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Pubertal abnormalities in adolescents with chronic disease

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Pubertal disorders in the context of chronic disease especially in those with chronic inflammatory disorders or those requiring prolonged periods of treatment with glucocorticoid are common reasons for referral to the paediatric endocrine clinic. Disorders of puberty are also common in adolescents with disability requiring management by paediatric endocrinologists. In these adolescents, impaired skeletal development is also observed and this can be associated with fragility fractures. Chronic inflammation, glucocorticoid and sub-optimal nutrition all impact on the hypothalamic-pituitary gonadal axis, and can also impact on skeletal development locally by their effects on the growth plate and bone. Addressing pubertal disorders is important to ensure adolescents with chronic disease are matched with their peers, promote adequate bone mass accrual and linear growth. Careful discussion with primary clinicians, the young person and the family is needed when instituting endocrine therapies to address puberty and manage bone health.

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Abbreviations

11βHSD	11β hydroxysteroid dehydrogenase type
AED	Anti-epileptic drugs
BMC	Bone mineral content
BMD	Bone mineral density
CD	Crohn's disease
CF	Cystic fibrosis
CFRD	Cystic fibrosis related diabetes
CPP	Central precocious puberty
DMD	Duchenne muscular dystrophy
DXA	Dual-energy X-ray absorptiometry
FSH	Follicle-stimulating hormone
GC	Glucocorticoid
GnRH	Gonadotrophin releasing hormone
IBD	Inflammatory bowel disease
IL1	Interleukin 1
IL6	Interleukin 6
IUD	Intrauterine device
JIA	Juvenile idiopathic arthritis
LH	Luteinising hormone
LHRH	Luteinising hormone releasing hormone
SDS	Standard deviation score
SLE	Systemic lupus erythematosus
TNBS	Hapten reagent 2,4,6-trinitrobenzene sulfonic acid
TNF-α	Tumour necrosis factor alpha
VF	Vertebral fracture

Introduction

Puberty is a period of rapid physical and psychological change which distinguishes a young person from an adult. Normal onset and progression through puberty are surrogate markers of general good health in a young person with a chronic disorder. Despite advancement of modern therapies for paediatric chronic diseases, abnormalities in puberty are still frequently encountered [Table 1]. Recent recognition of difficulty in maintaining adult sex hormone levels in some young people with neuromuscular disorders and cerebral palsy has further highlighted a need for vigilance with long term care [1–3]. Abnormalities of puberty in chronic disease states may present as:

(1) Delay in onset of puberty
(2) Slow or hesitant progression of puberty or pubertal arrest
(3) Absent puberty (hypogonadism)

As part of assessment and management of pubertal disorders, several factors need to be taken in account by the paediatric endocrinologist which include:

(1) Linear growth potential
(2) Bone mass accrual
(3) Psycho-social adjustment
(4) Impact of endocrine therapies on the underlying medical condition

Added to the challenges of having a chronic medical condition, delayed puberty and being physically immature compared to their peers may add to psychosocial distress in some of these adolescents.

Table 1
Overview of chronic diseases commonly associated with pubertal delay and its mechanisms.

Disease	Malnutrition	Glucocorticoid	Inflammation	Other
Gastrointestinal				
Inflammatory bowel disease	+	+	+	
Coeliac disease	+	−	+	
Rheumatological				
Juvenile idiopathic arthritis	−	+	+	
Respiratory				
Cystic fibrosis	+	+/−	+	
Chronic asthma	−	+	+	
Neuromuscular				
Duchenne muscular dystrophy	−	+	+/−	
Cerebral palsy	+	−	−	
Renal				
Chronic renal failure	+	−	+	Uraemia
Nephrotic syndrome	+ (protein loss)	+	+	
Cardiological				
Hypoxic congenital heart disease	+	−	−	Hypoxia
Onco-Haematological				
Thalassaemic major	+/−	−	−	Hypoxia; Iron deposition in gonads/pituitary
Leukaemia	+/−	+	−	Central
Late effects of cancer treatment	−	−	−	Cranial radiation, gonadal radiation, alkylating agents.
Psychiatric				
Eating disorder	+	−	−	
Strenuous exercise	+	−	−	Hypogonadotrophic hypogonadism

+ Causes pubertal delay.
− Does not cause pubertal delay.
+/− Maybe responsible for pubertal delay.

Delayed puberty in adolescents without chronic disease may be associated with increased internalising symptoms (e.g. depression, anxiety), disruptive behaviour disorder and substance use in young adulthood [4]. Abnormalities of puberty in chronic disease are often associated with poor pubertal growth, which may lead to reduction in adult height in a sub-set of these adolescents [5]. Preliminary evidence in chronic disease suggests that short stature in adolescence maybe associated with lower quality of life and perceived physical appearance scores [6,7].

Puberty in healthy adolescents lead to approximately 40–50% of bone mass accrual, mostly via increase in cortical thickness and trabecular mineralization, in parallel with increased in growth velocity [8]. Even in healthy individuals, later onset of puberty has been reported to be associated with failure to accrue optimal peak bone mass with lower bone mass in adulthood [9]. Skeletal fragility and increased risk of pathological fractures are recognised complications of chronic diseases [10,11]. Inflammatory cytokines, therapies for the underlying condition, in particular glucocorticoid or anticonvulsants; and poor nutrition all contribute to insult to the skeleton via multiple mechanisms. In adolescence, pubertal delay is another additional contributing insult to the skeleton during this crucial period and may further impair bone accrual.

This review will discuss the mechanisms underlying pubertal disorders in chronic disease and the close link between puberty and bone development. We will focus on the following chronic diseases:

(1) Conditions where persistent pubertal abnormalities maybe occur (i.e. hypogonadism) for example Duchenne muscular dystrophy (DMD) treated with prolonged high dose glucocorticoid (GC), cerebral palsy;
(2) Conditions where short term pubertal abnormalities occur; for example Crohn's disease (CD).

Delayed puberty

The onset and progression of puberty is determined by genetic and epigenetic factors, influenced by extrinsic factors such as environmental chemical, nutritional, psychological and cultural influences [12]. For a detailed up to date review of normal pubertal development in healthy adolescents, the reader is referred to a review in this issue [13].

Recent large studies showed that mean age of onset of breast development is 10.9 years in girls and mean age of testis size of 4 ml in boys is 11.6 years [14–16]. Delayed puberty is defined as the absence of signs of pubertal development, as breast development in girls and testicular volume >3 mL in boys, at an age greater 2 standard deviations later than the mean for ethnic and socioeconomic circumstance [17]. In most Western countries, this corresponds to 13 years for girls and 14 years for boys. A recent study in 1528 healthy adolescent boys in Denmark provided normative data for conversion of testes volume, genital stage and pubic hair stage to standard deviation scores (SDS) [16]. Similarly, a study in 769 healthy adolescent boys from the Netherlands provided data for conversion of testes volume on clinical examination with an orchidometer and by ultrasound measurement to SDS [15].

To address delayed puberty, assessment of pubertal status (by examination for breast stage in girls and testes volume for boys) needs to be incorporated into routine care of adolescents with chronic disease. This important aspect of medical management is increasingly recognized and incorporated into management guidelines. Six monthly pubertal assessments from the age of 9 years is now recommended as part of the updated international standards of care for boys with DMD [18] and should be included in monitoring of other chronic diseases. Self-assessment of puberty might be useful in large cohort studies [19], but is inaccurate for clinical assessment of an individual patient, and should not replace careful physical examination of puberty in those adolescents at high risk for pubertal abnormalities and specifically for pubertal arrest, a problem missed by many clinicians.

Most healthy adolescents complete pubertal development within 3–4 years from onset of puberty [20]. In some adolescents, where puberty has commenced, poor progression through puberty or pubertal arrest may result if the illness onset or severe flare happens during adolescence, resulting in slowing of pubertal growth spurt and lack of development of secondary sexual characteristics. In severe cases, pubertal regression has been reported [20]. The need for accurate and consistent reassessment of puberty, with follow-up, is therefore necessary.

Resistance to discussing and addressing puberty from some parents of adolescents with chronic conditions may relate to anxiety about issues of sexualisation especially for those with learning difficulties. In some life-limiting chronic conditions, parental denial of the natural history and progression of the condition may lead to some families wishing to keep the young person immature. Fears of potential for difficulties of menstrual management in girls with learning difficulties may be a factor associated with resistance by families and primary clinicians. Dialogue about the importance of puberty for numerous health outcomes of an adolescent with chronic ill health needs to be raised sensitively. Ignorance of benefits of maturation, both physical and psychosocial is frequently the basis for this type of concern and usually can be resolved by appropriate counselling [21].

Several disease related factors may impact on the frequency and degree of pubertal abnormalities in chronic disease. Conditions which frequently present in adolescence, like CD and rheumatic conditions like systemic lupus erythematosus (SLE), are often associated with pubertal delay in the first few years after diagnosis. Chronicity and severity of the illness contribute to disorders of puberty in adolescence for conditions that are present since early childhood. In some conditions, where the insult on growth, puberty and bone development is chronic and irreversible, like the use of glucocorticoid in boys with DMD or severe neuro-developmental disability, absent puberty associated with hypogonadism is common, but may be under-recognised. Chronicity, severity of illness and potential for improvement of the underlying condition therefore all need to be ascertained, to guide the endocrinologist to optimize management of these adolescents.

In summary, management of pubertal disorders in the young person with chronic ill health needs to be in close collaboration with the numerous clinicians managing the primary condition, the adolescent and the family.

Impact of inflammatory cytokines, prolonged use of glucocorticoid and poor nutrition on puberty and bone development

Three factors common to most chronic illnesses include: inflammatory cytokines, medications such as glucocorticoid and poor nutrition, all contribute to abnormalities in puberty, bone development and linear growth at systemic and also at local levels [22–24]. Pubertal delay in chronic ill health also leads to reduction in lean mass via cytokine activation, use of glucocorticoid and poor nutrition, which in turn may lead to poorer bone development [25]. Bone adapts to the largest force applied to it, in line with the Frost mechanostat theory [26,27]. As a result, diametric bone growth is further impaired, compounded by reduction in physical activity, often observed in adolescents with chronic conditions. For a detailed review on the impact on chronic disease, in particular the role of cytokines, glucocorticoid and nutrition on linear growth and the growth plate, the reader is referred to a recent comprehensive review on the topic [24].

Inflammatory cytokines

Chronic inflammatory conditions like CD, juvenile idiopathic arthritis (JIA) and SLE are associated with elevation of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), Interleukin (IL)-1 and IL-6, although may also be variably elevated in other conditions like DMD [28] and chronic renal insufficiency [29].

Animal studies of colitis clearly demonstrate that inflammation has a direct effect on onset of puberty. Whilst rats with restricted food intake (intake matched to those of rats with colitis) showed delayed onset and progression through puberty, puberty was further delayed in rats with hapten reagent 2,4,6-trinitrobenzene sulfonic acid (TNBS) induced colitis, highlighting the role of inflammation itself on puberty. It has long been observed that adolescents with persistently active inflammatory bowel disease (IBD) do not enter puberty despite caloric restoration [30]. Similarly, adolescents with cystic fibrosis (CF) may experience pubertal delay despite adequate nutritional status [31]. In those with CF, pubertal delay and poor growth may precede the diagnosis of cystic fibrosis related diabetes (CFRD) [32,33].

The underlying mechanism of the negative impact on puberty has been evaluated in a few experimental studies. Inflammatory cytokines have been shown to inhibit luteinizing hormone-releasing hormone (LHRH) and luteinizing hormone (LH) secretion in female rats [34–36]. IL-1 administration into the third ventricles of rats inhibits the LH surge via activation of the endogenous opioid peptide system in the hypothalamus [34]. This reduction of LH surge was also observed in studies of rats injected with lipopolysaccharide which leads to systemic inflammation [36]. In the male rat TNBS colitis model, LH and follicle stimulating hormone (FSH) levels were similar to controls but plasma concentrations of testosterone were significantly lower. These results may also suggest an impact of cytokines on decreased responsiveness of gonads to LH and FSH stimulation.

Inflammatory cytokines can also have a direct effect on bone. Experimental studies where primary cultures of rat osteoblasts and foetal rat parietal bone exposed to serum of children with CD demonstrated that osteoblast function, terminal differentiation, bone formation and matrix mineralisation were impaired [37,38]. Whilst not conventionally considered a condition associated with chronic inflammation, glucocorticoid naïve boys with DMD had raised systemic levels of IL-6 compared to healthy controls [28]. The pivotal role of cytokines, in particular IL-6, on increasing bone resorption was demonstrated by studies where calvarial bones of healthy mice exposed to serum from the *mdx* mouse model of DMD, led to greater osteoclastic activity, reversed by addition of IL-6 antibody [28]. Finally, cytokines may impact on osteoblast function by altering the 11β hydroxysteroid dehydrogenase type (11βHSD) system locally, to allow increased conversion from inactive GC (cortisone and prednisone) to their active counterparts (cortisol and prednisolone), even in the absence of exposure to systemic glucocorticoid [39,40].

In summary, experimental evidence confirms that inflammatory cytokines can have a direct effect on the hypothalamic-pituitary gonadal axis and on bone modelling during growth.

Nutrition

Sub-optimal nutrition is present in all chronic diseases. Severe nutritional deficits, especially in chronic gastro-intestinal conditions like CD, may be associated with low fat stores and therefore low leptin levels. Leptin plays an important role in regulation of the hypothalamic-pituitary-gonadal axis and pubertal development. Leptin (produced by adipocytes) acts as a signal to the brain to indicate sufficient energy for pubertal development and reproduction [41]. A reduction of fat mass and leptin synthesis suppresses gonadotrophin-releasing hormone (GnRH) and gonadotrophin (LH, FSH) release [41,42]. In the leptin deficient *ob/ob* mice, testes and ventral prostate weight are lower in males; with a lower number of follicles in the ovaries and immaturity of the uterus observed in females. Male rats with 20% reduction in food intake showed significantly lower levels of gonadotrophins and testosterone; weight of testes and seminal vesicles paralleled reduction in leptin levels [43]. However, studies in male and female mice with dextran sodium sulphate colitis demonstrated that puberty is delayed out of proportion to concurrent decrease in weight gain and leptin levels [44,45]. Whilst there is no doubt that poor nutrition, especially if chronic and severe, can impact on pubertal development, it is also possible that fat stores via leptin may act as a permissive factor that allows onset and progression through puberty only if overall conditions are favourable (eg energy and inflammatory status).

Similarly, animal studies showed that nutritional restriction impacted on bone mass. Growing rats fed on protein and/or energy deficient diet show markedly diminished bone mass at the femur, with alterations of morphometric and biomechanical measures [46]. An experiment in rats fed a diet restricted in carbohydrate intake for four weeks, whilst providing adequate protein, fat, minerals and vitamins, showed that osteocalcin levels were significantly lower compared to rats fed a non-restricted diet [47]. The impaired mechanical properties of the femur observed in rat studies of nutritional restriction showed complete reversal of longitudinal bone growth and bone parameters [48].

In summary, poor nutrition has a direct impact on puberty and bone development but may exert a greater negative impact in conjunction with underlying chronic inflammation.

Glucocorticoid

Systemically administered glucocorticoid, particularly if given over a prolonged period, can lead to delayed puberty. However, there are limited studies evaluating the underlying mechanism of glucocorticoid on the hypothalamic-pituitary gonadal axis in adolescents with chronic conditions or in animal models of glucocorticoid therapy. It is postulated that glucocorticoids impair pubertal onset and progression via inhibition centrally at the level of the hypothalamus and pituitary, although other postulated mechanisms include reduced secretion of sex steroid from the gonads or impaired end organ sensitivity to sex steroids. In rat models, glucocorticoid may directly suppress the hypothalamic-pituitary-gonadal axis [49] and influence gonadal function locally, via glucocorticoid receptors in ovary and testes [50,51]. Adolescents with IBD and delayed puberty have low or normal levels of gonadotrophins [30]. LH secretion is greatly suppressed by glucocorticoid treatment in adult women with rheumatic diseases, while decreased overnight LH pulse amplitude was observed in six out of eight boys with prednisolone-treated steroid sensitive nephrotic syndrome [52,53]. Frank primary hypogonadism in chronic inflammatory diseases is not common, although a study in older adolescents with juvenile dermatomyositis showed that FSH levels were higher than age matched controls, although still within the normal ranges, raising the possibility of an impact at the level of the gonads [54].

The impact of glucocorticoid on bone strength and bone growth is now well known. Glucocorticoid can impact on osteoblasts, osteoclasts and osteocytes via numerous mechanisms [55]. It is thought that glucocorticoid impacts upon osteoblastogenesis via suppression of bone anabolic proteins like bone morphogenetic proteins [56], osteoblast-specific factor 2 and insulin growth factor 1 [57]. Whilst osteoblasts appear to be the main target of prolonged glucocorticoid administration, an initial increase in osteoclast activity is observed and may be via increase in receptor activator of nuclear factor kappa beta ligand (RANKL) and down regulation of osteoprotegerin, the decoy receptor for RANKL [58]. Increased apoptosis of osteocytes, the mechanosensor of bone, has also been demonstrated with glucocorticoid therapy in experimental models [59]. Glucocorticoid can change the fate of osteoprogenitor stem cells, by reducing the pool of cells that can become mature osteoblasts and diverted into the adipogenic

pathway [60]. Glucocorticoid has been shown to increase bone marrow adiposity at the expense of mature osteoblasts, an observation which has been supported by increased marrow adiposity in rabbits treated with glucocorticoid [61] and in humans with Cushing Syndrome at presentation [62]. In addition, glucocorticoid can decrease intestinal calcium absorption and increase renal tubular urinary calcium expression which may lead to a negative calcium balance, resulting in mild secondary hyperparathyroidism in some subjects [63–65].

In summary, glucocorticoid can have an adverse impact on puberty and bone. However, in the clinical context of children with chronic disease, glucocorticoid use in clinical studies may also be reflective of the underlying chronic disease burden or inflammatory status.

Conditions where persistent pubertal abnormalities and hypogonadism may be present

Duchenne muscular dystrophy (DMD)

DMD is an X-linked recessive, life limiting disorder with progressive muscle weakness, associated with muscle inflammation, later degeneration, fatty infiltration and fibrosis [66]. Currently, there is no cure for boys with DMD. Prolonged use of glucocorticoid from the age of 4–5 years, as a disease modifying therapy, is recommended and now accepted as international standard of care [18]. High-dose glucocorticoid treatment, either as deflazacort (starting dose of 0.9 mg/kg/day) or prednisolone/prednisone (starting dose of 0.75 mg/kg/day) is given daily or in pulsed fashion (commonly as ten days on and ten days off, although high dose weekend regimen also used in some countries). Glucocorticoid has been shown to prolong ambulation by approximately 2 years. Longer term therapy has been shown to preserve upper limb function, preserve cardio-respiratory function and reduce need for surgical intervention of scoliosis [67]. However, prolonged use of glucocorticoid is associated with a range of adverse effects, including severe growth failure and osteoporosis, leading to fragility fractures and hypogonadism. In recent years, a new generation of adolescents and young adults are transitioned into the adult service having received over 10–15 years of glucocorticoid and continue to be maintained on glucocorticoid.

In the clinical setting, delayed puberty is a very common feature of glucocorticoid treated boys with DMD [68,69]. In our experience, absent puberty as a result of hypogonadism is likely to be universal in those maintained on high dose daily glucocorticoids in adolescence. The identification of low testosterone levels and small testes in young adults with DMD on daily glucocorticoid suggests that these individuals may have persistent hypogonadotrophic hypogonadism, necessitating lifelong treatment with hormone replacement therapy [70]. In some situations, glucocorticoid dose is reduced following loss of ambulation, especially when there are significant side effects. Currently, there is variability in prescription of glucocorticoids, especially after loss of ambulation in adolescence, as there is no robust evidence to guide practice. A small percentage of boys may discontinue glucocorticoid treatment. In those who discontinue glucocorticoid treatment, it is likely that puberty will progress.

There are still limited studies of pubertal development in DMD [Table 2] [69–74]. In twelve boys with DMD treated with deflazacort (age 14 years or older), six (50%) were prepubertal with testes volume < 4 ml on clinical examination [69]. Of the six with signs of puberty, one had only received twelve months of deflazacort and the other boy was on high dose weekend deflazacort. In four adolescents treated with alternate day GC (either deflazacort or prednisolone with mean age of 17.6 years), delayed puberty was reported in all. Three required treatment with testosterone therapy whilst one had slowly progressive spontaneous puberty [73]. Of the 48% of adolescents with DMD aged 14 years or older (who would have been treated with glucocorticoid for approximately 6–8 years) managed in Scotland who had clinical assessment of puberty, 79% had testes volume < 4 ml [71,75]. The ultimate contribution of glucocorticoid regimen (ie type of glucocorticoid, regimen and dose) on pubertal outcomes in DMD is not well documented and needs to be studied.

Poor bone accrual leading to osteoporosis in DMD occurs as a result of multiple factors, including progressive muscle weakness, prolonged use of glucocorticoid, poor linear growth and vitamin D deficiency. Fragility fractures are extremely common in glucocorticoid treated boys with DMD. In a retrospective study from Scotland, radiologically confirmed fractures were reported in 48% of the cohort, with femur fracture being the commonest long bone fracture reported. In this study, only 8% of

Table 2
Studies of delayed puberty in chronic diseases.

Duchenne muscular dystrophy (DMD):			
	Study methods	Findings	Sample size (% male)
Dooley et al., 2013 [69]	Retrospective study. Only patients on Deflazacort were included.	6/12 (50%) boys (>14 years old) treated with Deflazacort showed no signs of puberty	12 (100%)
Joseph et al., [71]	Retrospective study of boys with DMD managed in Scotland; 65% receiving glucocorticoid (GC) therapy and 25% received previous GC.	29 (32%) were >14 years old; pubertal assessment done in 14 (48%). 11 of 29 (79%) were prepubertal (testicular volume <4 mL). 5 of 11 boys were on IM testosterone and 2 on oral testosterone.	91 (100%)
Mayo et al., 2012 [72]	Prospective data collection from deflazacort treated boys in 1 centre.	All of the boys were prepubertal by the end of the treatment period.	39 (100%)
Merlini et al., 2012 [73]	Prospective open parallel-group study of alternate day low dose corticosteroids	4/4 (100%) boys treated with prednisolone had delayed puberty	4 (100%)
Rutter et al., 2012 [74]	Retrospective review of a case series of patients treated at 1 centre in the US with genetically confirmed DMD treated with daily prednisone (0.75 mg/kg) or deflazacort (0.9 mg/kg) who received growth hormone.	At mean age of 11.5 years, 97% were prepubertal at baseline and remained prepubertal at 1 year follow-up; only 1 boy had evidence of puberty at baseline and slight progression at follow-up.	39 (100%)
Wood et al., 2015 [70]	Retrospective analysis of 14 adolescents with DMD who were treated with testosterone.	Mean age of treatment was 14.5 years. 8 finished treatment after mean 3.1 years. Mean testicular volumes increased from 2.4 to 3.9 mL pre- to post-treatment. Few subjects had adult testosterone levels post treatment (mean 5.4 nmol/L).	14 (100%)
Cerebral palsy (CP):			
	Study methods	Conclusions	Sample size (% male)
Kuperminc et al., 2009 [84]	Prospective observational case −control study	Only 5 boys (aged 6−18 years old) achieved Tanner stage G3 or above Only 4 girls (aged 6 −18 years old) achieved Tanner stage G5 Spontaneous puberty was uncommon in children with CP, therefore numbers were too low to include puberty in final analysis	20 (45%)
Robertson et al., 1990 [82]	Prospective observation study of girls with neonatal encephalopathy	7 (4.3%) had early sexual maturation before the age of 8 years. 4 (10%) of the 40 girls with physical disability had early sexual maturation; 3 (2.5%) of 121 girls without physical disability matured early.	161 (0%)

Table 2 (*continued*)

Uday et al., 2017 [85]	Case report of 4 children with CP	3/4 (75%) of children were referred to endocrinology for delayed puberty 4/4 (100%) of children had gonadotrophin deficiency (low FSH and low LH)	4 (50%)
Worley et al., 2002 [83]	Multicentre, cross-sectional observational study	In girls: • Age of onset of puberty was similar to the general population • Median age of menarche for white girls with CP was 14.0 years (1.3 years delay compared to general population, 95% CI: 0.7−2.3) • More girls with CP had delayed puberty compared to the general population In boys: • Age of onset was earlier than in general population • Pubertal completion was delayed compared to the general population	207 (59%)

Inflammatory bowel disease (IBD):

	Study methods	Conclusions	Sample size (% male)
Brain et al., 1994 [97]	Retrospective survey of subjects with Crohn's disease (CD) or ulcerative colitis (UC) at St Bartholomew's Hospital (UK).	Onset of puberty was delayed in both girls and boys compared to normal controls. Girls were more delayed than boys. In 11 patients post intestinal reception, median time to pubertal onset is 0.45 years.	IBD: 37 (49%)
Ferguson and Sedgwick, 1994 [98]	Retrospective review of 105 patients admitted to Scottish Hospital between 1968 and 1983 with CD or UC. Sexual development was self-reported.	11 of 28 men and 13 of 22 women with CD reported delayed sexual development during puberty. 2 of 9 men and 3 of 11 women reported delayed sexual development during puberty. Menarche is delayed in women with CD if menarche happens after disease onset.	CD: 60 (52%) UC: 27 (52%)
Mason et al., 2011 [99]	Retrospective study of 30 boys and 11 girls with CD 14 boys with UC and 12 girls with UC. Pubertal growth assessed by calculating peak height velocity SDS and age at peak height velocity (PHV).	Age of PHV was delayed by a median of 0.45 years ($p = 0.004$) in boys with CD an 0.83 ($p = 0.06$) years in girls with CD compared to the normal population.	CD: 41 (73%) UC: 26 (54%)
Mason et al., 2011 [100]	Retrospective study of 8 boys with IBD undergoing testosterone therapy for pubertal induction	Pubertal induction using Sustanon 50 mg monthly or Andropatch 2.5/5 mg daily. 7 boys showed advanced pubertal status 6 boys had a height velocity increase of >50% C-reactive protein negatively associated with height velocity ($r = -0.786$, $p = 0.021$).	CD: 7 Indeterminate colitis: 1

(*continued on next page*)

Table 2 (*continued*)

Mason et al., 2015 [6]	Prospective study over 12 months in adolescents with IBD, measuring anthropometry, biochemical markers of growth and puberty, and assessment of quality of life	Median difference between chronological and bone age was 0.3 years (−2.5 to 3.0). Pubertal examination was not delayed. 2 adolescents (1 female and 1 male) with CD did not enter Tanner stage IV by the age 97% of the normal population would have been expected to enter this stage. Median urinary LH and FSH were similar to sex and puberty matched controls.	Total 63 (78%) CD: 45 (51%) UC/IBD unclassified: 18 (67%)
Wong et al 2010. [101],	Retrospective review of IBD patients who had investigation of the GH/IGF1 axis.	All children <12 years old prepubertal (n = 8), 7 (35%) of those >12 years of were Tanner stage 1, 7 (35%) were Tanner stage 2, 6 (30%) were Tanner stage 3.	28 (82% male) CD: 25 IBD: 3

GC, Glucocorticoid; DMD, Duchenne muscular dystrophy; mg, Milligrams; mL, Millilitres; CD, Crohn's disease; UC, Ulcerative colitis; UK, United Kingdom; IBD, Inflammatory bowel disease; LH, Luteinising hormone; FSH, Follicle-stimulating hormone; GH, Growth hormone; IGF1, Insulin-like growth factor 1; CP, Cerebral palsy.

boys presented with painful vertebral fractures (VF), a gross under-estimation of the true prevalence of VF [71]. The identification of VF regardless of bone mineral density (BMD) on dual energy absorptiometry (DXA) scans is diagnostic of osteoporosis in the young [76]. Studies in other groups of children with chronic disease, especially those treated with glucocorticoid, where routine screening of the spine for VF is undertaken, like childhood leukaemia, inflammatory rheumatic conditions and nephrotic syndrome, report much higher frequency of VF [77–79]. In adolescence, at the time when more boys with DMD are likely to lose ambulation, hypogonadism adds to the skeletal insult.

The updated international standards of care for DMD (2018) calls for routine pubertal assessment to be performed in every boy with DMD from the age of 9 years; and for testosterone therapy to be instituted to normalize hormonal milieu if there are no signs of puberty by age 14 years [18]. In a recent study from the DMD STAR*net* database, only 1.7% of boys with DMD aged 14 years and older were on testosterone [80]. Local pathways and discussion between neuromuscular clinicians and endocrinologists are needed to implement the 2018 standards of care with regards to monitoring and management of puberty.

In summary, in boys with DMD treated with high dose daily glucocorticoid, hypogonadism is extremely common, if not universal. Together with the high fragility fracture burden, a plan for long term treatment of bone health and hypogonadism needs to be made in conjunction with the adolescent patients and adult endocrinologists, together with careful monitoring of the underlying condition.

Cerebral palsy (CP) and neurological disorders without use of GC

Cerebral palsy (CP) refers to a heterogeneous group of conditions with permanent, non-progressive central motor dysfunction affecting muscle tone, posture and movement, due to abnormalities of the developing foetal or infantile brain. Motor impairment varies in severity and is graded by the Gross Motor Function Classification System (GMFCS) levels I to V, with GMFCS level V being the most severe. Epilepsy occurs in up to 36% of children with CP, often managed by anti-epileptic drugs (AED) [81].

Several factors play a role in pubertal onset and progression in these adolescents. Chronic ill health, associated midline defects with hypothalamic pituitary axis dysfunction, poor nutrition with low fat mass and the use of inhaled glucocorticoid for some with chronic respiratory issues are common contributing factors to delayed puberty. Pubertal disorders in CP can range from very early-onset central precocious puberty (CPP) to delayed or arrested puberty, with some differences between genders. Premature adrenarche is also common in CP, especially in those with low birth weight, neural tube defects, hydrocephalus or spina bifida, without necessarily progressing into true puberty.

Girls in particular maybe at risk of developing CPP, present in three out of 26 (12%) girls with CP [82]. Intermittent and slow progression through puberty after an initial early onset is common The North American Growth in Cerebral Palsy Project demonstrated that although girls with CP experienced thelarche at a similar age to the general population, completion of breast development and menarche occurred approximately 2 years later than the general population [83]. Whilst less frequent, this pattern of slow pubertal development has also been reported in boys with CP [83,84]. Studies with puberty outcomes in adolescents with CP are included in Table 2 [82–85].

The reason for delayed puberty or hypogonadism in the context of CP may be due to damage to the hypothalamus and pituitary as a result of mid-line brain abnormalities (for example septo-optic dysplasia) or traumatic brain injury at the time of birth or as a result of central nervous system infection. Assessment of other pituitary hormone deficiencies is therefore crucial in an adolescent with CP and delayed puberty, as hypogonadotrophic hypogonadism as part of hypopituitarism is possible [85]. A recent review of the endocrine consequences of adolescents with disabilities discussed these issues in detail and included practical management, with particular reference to issues relevant to this population [86].

Immobility, use of AED and poor nutrition plus vitamin D deficiency, especially in those who are not gastrostomy fed, all contribute to sub-optimal bone accrual in children with CP [87,88]. The reduction in muscle mass in children with moderate to severe CP results in a fracture-prone, small, gracile bone with a thin cortex [89–91]. A greater severity of motor impairment, feeding difficulties, poorer growth and weight z-scores are all factors associated with lower bone mineral density [92]. AEDs such as carbamazepine, phenobarbitone and phenytoin upregulate liver enzymes and accelerate metabolism of 25-hydroxyvitamin D [92], while valproic acid may have a direct effect on osteoblast and osteoclast activity, causing increased bone turnover and breakdown [93]. Fractures are reported in as high as 12% of children with CP [1,94], with the commonest site of fracture at the femur (shaft and supracondylar region) [95]. Such fractures often occur with minimal trauma, for instance during routine care and handling, or with lack of clear-cut history, as the child may often be non-verbal. In such instances, suspicion of non-accidental injury may be raised, generating angst amongst carers or family members.

The consequences of pubertal delay on bone accrual is worst in those with the most severe physical disability ie those with GMFCS level V who are not weight bearing [91]. Management may be particularly challenging as a large proportion of affected young people also have learning difficulties. Careful discussion of the importance of addressing puberty in a timely fashion with the family is important, to alleviate concerns about worsening of seizures, fears regarding potential for sexualized behaviour, menstrual difficulties and the possibility of unwanted pregnancy in girls [21,96].

In summary, the paediatric endocrinologist may be involved with assessment and management of a range of disorders of puberty in children and adolescents with cerebral palsy and neuro-disability. Permanent hypogonadism in some of these adolescents maybe as a result of structural brain defect and requires careful evaluation for all hormone deficiencies. Pubertal induction and hormonal support, where needed, should be recommended to clinicians and families of affected children. However, management of puberty and bone health of these young adolescents needs to take into account the young person's physical and intellectual limitations, issues of concerns to the family and carers, like hygiene, sexualized behaviour and impact on the underlying condition, like seizures.

Conditions where short term pubertal abnormalities may be present

Crohn's disease (CD)

Delayed puberty is common in adolescents with chronic inflammation (eg CD and SLE) where the condition commonly presents at an age where puberty would normally commence and progress. In addition, pubertal disorders are also commonly seen in other chronic inflammatory rheumatic conditions where disease management continues to be challenging in adolescence, like severe systemic JIA and juvenile dermatomyositis (JDM). For purposes of this clinical review, we will focus on discussion in CD [Table 2] [6,97–101], a condition where risks for pubertal delay are high due to the combination of high cytokines, GC use and poor nutritional status, compounded by poor vitamin D absorption and metabolism.

CD is a chronic inflammatory condition of the gastrointestinal tract, often relapsing and remitting in nature. Inflammation in CD can be transmural and may involve any part of the gastrointestinal tract,

from oropharynx to the perianal area. Glucocorticoid is an effective treatment for acute relapse, although exclusive enteral nutrition can also be used to induce remission in mild to moderate CD, a regime used commonly in some countries as first line therapy [102–104]. Background maintenance therapy with immunomodulators (azathioprine and methotrexate) aims to reduce inflammation and prevent future acute relapse. In those with severe and widespread disease or glucocorticoid dependent CD, escalation to biological therapy such as infliximab or adalimumab is recommended, used earlier and much more frequently in the last decade [105]. In addition, the use of faecal calprotectin to optimise therapy and guide further investigations of the underlying disease using magnetic resonance imaging and repeat endoscopy allows for more aggressive disease management [106].

CD is often diagnosed in late childhood/early adolescence, although there is often a prolonged period of insidious symptoms for several years prior to diagnosis [107]. Pubertal delay and growth failure can be the initial presenting problems, in the absence of obvious gastrointestinal symptoms [108]. As the condition often presents during a period when puberty would normally commence and progress, it is not surprising that delayed puberty is frequently observed at time of diagnosis. Studies of pubertal development in CD are summarised in Table 2 [6,97–101]. Data from the mid-1990's showed that onset of breast development was delayed by 1.5 years in 75% of girls with CD [97,98], whereas testicular development was delayed by almost a year in CD [97]. Despite modern therapy, a contemporary retrospective study identified persistent pubertal delay in adolescents with CD, demonstrated by delay in age of peak height velocity [99]. A more recent prospective study including clinical evaluation of puberty by a paediatric endocrinologist, demonstrated that pubertal delay is still observed in adolescent girls. In boys, pubertal delay was not as common but poor pubertal growth spurt was observed [6].

Musculoskeletal deficits are still reported in adolescents with CD managed with modern therapy. A study in a cohort of children with inflammatory bowel disease including 35% of CD identified that VF were present in 11% of the subjects using systematic spine imaging in contrast to 3% of healthy controls. Over 80% of this cohort had received oral glucocorticoid therapy [109]. However, a recent study that included systematic spine imaging, of 73 children and adolescents with CD at diagnosis, only one subject (1.4%) had evidence of VF on imaging. This is in contrast with the frequency of VF of 7% at diagnosis of childhood inflammatory rheumatic conditions [110], highest in those with SLE, JDM and systemic JIA. Over a period of three years, although a majority in subjects did not have VF at baseline, 12.4% developed incident VF [79]. Low lean mass and muscle function associated with lower total body, lumbar spine, trabecular bone mineral density and cortical area are present in children with CD at diagnosis [111]. The low frequency of VF but identification of musculoskeletal deficits was also confirmed in a study of 70 adolescents with CD, with a mean of approximately 3 years since diagnosis [112]. Follow-up studies into young adulthood suggest that peak bone mass in CD may be impaired [113], which may increase fracture risk in adulthood.

Given the relapsing and remitting nature of CD, on the background of low-grade chronic inflammation, the insult to the hypothalamic-pituitary-gonadal axis and bone in adolescents with CD is much more difficult to predict. Impact on puberty and bone may therefore depend on severity and frequency of acute relapse. Use of anti TNF therapy with discontinuation of glucocorticoid may lead to improvement in linear growth [114,115] and progression in puberty, with activation of the hypothalamic-pituitary-gonadal axis and associated increase in sex steroids [116]. In these adolescents with delayed puberty, pubertal induction may be needed although ongoing hormone replacement therapy is not often required. Improvement but not complete normalization of trabecular BMD and cortical area was observed in paediatric CD following anti-TNF therapy [117], which may reflect ongoing mild, low grade inflammation. Persistence of musculoskeletal deficits in adolescents with CD treated with anti-TNF therapy highlights the need to target other insults on the skeleton like delayed puberty [118].

In summary, overall delayed puberty may be less common with the use of modern glucocorticoid sparing therapies in paediatric CD. However, this may still be present in a sub-group of adolescents with CD, especially those with severe or chronic low-grade inflammation. For this group management by paediatric endocrinologists is required. Persistence of musculoskeletal deficits despite modern therapy in CD may lead to a lower peak bone mass in adulthood, highlighting the need to tackle all issues which contribute to muscle-bone deficits. Addressing puberty is paramount but other lifestyle issues should also be targeted (eg physical activity).

Monitoring of puberty and bone health in chronic disease

Our suggested approach to monitoring of puberty and bone health is summarised in Fig. 1. Routine pubertal assessment should be conducted by the primary clinician, ideally from late childhood. Alongside assessment of puberty, evaluation of linear growth is important, but may be extremely challenging in adolescents with physical or learning disability and those with limb contractures or scoliosis. Alternatives may include monitoring of sitting height or recumbent length. Measurement of body segment like arm span, ulnar length to be used in prediction equations to estimate total height maybe other options. Whilst such prediction equations may be valid for estimation of height in healthy children [119], in our experience this is often inaccurate in children and adolescents with chronic conditions, as age is included in these prediction equations. These equations assume that linear growth increases in parallel with chronological age in children with chronic conditions, which is not the case in relapsing and remitting conditions and those where growth failure is progressively severe (for eg in long term use of glucocorticoid). A recent preliminary study showed that DXA total body images can be used to measure height very precisely and reliably in children with chronic disease [120]. This technique should be incorporated into standard clinical practise for monitoring height in immobile children and size correction of DXA bone parameters.

In accordance with recent guidance from the International Society for Clinical Densitometry (2013), assessment of vertebral morphometry using lateral thoracolumbar spine X-ray, should be performed as guidance for clinical diagnosis of osteoporosis in children and adolescents [76]. Lateral thoracolumbar spine imaging should be performed at baseline around the time of diagnosis and repeated every 1–2 years for boys with DMD in accordance with the updated standards of care [18]. These should also be incorporated into bone health monitoring programs of other children and adolescents with severe chronic inflammatory conditions, especially where high dose and prolonged periods of therapy with glucocorticoid is expected. To reduce radiation exposure, consideration should be given to replace lateral spine x-ray with DXA vertebral fracture assessment. Recent validation studies in children with chronic conditions showed that DXA acquired images of lateral thoracolumbar spine x-ray are just as good as standard lateral spine x-rays for assessment of VF [121,122].

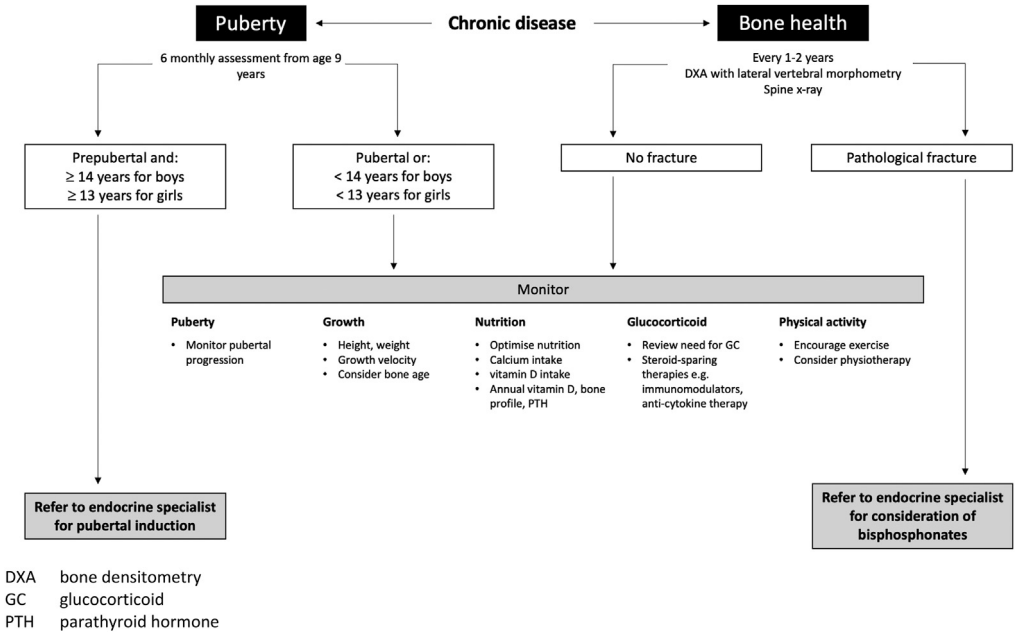

Fig. 1. Monitoring and management of puberty and bone health children with chronic diseases.

Pubertal induction in the context of chronic disease

In general, treatment with sex steroids should be considered in adolescents with delayed puberty. Sex steroids need to be introduced at a timely fashion to allow adequate development of secondary sexual characteristics but should also consider issues like potential for linear growth and the need to optimise bone mass accrual. Discussing the wishes of the adolescent is important, however dialogue with the primary clinician on the possibility of improving the underlying disease status is also crucial.

In some chronic inflammatory conditions, often, a short period of treatment (3–6 months) may be sufficient, leading to improvement in virilisation or feminization and increase in height velocity. This short period of treatment is often sufficient to prime the hypothalamus, leading to appropriate progression through puberty, but only if the underlying disease is under control with low cytokine activation. It is crucial that intervention with sex steroid therapy is introduced at an opportune time when disease is relatively well controlled and growth suppressing agent use is minimal. Optimisation of the underlying condition, improving nutrition and using the lowest possible glucocorticoid dose should be concomitant first line management.

In some conditions, especially those with unremitting underlying causes for pubertal delay or in subgroups of adolescents with chronic inflammatory conditions where persistent inflammation is present despite escalation of therapy or if frequent acute relapses are present, a longer period of sex steroid treatment or maintenance of treatment until completion of puberty should be considered. Our preferred approach in this group of adolescents is for commencement of sex steroid for induction of puberty and maintaining therapy till acquisition of adult secondary sexual characteristics and completion of linear growth. Sex steroids can then be discontinued for re-assessment of possible need for long term therapy, which may be needed in some who continue to have poorly controlled disease or who are maintained on high dose glucocorticoid.

Although pubertal induction with sex steroid is often recommended by paediatric endocrinologists for those adolescents with pubertal delay, there is a paucity of studies examining the efficacy of sex steroids for pubertal inductions in chronic conditions [Table 3] [70,100,123,124]. Treatment regimens are based on those tailored for patients with constitutional delay or hypogonadism (hypogonadotropic or hypergonadotropic) [125,126]. In boys with DMD, a retrospective study of 14 boys showed that growth response was sub-optimal after testosterone treatment for a mean for three years, although therapy was overall well tolerated [70]. In the majority of those who had re-assessment of gonadal status as young adults after discontinuing testosterone therapy, low testosterone levels and testes volumes of <5 ml point to the possibility of hypogonadotrophic hypogonadism in DMD, likely a result of long-term glucocorticoid suppression of the HPG axis. More studies of addressing puberty in adolescents with chronic disease to include outcomes of bone, body composition and quality of life are required, to understand and tailor treatment to the different needs of these adolescents.

Table 3
Studies examining the efficacy of sex steroid therapy in adolescents with chronic conditions.

	Number of patients	Age of therapy (years)	Treatment	Height velocity change (cm/y)	Others
DMD					
Wood et al 2015 [70]	14	Mean 14.5	IM sustanon, IM Nebido, oral Restandol, Tostran gel	0.45 to 3.6	Positive family feedback, 8 completed treatment only
Lim et al 2017 [124]	4	12–15	Testosterone undecanoate IM 40 mg–120 mg	NR	Stabilised vertebral fractures
CF					
Landon and Rosenfeld 1984 [123]	5	13–18	IM Testosterone enanthate 200 mg x4	2.2 to 7.2	Improvement in self image
IBD					
Mason et al 2011 [107]	8	Median 14.8	IM Sustanon 50 mg, Andropatch 2.5/5 mg	1.6 to 6.9	Low HV associated with higher CRP

IBD, Inflammatory bowel disease; CF, Cystic fibrosis; DMD, Duchenne muscular dystrophy; Cm, centimetres; Y, year; NR, not reported; HV, height velocity; Ref, reference.

Different treatment regimens are detailed in Table 4. Testosterone and oestradiol formulations commonly used include oral, intramuscular, or transdermal routes. In addition, special consideration is required for specific patient groups. For those with malabsorption or liver disease (e.g. CD, CF), transdermal or intramuscular preparations should be given to avoid issues with absorption and first-pass metabolism via the liver. Children with severe CP often require long-term AED treatment, which increases hepatic oestrogen excretion rate, necessitating higher oral oestradiol doses or transdermal preparations to achieve an adequate effect. Consideration should also be given to the use of transdermal oestradiol in an adolescent who is immobilised in a wheelchair with knees bent and a theoretical risk of thromboembolism [127]. Menstrual management in a patient with neurocognitive disabilities may be challenging for families and caregivers and adequate counselling regarding management and options of menstrual suppression is required prior to pubertal induction [21,128].

In adolescents with chronic disease and delayed puberty who are growing slowly, especially those who are short, management is challenging. In chronic disease, cytokine activation and high dose glucocorticoids lead to a degree of growth plate hormone resistance to GH [24]. Randomized trials of the use of high dose recombinant human growth hormone in chronic disease demonstrate that modest improvement in growth velocity can be achieved over a short period. For a detailed review of the use of rhGH in chronic disease, the reader is referred to two reviews on the topic summarizing all trials in chronic diseases like CF, JIA and CD [22,24].

Puberty suppression and menstrual management in the context of chronic disease

If onset of puberty is precocious (breast development < 8 years for a girl; and testes enlargement < 9 years in a boy) or relatively early (signs of puberty between 8 and 10 years) in a child with neuro-disability, pubertal suppression can be considered. However, goals and benefits of treatment need to be discussed with a family. In our experience, introducing pubertal suppression with GnRH agonist injections in some children with neuro-disability can be challenging and may generate more anxiety for the family and the young person. If GnRH analogue is used, families and other primary clinicians need to be clear that this is only a temporary strategy, as GnRH analogue should not be continued beyond 12 years. Progression through puberty is needed for adolescent bone accrual, bearing in mind that the majority of these adolescents are often non-weight bearing. In adolescents with precocious or early puberty, bone mass is generally above average when compared to children of the same age. During therapy with GnRH agonist therapy, bone mass accrual rate should then return to prepubertal levels until GnRH agonist is ceased. However, the problem for this group of children is of appendicular skeletal fragility due to lack of weight bearing and lack of muscle. Early puberty clearly has benefits on bone mass accrual, cortical thickness and thus reduces fracture risk. A balance must therefore be struck for any given individual, between need for pubertal suppression and management of bone fragility. If GnRH agonist is used in children with precocious or early puberty for the purposes of managing challenging behaviour following the onset of puberty, an exit strategy needs to be in place following discontinuation of therapy and should be discussed early.

For a family, an over-riding major concern for girls with neuro-disability who are in puberty may be fear of imminent menstruation or of concerns about menstrual hygiene [129]. If early breast development is identified, the family should be counselled that menarche will likely occur after about 2–3 years and in some instances even later. It is not uncommon for intermittent activation of the hypothalamic-pituitary-ovarian axis in girls with neuro-disability, with slow pubertal progress, bone age only minimally advanced, little uterine development on ultrasound and low gonadotropins and oestradiol levels. The family should be counselled on the possibility of oestrogen withdrawal bleeds, often misinterpreted as true menstruation. If puberty is relentlessly progressive, GnRH agonist or progestogen may be utilized to delay progress.

If puberty is delayed, arrested or absent, pubertal induction will increase bone mass accrual, improve brain maturation and social interaction within the capacity of the individual and hopefully thus provide some family encouragement. The reader is referred to reviews on the subject of puberty and disability [21,86,126,128]. Families should be informed early about possible options for menstrual control and contraception, should it be needed. A progestogen bearing intrauterine device (IUD) is usually the best option as it provides 4–5 years of contraception plus amenorrhoea in 90–95% of users, without adverse effect on bone mass accrual and maintenance. Depot progestogen should only be used

Table 4
Medications used for induction of puberty.

Medication	Dose	Cautions
Boys		
Intramuscular		
Testosterone enanthate, cypionate, propionate	Short course induction: 50–100 mg monthly for 3–6 months. Repeat course of treatment after 6–12 months if required. Full induction: Start at 50 mg monthly, increase by 50 mg increments every 6–12 months until 100–150 mg, then decrease interval to every 2 weeks.	Enanthate ester has a longer duration of effect than propionate.
Testosterone undecanoate	Use of adult maintenance dose only: 750–1000 mg every 10–14 weeks	Lipid micro-embolism (very rare)
Transdermal		
Testosterone 1% gel	No literature regarding short course induction. Full induction: Start at one-third of 50 mg/5 g sachet (i.e. 10–20 mg) daily or every second day for the first year, gradually increasing by one-third of a sachet daily every year to 2–3 full sachets daily (100–150 mg) by the 3rd year. Dose determined by measured blood level	
Oral		
Testosterone undecanoate tablets	Full induction: Start 40 mg once daily, increase by 40–80 mg every 6 months until a maximum dose of 80 mg TDS after 2–3 years.	Oral testosterone has a short half -life and must be taken with food for satisfactory absorption.
Girls		
Oral		
Ethinyl oestradiol (EE)	Start at 2 μg daily, increase every 6 months to 5, 10, and 20 μg daily (adult dose)	Liver toxicity Potentially greater risk of thromboembolism and arterial hypertension than 17β preparations
17β-oestradiol tablets	Start at 0.25–0.5 mg daily, increase by 0.5 mg every 6 months until 2 mg daily (adult dose)	Natural oestrogen, preferable to synthetic oestrogens. First pass metabolism and potentially greater thromboembolic/hypertension risk compared to transdermal preparation.
Medroxyprogesterone acetate	Used for menstrual cycle after reaching adult breast development/oestrogen dose. 5–10 mg daily for during the last 10–14 days of the menstrual cycle.	
Combined oral contraceptive pills (COCP)	Not used for pubertal induction. Can be used once reaches adult breast development and growth velocity is < 2 cm/year	Liver toxicity as per EE above. Higher thromboembolic/hypertension if higher doses of EE (preparations vary between 20 and 50 μg)
Transdermal		
17β-oestradiol patches	Start 1/8 to ¼ of 25 μg/24hr patch twice weekly, increase by ¼-1/2 patch every 6 months until adult dose of 50–100 μg/24hr.	Some patients (e.g. those with neurodevelopmental disabilities) may not tolerate patches.

Table 4 (*continued*)

Medication	Dose	Cautions
Parenteral		
Medroxyprogesterone acetate (MPA)	150 mg IM every 3 months	This can be used to inhibit menstruation, but only in combination with add-back oestrogen to prevent switching off the hypothalamic-pituitary-ovarian axis, resulting in boss loss.

TDS, three times daily; EE, Ethinyl estradiol; Mg, milligrams; μg, micrograms; COCP, combined oral contraceptive pills; MPA, Medroxyprogesterone acetate; IM, intramuscular.

in combination with oestrogen in girls with a disability as it is a powerful suppressant of the hypothalamic-pituitary-ovarian axis unopposed and thus reduces bone quality [130].

Bone health management in the context of chronic disease

Given the detrimental effects of many chronic diseases on bone health, non-pharmacological interventions are a crucial part of managing a child with chronic illness. Physical activity increases bone loading and muscle strength and is associated with improved bone mineral content (BMC) in both growing children [131]. Clinicians need to take a pro-active approach in discussing exercise as part of therapy for children with chronic diseases. For those unable to weight bear, other therapies such as high-frequency low-magnitude vibration has been shown to improve bone mass and muscle strength, although this is often not available in the clinical setting [132]. Optimizing bone health in these adolescents requires attention to nutrition, including supplemental feeds if indicated, adequacy of calcium and vitamin D intake. Judicious reduction of glucocorticoid if possible, and introduction of glucocorticoid sparing therapies are important management strategies, Bisphosphonates are the only drugs for which a substantial amount of experience is available in children, though very little is known about the effectiveness and safety of bisphosphonates in children with secondary osteoporosis. However, treatment may be considered in select patients with symptomatic osteoporosis, such as those with symptomatic VF or those with moderate VF (even if asymptomatic) especially in the context of ongoing skeletal insult, for example adolescents with DMD who will remain on glucocorticoid or other chronic diseases where the underlying disease or use of glucocorticoid cannot be minimised [133,134]. There is a paucity of clinical trials of the use of bisphosphonate as prophylactic therapy to prevent fragility fractures in childhood chronic disease and therefore its use for primary prevention is not routinely recommended. In children with CP, a systematic review of five studies concluded that bisphosphonate use increases BMD and may decrease the rate of fragility fractures, although it is unclear if this is related to therapy with bisphosphonates [135]. In the presence of fragility fractures including moderate asymptomatic VF, bisphosphonate therapy administered intravenously should be discussed. A period of 1–2 years of treatment with bisphosphonate is recommended, in conjunction with strategies to improve the underlying disease status. Pubertal induction with sex steroids may work in synergy with bisphosphonates to improve bone accrual. In adolescents with persistent insult to the skeleton and those who are on continuous glucocorticoid for their underlying disease, sex steroid therapy as induction and maintenance of puberty maybe sufficient to normalize bone accrual allowing discontinuation of bisphosphonate therapy. If there are ongoing fragility fractures, bisphosphonate maybe continued with consideration of using a lower dose of bisphosphonate or given less frequently with careful monitoring with DXA BMD [136]. Extreme care is needed if bisphosphonate is continued due to ongoing fractures to avoid the situation of creating inert bone.

Summary

Pubertal disorders are common in adolescents with chronic diseases. Monitoring of puberty by primary clinicians is crucial. Timely referral to the paediatric endocrine clinic for further assessment and management of puberty is important for improvement of bone accrual, linear growth, psychosocial well-being and quality of life for the young person and the family.

Practice Points

- Despite advancement of modern therapies for childhood chronic diseases, abnormalities in puberty are still frequently encountered.
- Abnormalities of puberty in chronic disease may present as delay in onset of puberty, slow progression through puberty, pubertal arrest or absent puberty (hypogonadism).
- In adolescents with neuro-disability, especially girls, early puberty is commonly observed although progression to hypogonadism is possible in some.
- Inflammatory cytokines, glucocorticoid treatment and poor nutrition all contribute to pubertal delay and poor bone accrual via their impact systemically on the endocrine axis or at a local level.
- Chronicity, severity of the insult and the potential for improvement of the underlying condition will guide the endocrinologist on management of pubertal delay in chronic disease.
- Timely pubertal induction in adolescents with delayed puberty should be considered, especially during an opportune time when disease is relatively well controlled.
- In pubertal girls with neuro-disability, imminent menstruation and menstrual hygiene are often major concerns for the family and appropriate counselling regarding timing of menarche, oestrogen withdrawal bleeds, and options for menstrual control and contraception are necessary.
- Bisphosphonate therapy can be considered in adolescents with fragility fractures including moderate or severe asymptomatic vertebral fractures identified from routine imaging.

Research Agenda

- The frequency of pubertal abnormalities from research studies which include clinical assessment of puberty in adolescents with chronic disease is needed.
- The impact of new therapies in chronic disease on puberty, linear growth and bone accrual should be evaluated in well-designed studies.
- The pathophysiological mechanism of delayed puberty due to glucocorticoid exposure, cytokine activation and malnutrition requires further research in translational research studies.
- Clinical trials of sex steroid therapy in adolescents with chronic disease which evaluate outcomes on puberty, bone accrual, body composition, linear growth, quality of life and the underlying disease status are required.
- The role of pharmacotherapy (e.g. bisphosphonates) in the management of osteoporosis and fragility fractures in adolescents with chronic disease with delayed puberty should be further clarified in future research.

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