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COMMENT

BMI changes through childhood: the impact on puberty, linear growth and hormonal regulation

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The prevalence of childhood obesity has increased substantially over the past two decades with now approximately 18.5% of US youth between the ages of 2 and 19 years being classified as obese according the Centers for Disease Control.[1] In addition, obesity has been shown in numerous studies to be associated with an early onset of puberty.

The impact of adiposity on reproductive function has been long known. Dr. Rose Frisch in her manuscript in *Science* in 1974 demonstrated that a threshold of 17% body fat was required for menstruation in mature females.[2] Adequate fat stores would indicate that sufficient food was available to provide support for a growing fetus as well as support health of the mother during pregnancy. Even before the earliest reports of the impact of body fat on menstruation, the association of obesity with early puberty have been investigated. Reports as early as 1970 demonstrated that menarche occurred earlier in obese girls as compared to their normal weight peers.[3] In a combination of two larger studies, girls who matured early were more likely to be obese than those who matured later.[4] Power and colleagues examined a British birth cohort finding a strong association between body mass index (BMI) and timing of puberty.[5] These findings agree with more recent studies. Aris and colleagues examined the association of childhood BMI with pubertal timing in a cohort from the United States and Belarus and found a positive association between childhood BMI and advanced pubertal development.[6] Lazzeri and colleagues in a nationally representative study of Italian youth found again that BMI was inversely associated with the age of menarche in females.[7] Similarly in a Danish study of boys, testicular enlargement occurred significantly earlier in obese youth as compared to normal weight peers.[8]

From these studies and many more, it is evident that obesity confers an increased risk of early puberty in youth; however, whether such effect requires a chronic exposure to obesity throughout the preadolescent period is unclear. Specifically, if one is obese during childhood but regains normal adiposity prior to adolescence, is the timing of puberty now normal? Or, if the onset of obesity is delayed, are those individuals protected from early puberty?

The study by Fan and colleagues in this issue begins to address these questions by the novel approach of evaluating pubertal timing as it relates to alterations in the BMI trajectory through childhood and early adolescence.[9] The authors identified four patterns of BMI trajectories over time: normal BMI, rapid BMI growth, persistently overweight/obese, and early transient overweight/obese. The study defined these BMI trajectories using multiple statistical methods, which is a strength of this study. They found that obesity at any period was associated with a higher risk for early puberty as compared to peers with normal BMI throughout childhood; however, those who were persistently overweight carried the highest risk for early puberty. Also, 15% of the variance in timing for pubertal progression could be explained by a combined genetic score, sleep quality, and fat-free mass in the persistently overweight group. The body composition was measured by electrical impedance; while good for large population studies, it is not as sensitive as dual-energy X-ray absorptiometric measurements, which could be a limitation of these associations.[10] As fat-free mass is the combination of lean mass and bone, the association of puberty progression with fat-free mass could also be a result of testosterone production, which was not assessed in the present study, as an anabolic hormone increasing lean mass. In addition, adipose tissue signaling modulating bone development may also play a role, but this did not appear to be included in the analysis. The authors found that girls who were consistently overweight/obese had the highest risk for early breast development; while girls that were transiently overweight/obese had the highest risk for early menarche. On examination of the BMI trajectories in these two groups, the girls who were transiently overweight had at least as high if not higher BMI than the girls in the consistently obese group at the earliest time point. One might assume from this that increased fat mass may be associated with early puberty specifically in the females; however, the authors did not appear to investigate this possible association in a sex-specific fashion. Males who had either a rapid rise BMI or were consistently overweight/obese were more likely to experience early testicular enlargement; however, the study was limited in that it used only participant recall for these findings rather than assessment by an experienced clinician. Their findings do suggest that the timing of the adiposity gain may exert differing effects on pubertal progression that may be tempered by sex.

Studies of the impact of weight loss on pubertal progression have yielded differing results. Fan et al. found that, in females, those with a decline in BMI were at the highest risk for early menarche. However, Reinehr and colleagues found that a reduction in BMI standard deviation score (SDS) was associated with a decreased likelihood of puberty in girls but earlier onset of puberty in boys.[11] While neither study investigates the mechanism by which weight loss might alter pubertal timing, Reinehr et al. postulated that the changes in weight would alter hormone levels.[11] For example, weight loss could result in a decline in leptin reducing the signaling of pubertal onset and delaying puberty while an increase in weight may increase estrogen through

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increased aromatase activity in adipose tissue signaling at an earlier onset of puberty.[11] As understanding of the key hormones involved in pubertal initiation increase, the impact of weight change on pubertal timing and progress may become more clear.

An additional observation of Fan and colleagues is that the children with normal BMI trajectory through childhood had a final height that was slightly less than the target height, while those exposed to obesity in childhood had a slightly taller final height than their target height.[9] Some concerns raised with these observations are that the parental heights as well as the near final height were all obtained by recall, which could introduce bias into the analysis. These height differences were most pronounced in the group with early obesity that then demonstrated a decrease in BMI through adolescence. However, the number of participants were the smallest in this group and thus caution is advised. The lack of longitudinal height measures complicates some of the interpretation in Group 4 as BMI SDS can drop either because of less weight gain or increased linear growth. Perhaps the great drop in Group 4 females reflect some increase in growth and perhaps the association of lean mass in males of Group 4 is explained by testosterone secretion.

The impact of obesity on adult height and growth velocity have been examined in several studies in recent years. Holmgren and colleagues found in a cohort of Swedish children that adult height was not related to BMI, but rather childhood BMI was associated with more growth before the onset of puberty.[12] They also demonstrated that peak BMI during childhood was inversely correlated with pubertal height gain. In an early cohort in Sweden, He and Karlberg found that, while there was difference in final height, for each 1 BMI unit increase in childhood, height was increased by 0.23 cm in boys and 0.29 cm in girls.[13] Compensating for this early increase, each increase in BMI reduced height gain in the adolescent years by 0.88 cm and 0.51 cm in boys and girls, respectively. In addition to evaluating the effects of BMI on pubertal timing, Aris and colleagues also investigated the impact of obesity on growth.[6] In both the cohorts from the US and Belarus, a higher BMI in childhood was positively associated with height velocity in childhood but negatively associated with height velocity in adolescence. They also found that that the early growth resulted in greater trunk length, but this association did not hold true for leg length. Fan and colleagues demonstrate that overall obesity did not negatively impact overall height gain, and they did not mention any height difference among the four trajectories at baseline, so it is difficult to assess whether the differences in height are due to childhood growth versus the pubertal growth spurt. Overall, the current literature would suggest that the effect of obesity and early puberty on final height is insignificant.

The mechanisms that determine the onset of puberty are still being explored including those by which obesity affects pubertal timing and growth. It is clear that pubertal onset is linked with the state of energy reserve. Malnutrition has been linked with delayed puberty,[14] and growing evidence would now support that energy excess in obesity causes early puberty.[15] While a direct mechanistic link had not been established between obesity and early puberty, recent work suggests that energy-sensing systems are involved. Leptin, secreted by adipose tissue, serves as one of the main energy-sensing hormones.[16] Leptin, which increases with obesity,[17] plays a permissive role for the puberty process. Increasing evidence seems to support that leptin may have a role in the activation of the kisspeptin neurons within the arcuate nucleus of the hypothalamus, which are one of the primary mediators of puberty.[15] In animal models, kisspeptin neurons express leptin receptors, and leptin administration increases kisspeptin expression.[18] In a cross-sectional study of youth, a rise in leptin was noted at least 2 years prior to any increase in luteinizing hormone or estrogen suggesting that leptin is key to the progression of puberty.[19]

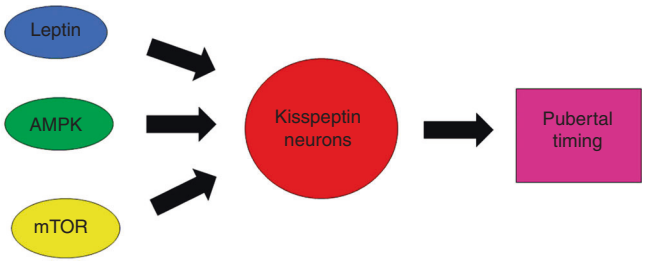

Fig. 1 Pubertal timing is directed by a complex interplay of energy-sensing hormones such as leptin, AMPK, and mTOR that result in increased expression of kisspeptin affecting the timing of puberty. As these energy sensors are increased in obesity, they may play key roles in the influence of obesity on pubertal timing.

While leptin may be a key factor connecting obesity with early puberty, other energy-sensing pathways may also be involved. Mammalian target of rapamycin (mTOR) is one such factor that is activated in states of energy excess allowing anabolic processes such as protein, lipid, and nucleotide synthesis while suppressing catabolic mechanisms.[20] mTOR also provides feedback to the hypothalamus regarding nutrient availability.[15] In rodent models, mTOR activation results in activation of the pubertal axis while central inactivation of mTOR was shown to delay puberty onset.[21] Another energy sensor, AMP-activated protein kinase (AMPK), is activated in times of energy depletion to then signal food intake and energy expenditure with the hypothalamus.[15] Again in rodent models, AMPK activation suppressed *Kiss1* expression in the hypothalamus delaying puberty onset.[22] Taken all together, a complex network of energy-sensing appears to underlie the association of childhood obesity with earlier onset of puberty in youth (see Fig. 1).

As demonstrated by Fan and colleagues, obesity has clearly been shown to impact pubertal timing. They have demonstrated that any period of obesity impacts the time of onset of puberty, but children with persistent obesity are at the highest risk. Weight loss in puberty or later onset of obesity do not seem to provide much protection from early pubertal development. The alterations in pubertal timing seem to have a lesser impact on adult stature. In the interpretation of the results, caution is warranted as the participant numbers are very small especially in the transient obesity group, and much of the data regarding height and pubertal initiation are by recall rather than a direct measurement. Also, the overall risk for early puberty was found to be very low based on their reported odds ratios. The alterations in timing are most likely mediated by hormones and proteins sensitive to energy regulation that also impact the hypothalamic–pituitary–gonad axis. Alterations in pathways involved in energy homeostasis may prove to be the key in the effects of pubertal timing imparted by obesity.

AUTHOR CONTRIBUTIONS

Both authors conducted review of literature for the manuscript. J.B.T. wrote the manuscript. Both authors revised the manuscript and approved the final version.

ADDITIONAL INFORMATION

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