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Delays in Puberty, Growth and Accrual of Bone Mineral Density in Pediatric Crohn's Disease: Despite Temporal Changes in Disease Severity, the Need for Monitoring Remains

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Crohn's disease (CD) is an immune-mediated process causing injury to the small intestinal and colonic mucosa, leading to local and systemic inflammation (1). Although hallmarked by symptoms such as weight loss, abdominal pain and bloody diarrhea, CD can have an insidious onset that escapes clinical detection. CD has been associated with shortfalls in linear growth and—when disease onset occurs prior to puberty—with substantial delays in the timing of puberty (2). The insidious onset and linear growth failure are primarily associated with small bowel involvement (3, 4) and are generally not seen in ulcerative colitis (UC), another inflammatory bowel disease (IBD) in which disease activity is restricted to the colonic mucosa. The delay in puberty in CD can exacerbate other potential disease sequelae, including decreased bone mineral density (BMD, from multiple factors including a lack of sex steroids at an appropriate age), short stature (from potential loss of pubertal growth spurt)(2, 5), and decreased self-esteem (from timing of puberty later than one's peers). The potential for these sequelae raises the need for close monitoring of pubertal status among adolescents with CD.

Although the prevalence of these findings in the setting of CD has been reported historically to be relatively common, more current evidence suggests continued but overall more modest delays in puberty and growth failure in the advent of more modern treatments—a trend also seen in other pediatric chronic diseases such as cystic fibrosis. In this review we will cover data regarding these endocrine sequelae of CD, consider mechanisms related to their pathophysiology and discuss potential approaches to diagnosis and treatment.

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Prevalence of Endocrine Co-morbidities

Puberty

Reports on the prevalence of delayed puberty in CD reflect at a minimum the potential for significant delays (Table I). A 1994 evaluation of young women with CD diagnosed before puberty who were hospitalized between 1968–1983 reported that menarche occurred at or after age 16 years in 73% of these young women—compared with 0% of those with UC (6). A report from 1994 found a mean age of breast development among outpatients with CD and UC of 12.6 years compared with 11.1 years for controls (7). In this same survey boys with IBD were assessed for timing of testicular enlargement, exhibiting a delay of 0.8 years compared with controls (7). These studies suggest a significant delay of puberty in CD—among girls in particular. However these reports are from a time when care was likely different from today, with increased reliance on glucocorticoids and without biologic medications as an option.

More recent evaluations of the timing of puberty have predominantly used surrogates of pubertal events (such as the timing of growth spurts) as an assessment of pubertal timing. Some of these reports have suggested more modest delays than seen previously among girls with CD. One group reported that for adolescents with pre-pubertally diagnosed CD the timing of the pubertal growth spurt was delayed for girls by 0.8 yrs (mean values 12.8 yrs vs. 12.0 yrs for controls) and for boys by a median 0.5 yrs (14.5 yrs in CD vs. 14.0 yrs for controls)(8). These data were from a period spanning 1994–2007, still prior to the widespread use of infliximab and other biologic medications. Another group used bone age as a measure of delay in maturation. They retrospectively evaluated patients with CD (dates of observation not reported) and found a delay of 1.16 years—which was not stratified by sex (9). Finally, another group evaluated data in a cross-sectional study performed 2007–2009, with 60% of subjects on immune modulators and 20% receiving infliximab. In this cohort there was a delay of bone age compared with chronological age of 1.3 years for girls and 0.7 years for boys (10). The same group found significant delays in the age of menarche, with a median age of 13.9 years among girls with CD, compared with 12.0 years among control subjects from the National Health and Nutrition Examination Survey 2007–2008 (11, 12). In this cohort with CD it is notable that of 20 girls who had already reached menarche at the time of evaluation, 14 (70%) were greater than 12.0 years old when their CD was diagnosed—likely reflecting a strong influence of the insidious onset of CD contributing to the delayed puberty. Nevertheless, an additional 16 girls had been diagnosed with CD before 12.0 years (at a mean age of 8.9 years) and at least 13/16 of these girls already exhibited delays in menarche beyond 12.0 years. Thus, although delays may have lessened slightly with modern treatments, current data would suggest continued delays in pubertal timing in CD.

Despite the theoretical decrease in prevalence of pubertal delay in CD, there certainly remains at a minimum a sub-set of children with significant delay in pubertal timing—potentially exacerbating the other co-morbidities of growth and low BMD. These affected individuals represent those who are diagnosed late in the course of their disease or individuals who respond poorly to current treatments (13). Nevertheless, the apparent decrease in the degree of delayed puberty highlights the potential that some patients with delayed puberty in CD may represent individuals with extensive small bowel involvement in their CD or with other causes of delayed puberty, such as genetic and other factors (14). Maintaining a broad differential in these settings could thus assist in earlier identification of other etiologies of delayed puberty.

Growth

The timing of puberty is important for growth potential both because of its relationship to the pubertal growth spurt and because sex hormones are the mediators of epiphyseal fusion and permanent cessation of growth. Even though the delay in puberty would theoretically result in preservation of growth potential (with affected individuals "saving up growth" related to the delay), some authors have suggested that CD may result in a blunted pubertal growth spurt with subsequent lower final heights (2). CD has historically been linked to shorter final height (5). In a systematic review, studies published prior to 2000 listed a history of growth failure among 13–33% of patients at diagnosis and 10–29% at follow-up, and studies published since 2005 of unselected patients with CD reported growth failure among 9.5% of patients at diagnosis and 6.9–27% at follow-up (5, 15–26)(Table II). The persistence of growth delay suggests against catch-up growth following initiation of treatment. The potential for growth preservation in CD was demonstrated by Lee et al, who found a large proportion of their cohort had significant delays in linear growth at the time of diagnosis of CD, with 27% of subjects having heights $<5^{th}$ percentile (19), but that adult height was overall not different from the general population (9), suggesting that lasting effects on stature may also have improved with more recent treatments.

Inter-sex differences have been noted with respect to growth, with multiple studies reporting that males have a bigger height deficit at diagnosis (10, 26, 27) and have a greater height deficit as adults (27, 28). Final height deficits may not be as severe, with one study estimated that final height was decreased by −0.48 SD for females and −1.0 SD for males (27), and 2 other studies estimated the deficit in final height to be approximately −0.25 SD (4, 9).

Bone Mineral Density

BMD may be the most concerning of all of the puberty-related co-morbidities in that recent studies have reported that 43–46% of children with CD had BMD z-scores <−1 SD at diagnosis (29, 30), and relative BMD did not improve during treatment for IBD (30)(Table III). Children with IBD have lower trabecular volumetric BMD at diagnosis. This has been demonstrated by biopsies showing slightly lower cortical thickness and lower trabecular turnover (31) and by quantitative computerized tomography (qCT) showing lower trabecular thickness but not cortical thickness (32). The effects of delayed puberty were not assessed in these studies. Given the requirement of sex steroids for normal bone mineralization, the absence of sex steroids during early adolescence is likely to worsen BMD accrual—the majority of which occurs during adolescence (33–36). Even though the low BMD in CD does not appear to contribute to an increase in fractures during childhood (31, 37), adults with CD persist with low BMD and have an increased fracture risk (38–40).

Summary of prevalence of endocrine sequelae in CD

Although clinical and laboratory data would suggest improved disease course from non-steroidal treatments for IBD, including immune modulators and biologics, it is clear that significant abnormalities in pubertal timing, linear growth, and low BMD continue to be noted, particularly at presentation of CD, prior to treatment initiation, though there also appears to be a lack of significant catch-up growth during childhood years. These continued endocrine abnormalities underscore a need for vigilance in following these processes in children with CD—with particular attention to addressing potential mechanisms behind these abnormalities.

Mechanism

The etiology of the endocrine sequelae of pediatric CD considered here share commonality in systemic inflammation and in poor weight gain. This poor weight gain is due to poor absorption of nutrients, reduced appetite and reduced protein and caloric intake. Resting energy expenditure may not be reduced in conjunction with reduced body mass index as would normally be expected (41). Weight gain, degree of adiposity and levels of leptin are all known factors important in gonadotropic regulation in females, providing a likely link between low body fat and pubertal delay (2). Among girls with CD, gonadotropin function has been linked to body weight (42) and basic science models of CD reveal that pair-fed animals (with similar levels of leptin as diseased animals) have pubertal delay following calorie limitation alone (43–45).

Nevertheless, disease activity has also been linked to further delays in CD raising potential for effects due to other disease factors (2, 13). One potential source is systemic inflammation. Systemic inflammatory cytokines exert negative effects on gonadotropic regulation, as supported by effects of inflammation on LH regulation (46) and by the pubertal delays beyond that seen from low body weight alone in basic models (43–45). In an animal model of IBD, treatment with anti-inflammatory medication (anti-TNF-α) resulted in a partial normalization of puberty (47). This effect has not yet been demonstrated in clinical studies. It is notable that patients with colon-only CD or UC do not typically have linear growth delay, despite similar or higher levels of systemic inflammation to patients with small bowel CD who do have linear growth delay (5). Whether this is due to differences in nutritional status, or the quality of the inflammation and its effect on growth, is not known. Additionally, the groups with extensive colonic involvement may be more likely to present to medical attention earlier points in their disease course, lessening the pubertal delay.

Linear growth is also affected by nutritional deficits and systemic inflammation (48–51). At least some of the poor growth velocity is due to the effect of inflammation on IGF-1 expression from the liver (52), though effects at the growth plate may also occur. Interestingly, the effect of chronic inflammatory disease on growth is more severe among boys compared with girls (10). This appears to be due in part to a differential effect of inflammation on IGF-1 levels, which are more markedly suppressed in males compared with females with CD (10). Treatment with anti-inflammatory medications such as infliximab increases levels of IGF-1 (51) and growth velocity (53) in IBD, though this treatment clearly improves weight gain as well, making it difficult to ascertain whether the growth effects are from suppression of inflammation or improvement in nutrition status. Finally, linear growth in CD can be further suppressed by treatment with glucocorticoids, which exhibit direct inhibitory effects at the level of the growth plate (54).

The effects of CD on low BMD is affected by nutritional status (55) including a decrease in absorption of vitamin D (35, 56, 57). Glucocorticoid treatment inhibits differentiation of osteoblasts and increases the ligand for the receptor activator of nuclear factor kappa B (RANKL)(58). Additionally, lower BMD in CD is linked to deficits in muscle mass, a key determinant of bone mass in children (59). Compared with controls, pediatric patients at diagnosis of CD have greater deficits in muscle mass than in BMD and these lean mass deficits correlate strongly with BMD deficits (60). Glucocorticoid treatment can further exacerbate whole-body protein breakdown in CD (61). Nevertheless, low BMD in CD has been primarily linked to systemic inflammation which suppresses bone formation as evidenced by low markers of bone formation (30, 58), acting largely by inhibiting osteoblast differentiation (62). Maintenance treatment with infliximab in CD improves bone formation and BMD (58, 63).

The presence of these endocrine co-morbidities in individual patients should prompt consideration of current treatment regimen as well as a broad differential for other causes of these issues, particularly in a child whose CD appears well-controlled. Deficits in BMD are particularly common and require adequate attention for all children and adolescents with CD.

Prevention and treatment of endocrine co-morbidities

Efforts at prevention and treatment of delayed puberty and other endocrine sequelae in pediatric IBD require a team approach with the primary treatment team. This is particularly true in understanding the difficulties in inducing disease remission. The first line treatment for endocrine sequelae in CD should always be adequate nutrition and optimal treatment of the underlying CD. If the primary team has been delaying an escalation of treatment such as maintenance infliximab, significant endocrine sequelae may help to trigger these interventions. Similarly, if high-dose glucocorticoids are being used, significant endocrine sequelae may help to steer toward alternate therapy when possible. At times CD and its endocrine sequelae may be refractory to standard treatment and endocrine intervention may be warranted.

For all children with CD, attention should be paid by the primary team to the degree of pubertal delay and its effects on expected height and bone mineralization—with a low threshold for endocrine referral. In cases of significant pubertal delay, careful consideration may be given to treating with sex steroids to augment progression of puberty, weighing this consideration with any potential loss of final height as a result of treatment—particularly in the case of girls treated with estrogen. In extreme cases of short stature, treatment with growth hormone may also be judiciously considered to prevent potential permanent loss of height potential.

Treatment for delayed puberty itself requires a cautious approach because of the potential impact of pubertal timing on final height. Clearly, healthcare providers of children and adolescents with CD should follow growth closely and consider assessing bone age measurements early in the course for children who appear to have delayed puberty or growth failure. In either sex, initiating therapy to advance puberty before usual timing of puberty for bone age (e.g. a bone age of 10 years in females and 11 years in males) could result in a shorter time frame in which to grow and a shorter final height (14). In females the use of higher doses of estradiol too early could result in rapid bone age progression and closure of epiphyses. Nevertheless, excessive pubertal delay may result in a loss of pubertal growth spurt, contributing to lower final height as well (2). Thus the decision to treat must be weighed based on these risks and potential benefits. Further benefits include improved BMD from sex-hormone mediated bone mineral content accrual and—not insignificantly—the improved quality of life of treated adolescents experiencing a timing of pubertal changes similar to their peers.

In intervening to initiate pubertal progression, boys and girls are treated with courses of sex steroids with a goal to “jump-start” puberty such that the adolescent then progresses to a more advanced Tanner stage and subsequently produces levels of sex steroids appropriate for his/her Tanner stage. Males are typically treated with short-term courses of depot-testosterone (14). Even though gels and patches can also be offered, use of depot-testosterone avoids potential problems with topical preparations, including poor compliance and accidental transfer to female family members. This treatment course is inexpensive and safe. Subjects should be counseled to seek medical attention immediately if they experience a rare side effect of priapism. Overall, clinical experience would support that affected boys are quite satisfied with this treatment.

Girls with significant pubertal delay affecting quality of life could similarly be treated with estradiol, though this should be weighed more heavily against loss of height potential (2). In addition, there are epidemiological data suggesting that estradiol may exert a pro-inflammatory effect (64), theoretically worsening disease severity. Use of lower dose preparations of transdermal 17β estradiol (e.g. 0.025 mg/d) can be used initially for the first 9–12 months to induce puberty at a more physiological pace, providing secondary sexual characteristics that may be desired by the adolescent and modest effects on growth without overly-rapid advancement of bone age (14). In the setting of continued poor disease course, longer treatments with sex steroids may be necessary but again this must be weighed against risks regarding disease severity.

Regarding the effects of sex hormones on linear growth, non-aromatizable androgens such as oxandrolone at a dose of 2.5 mg daily have also been reported to be safe and effective at stimulating growth in boys and girls with cystic fibrosis (also involving a mixture of nutritional deficiencies and intermittent systemic inflammation) over time frames of 1–3 years but have not been reported in CD (65).

Human growth hormone has also been widely investigated in these settings and should be discussed in more detail as a separate discussion. Overall, its use in these settings does not meet FDA approval, though for children who have persistent growth failure raising alarm that they will not achieve a height in the normal range, growth hormone is effective in increasing growth velocity (66, 67). These needs should be balanced by other considerations including underlying therapy and the high cost of growth hormone treatment (68). Recent data showing modest adult height decrements compared with individuals without CD would suggest a degree of catch-up-growth over time without growth hormone treatment in the majority of patients (4, 9). The authors of this review begin considering its use in only significant growth delays where the final height potential appears significantly compromised.

As a group children with CD have lower BMD than the general pediatric population and have high rates of vitamin D insufficiency (35, 56, 57). Optimization of vitamin D and calcium delivery is advisable as this may theoretically help decrease deficits in BMD—though it should be noted that treatment with vitamin D has not been shown to improve BMD in CD (69). The North American Society of Pediatric Gastroenterology Hepatology and Nutrition recommends yearly screening of vitamin D (in the spring) and treating levels <20 with courses such as 50,000 IU vitamin D /week x 6 weeks (70, 71).

Multiple barriers may make application of these issues difficult, including assessing the severity of CD and weighing normal variation in processes like pubertal timing with effects due to CD. Close monitoring of disease symptomatology and testing of intestinal inflammation via measurement of fecal calprotectin may assist in diagnosis of occult increases in disease activity (71). Additional steps targeting puberty and growth can be added should disease severity and endocrine sequelae persist despite escalation in CD-specific treatment.

Conclusions

In the care of children with CD, it remains important for primary teams to follow pubertal maturation thoughtfully, given the related issues of growth and bone density. Although the degree of pubertal delay appears to be less severe in the advent of current treatments, there remains a subset of affected children. These children and adolescents may benefit from cautious assistance with puberty initiation at a proper developmental stage. Because of

existing deficits in BMD in these diseases—further exacerbated by delays in sex hormone exposure—attention to vitamin D therapy is more widely needed.

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Table 1

Data regarding timing of pubertal events or skeletal maturation in children and adolescents with Crohn's disease.

	Assessment of pubertal delay	Crohn's disease	Controls
Menarche			
Ferguson et al (6), 1994	Percent with menarche ≥16 years old	73%	0% (UC patients)
Gupta et al (11), 2012	Age at menarche	13.9	12.0
Breast development			
Brain et al (7), 1994	Age at Tanner 2 breast development	12.6 (includes UC patients)	11.1
Testicular enlargement			
Brain et al (7), 1994	Age at 4 cc testicular volume	13.2	12.4
Pubertal growth spurt			
Mason et al (8), 2011	Age at initiation of growth spurt, girls	12.8	12.2
	Age at initiation of growth spurt, girls	14.5	13.7
Bone age delay			
Hood et al (9), 2011	Bone age delay	1.16 year delay	(compared to bone age standards)
Gupta et al (10), 2011	Bone age delay, years	Girls: 1.3 year delay Boys: 0.7 year delay	(compared to bone age standards)

Table 2

Prevalence of growth failure in pediatric Crohn's disease at diagnosis and follow-up.

	Criteria for assessing growth failure	Growth failure at diagnosis	Growth failure at follow-up
Gryboski et al (16), 1978	Ht <3rd %tile	33%	21%
Puntis (24), 1984	Ht and wt <3rd %tile	31%	15%
Barton et al (14), 1990	Ht <3rd %tile	28%	22%
Motil et al (21), 1993	Ht <5th %tile	NA	23%
Gryboski et al (15), 1994	<−1 SD in Ht %tile	45%	10%
Langholz et al (17), 1997	Ht and Wt <5th %tile	13%	26%
Mamula et al (19), 2002	Ht <5th %tile	N/A	29%
Pozler (23), 2006	Ht z score <1.5	N/A	15%
Mesker et al (20), 2009	Ht <5th %tile	9.5%	16.3%
Pfefferkorn et al (22), 2009	Ht <3rd %tile	10%	6.5%
Lee et al (18), 2010	Ht <5th %tile	NA	27%
Vasseur et al (25), 2010	Ht z score	9.5%	6.9%

NA = not available. (Adapted from Abraham et al. J Clin Gastroenterology 2012 46:581–589).

Table 3

Prevalence of low bone mineral density among children and adolescents with CD.

	BMD measure	CD	UC	Control
Sylvester et al (29), 2007	Total body			
	<−1	43.1 (p=0.04)	38.9 (NS)	22.4
	<−2	8.6 (NS)	5.6 (NS)	0
Schmidt et al (28), 2009	Lumbar spine			
	<−1	41.4 (NS)	38.9 (NS)	28.6
	<−2	12.1 (NS)	5.6 (NS)	2.0
	Lumbar spine			
	<−1	46.7	47.0	
	<−2	26.7	24.1	

Percent of children and adolescents with CD who have BMD z-scores (by dual-energy x-ray absorptometry, DXA) that are <−1 and <−2 standard deviations below the mean, compared with those with UC and healthy controls, reported either as whole body or lumbar spine BMD. Significance is shown vs. control subjects (NS: p>0.05).