risk of premature pubarche in boys, as well in girls. Finally, the Copenhagen Puberty Study [12] evaluated the causal effect of increased adiposity on secular trends in earlier pubertal onset among Danish boys. The age at pubertal onset has decreased, whereas BMI z-score has increased between 1991-1993 and 2006-2008. Interestingly, after adjustment for BMI, the difference in the age of pubertal onset was no longer significant, suggesting the advancement of puberty was associated with increased BMI. So far, there is still inconsistency between the studies on impact of obesity on pubertal maturation in boys, although evidence that obesity might play a role in earlier onset of puberty is increasing.

CONCLUSION

A lot of large scaled epidemiologic studies indicate that secular trends of earlier pubertal maturation in girls are related with increased BMI or adiposity in the past 30 years. Activating effect of leptin on GnRH-gonadotropin axis is thought to be one of the possible mechanisms linking between body fat mass and earlier pubertal onset. Hyperinsulinemia in obesity may also contribute to earlier puberty by stimulation of androgen secretion, activation of aromatase in fat tissue and reduction of SHBG production from liver. Low birth weight and rapid catch up growth is known to be linked to hyperandrogenemia and subsequent early puberty. In contrast with girls, the data on the association of adiposity with pubertal onset in boys are much limited and, if any, the results are inconsistent. There are some limitations for studies in boys. Distinct pubertal mile-

stones that can be easily obtained from an interview are not available, and pubertal staging by physical examination is more difficult in boys. Therefore, efforts are needed to overcome several limitations in future studies, such as objective pubertal staging, reliable measurement of body fat mass other than BMI, hormonal markers for pubertal development, and longitudinal study design to overcome genetic, nutritional and environmental variables.

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