Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2018 February ; 25(1): 61–66. doi:10.1097/MED.0000000000000382.

Endocrine Manifestations of Down Syndrome

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Abstract

Purpose of review: To summarize the recent developments in endocrine disorders associated with Down syndrome (DS).

Recent findings: Current research regarding bone health and DS continues to show an increased prevalence of low bone mass and highlights the importance of considering short stature when interpreting DEXA. The underlying etiology of low bone density is an area of active research and will shape treatment and preventative measures. Risk of thyroid disease is present throughout the life course in DS. New approaches and understanding of the pathophysiology and management of subclinical hypothyroidism continue to be explored. Individuals with DS are also at risk for other autoimmune conditions, with recent research revealing the role of the increased expression of the AIRE gene on 21st chromosome. Lastly, DS specific growth charts were recently published and provide a better assessment of typical development.

Summary: Recent research confirms and expands on the previously known endocrinopathies in DS and provides more insight into potential underlying mechanisms.

Keywords

Down Syndrome; Endocrine Disorders; Bone; Growth; Puberty; Thyroid

Introduction:

Down syndrome (DS) is the most common chromosomal condition, affecting 1 in every 787 liveborn babies^{1,2}. This translates to around 5,000 babies with DS born annually in the US². DS is associated with intellectual disability as well as medical issues ranging from congenital heart disease, obstructive sleep apnea, celiac disease, to endocrinopathies³. Endocrine disorders such as thyroid dysfunction, low bone mass, diabetes, short stature, infertility, and propensity to be overweight/obese are much more common than the typical

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Conflicts of interest
None

population⁴. Accurate diagnostics and effective treatments for these conditions do exist, however best practices for many of these endocrine conditions have not yet been established.

Recent research provides further understanding about the pathophysiology and management of endocrine disorders that without treatment can impact health and development. As life expectancy for individuals with DS has significantly improved, with a median age of 4 in the 1950s to 58 as of 2010¹, the medical community is challenged with continuing to optimize our medical treatments to reduce morbidity and maximize function. The following article will review the most current advances, areas of debate, and provide a thoughtful expert opinion on how best to care for patients with DS.

Bone Health:

Bone accrual is a complex process impaired by obesity, low physical activity, low calcium, low vitamin D, decreased muscle mass, decreased sun exposure, malabsorption syndromes, and anti-epileptic medication use⁴. Patients with DS have increased prevalence for these factors, increasing their risk for poor bone mineral density (BMD).

Measurement of BMD is commonly done with dual energy x-ray absorptiometry (DXA). DXA is a two-dimensional scan reporting *areal* BMD (aBMD, g/cm²), which does not account for volume of the bone. This can *underestimate* BMD in short patients. Volumetric BMD (vBMD, g/cm³) and bone mineral apparent density (BMAD, bone mineral content ÷ (area² × height)) more accurately reflect BMD in shorter patients^(4–8). Importance of evaluating vBMD or BMAD is highlighted in several studies when differences in aBMD between subjects with DS and controls *were not sustained* when comparing vBMD or BMAD^{5,7}.

There is conflicting research regarding whether BMD is reduced in individuals with DS. More recent studies have shown lower BMD in individuals with DS than in controls^{8–10}. BMAD in the femoral neck decreased with aging after early adulthood for both adults with and without DS, but the rate of change is greater in individuals with DS⁸. This may explain why other studies^{5,7} of younger adults did not find significant differences between vBMD or BMAD of adults with DS and controls. The current consensus that BMD worsens with age in adults with DS was validated by Carfi's team when they found the BMAD of adults with DS aged 40–49 was similar to that of controls aged 60–69⁸.

BMD is a measure of bone density, but is not a measure of bone quality or function. Recent studies used the Ts65Dn mouse model, which is triploid for approximately 75% of the genes located on human chromosome 21¹¹. Fowler's team found Ts65Dn mice had decreased trabecular bone volume compared with controls, which negatively impacted mechanical loading. On quantitative ultrasound heel measurements, adults with DS had better scores than controls⁵. Further studies are needed to address whether patients with DS have abnormalities of their bone microarchitecture that can predispose them to fracture. In regard to bone formation, data is conflicted on whether low BMD in DS is due to excessive bone turnover/resorption or inadequate bone formation. See Table 1 for further details.

Bone mineralization is dependent on calcium status. Similar concentrations of serum calcium and phosphorus are seen in people with DS compared with controls^{6,12,14}. Adult studies have found similar concentrations of parathyroid hormone (PTH) in patients with DS and controls^{5,12}, while studies in children have found higher levels of PTH in children with DS¹⁴. Vitamin D deficiency is prevalent in those with DS, but may only be slightly more common than in the general population¹⁴. Various interventions have attempted to improve BMD in this high-risk population, including weight bearing exercise, plyometrics, and whole body vibration training^{15–18}; all improved BMD in individuals with DS. Adding calcium and Vitamin D supplementation to an exercise program lead to greater improvement in BMD than either nutritional or activity intervention alone¹⁵. Therefore, children with DS may require higher Vitamin D supplementation^{12,13} than the recommended dietary allowance of 400IU daily.

Pharmacologic interventions to improve BMD in humans include bisphosphonates and intermittent PTH. Ts65Dn mice receiving intermittent PTH therapy improved trabecular microarchitecture and thickness and increased number of osteoblasts on bone surface¹¹. Fowler argues that bisphosphonates, which typically decrease bone turnover, would not be beneficial in patients with DS, as their research showed decreased bone formation at baseline¹¹.

With increasing life expectancy, bone health in patients with DS is an area of growing importance. DXA results of BMD should take into account the height of the patient. Differences in BMD can be seen early in life and worsen with aging. Structured activity and dietary supplementation can improve bone health. More research is needed to determine the specific mechanism of low BMD in this population as well as their fracture risk prior to recommending pharmacologic interventions.

Puberty/Fertility:

Early studies found adults with DS had higher levels of FSH and/or LH, consistent with hypergonadotropic hypogonadism^{12,19}. Despite elevated gonadotropins, actual concentrations of sex hormones were similar to controls^{12,19,20}. The current leading theory is that hypergonadotropic hypogonadism is present in infancy, progresses throughout late puberty to adulthood^{20,21}, and is due to both Sertoli and Leydig cell dysfunction in men²⁰. Despite gonadal dysfunction, puberty in patients with DS can be expected to occur on time and progress at a typical rate^{21–25}. Caregivers should be counseled on this so they can prepare children with DS for upcoming pubertal changes. Although hypogonadism is common, infertility should not be assumed. Both men and women with DS have fathered/mothered children^{22,23,26,27}, highlighting the need to have an open discussion with adolescents and adults with DS about sexuality and parenthood.

Thyroid:

Individuals with DS have higher rates of thyroid dysfunction. Abnormalities include subclinical hypothyroidism (SCH; also referred to as hyperthyrotropinemia), congenital hypothyroidism (CH), and thyroid autoimmunity such as Hashimoto's Disease (HD) or

Grave's Disease (GD). The American Academy of Pediatrics (AAP) recommends thyroid screening to be performed at birth, 6 months, and then annually beginning at 1 year old, with increased frequency in SCH³. Despite these recommendations, up to 25% of those >1 year of do not receive recommended screening²⁸. Recent research regarding thyroid disease in DS has further defined the natural history of thyroid disease and delineated the pathophysiology of SCH and autoimmune thyroid disease in this population.

To characterize the course of thyroid disease in DS, Pierce et al. performed a large retrospective study of patients with DS and found a similar prevalence, with 24% of patients affected and SCH as the most common diagnosis²⁹. Patients with DS also had a higher prevalence of congenital hypothyroidism with some cases identified on thyroid tests performed within the first 6 months of life that were not picked up on newborn screening. A recent retrospective study of 159 neonates with DS raises concern that T4-based newborn screening may miss many cases of CH³⁰. Based on these findings, Pierce et al. recommend increased screening frequency <6 months of age. While the risk of thyroid abnormalities increased 10% yearly, 13% of patients had transient dysfunction²⁹. Previous research supports this finding, as SCH is not a precursor to definite hypothyroidism³¹. Among both CH and SCH patients, trials off levothyroxine may be considered if TSH elevation remains mild (<10) and no dose escalations were required after initiating therapy.

In addressing the high frequency of TSH elevation among individuals with DS, Meyerovitch et al. analyzed the distribution of TSH and FT4 levels compared with age- and sex-matched controls³². A significant upward shift of the curve was present for TSH among patients with DS, with the 2.5 to 97.5 percentile ranging 1.3–13.1 mIU/L compared to 0.4–6.6 mIU/L in controls. They argue that this is not due to SCH, but rather to a resetting of the hypothalamic-pituitary-thyroid (HPT) axis. Based on this, Meyerovitch et al. recommend treating SCH only if TSH remains >95th percentile (>9 mIU/L based on their data). This recommendation is consistent with recent literature regarding children without DS, in whom TSH elevation may be transient and treatment is recommended if clinical symptoms or TSH elevation >10 mIU/L persists³³.

The clinical significance of SCH and whether it warrants treatment has been debated and few RCTs to date have evaluated early treatment. Van Trostenburg et al. performed a single-center, double-blinded, randomized controlled trial of early treatment with Levothyroxine among a sample of 224 neonates with DS. They reported mild improvements in motor development and height in treated infants compared to controls at 2 years³⁴, however, follow-up at 10 years of age found no developmental differences between groups³⁵. Zwaveling-Soonawala et al. recently evaluated the effect of early treatment on thyroid function at 10 years of age within this cohort³⁶. They found that early treatment with levothyroxine was associated with a mild increase in FT4 level however no change in TSH level compared to controls, potentially representing a “resetting” of the HPT axis set-point. Additionally, there was less autoimmune thyroid disease in the treated group suggesting a potential protective role for early levothyroxine treatment.

Patients with DS with TSH >10 mIU/L are more likely to have evidence of thyroid autoimmunity²⁹ and more likely to progress to overt hypothyroidism in the setting of

positive thyroid antibodies³⁷. In a multicenter retrospective trial, Aversa et al. found that autoimmune thyroid disease in DS has less female predominance, a lower age at diagnosis, less family history of thyroid disease, and increased association with other autoimmune diseases compared with the general population³⁸. HT converts to GD more frequently in DS compared to the general population³⁹. In a retrospective study of DS patients who transitioned from HT to GD, the majority had SCH at diagnosis. The course was overall mild, with clinical stability on low dose methimazole, no need for definitive treatment, and some patients experiencing remission⁴⁰.

Autoimmunity and Type 1 Diabetes:

Beyond autoimmune thyroid disease, individuals with DS carry an overall increased risk of autoimmunity. Among a population of children with autoimmune thyroid disease, Aversa et al. found that children with DS had higher rates of extrathyroidal autoimmune compared to children without DS. Most common autoimmune diagnoses were alopecia areata, vitiligo, and celiac disease⁴¹.

There is also an increased risk of Type 1 Diabetes (T1D) in individuals with DS that is often diagnosed earlier in life compared to individuals without DS. As a result, debate exists regarding the mechanism of T1D in DS. Butler et al. found no difference in pancreatic fractional beta cell area in those with DS compared to those without⁴². Two recent studies found increased rates of diabetes-associated auto-antibodies in individuals with DS compared with the typical population without the expected increase in diabetes-associated HLA genotypes^{43,44}. Abnormal expression of the AIRE gene, located on chromosome 21 (21q22.3 region) has recently been identified as a likely cause for increased autoimmunity in DS. As the AIRE gene regulates T-cell function and self-recognition, dysfunction may result in autoimmunity. Recent research confirms abnormal AIRE expression within children with DS, with Skogberg et al⁴⁵ finding increased expression in infants and Gimenez et al finding decreased AIRE expression in older children⁴⁶. These results suggest that abnormal AIRE expression on chromosome 21 may have important implications for autoimmunity in DS, although more research is needed.

Growth and Obesity:

The first DS-specific growth charts in the US were published in 1988⁴⁷, as children with DS have different growth rates compared with typically developing children. These initial growth charts noted delayed linear growth and increased overweight. With medical advances, concern arose that these initial growth charts no longer represented the current population of individuals with DS. Updated growth charts reflecting a cohort of US children with DS were released in 2015 which revealed significant improvement in weight status for children <36 months of age, who were previously underweight⁴⁸. While males 2–20 years old were taller overall than previous charts, this effect did not exist for females. Despite the increasing childhood obesity in the US over this time as well as the known increased prevalence of overweight within the population with DS, there were similar rates of overweight compared with the 1988 growth charts.

With regard to BMI, however, the DS-specific charts must be interpreted with caution due to the increased prevalence of obesity among individuals with DS⁴⁹. Compared to typically developing children with the same BMI, body composition analysis with DXA scans shows that children with DS have lower lean mass index and higher fat mass index⁵⁰. As a result, while the DS BMI charts are ideal for comparison with peers, the CDC 2000 growth chart and its 85th percentile BMI should be used to identify excess adiposity in children with DS.

Conclusions:

Down syndrome is the most common chromosomal condition. Pathophysiology of bone health this disorder is an area of active research and of growing importance as life expectancy increases. The belief that these patients are infertile is untrue, and they experience puberty at a similar rate/tempo as other children. Autoimmune disease, particularly thyroid disease, is prevalent and new research is focusing on the underlying genetic cause of autoimmunity. Obesity remains common, as does short stature, with new growth curves available for reference.

Acknowledgements

We would like to thank Drs. Lynne Levitsky and Deborah Mitchell for their guidance with this review.

Financial support and sponsorship

Dr. Whooten is supported by the NIH National Research Service Award, #5T32HD075727-05.

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Key Points:

- Specific etiology of decreased bone mineral density in this population an area of active research.
- Puberty develops typically in individuals with DS, and fertility is possible.
- Thyroid dysfunction is common in individuals with DS. Controversy remains regarding treatment of subclinical hypothyroidism given unclear benefits.
- Risk of several autoimmune conditions is increased in DS, possibly be due to altered expression of AIRE gene.
- DS specific growth charts were published in 2015. See: <http://peditools.org/>

Table 1

Comparison of Studies evaluating Bone Formation and Resorption in DS

Study	DS Group	Control Group	Marker of bone formation	Marker of bone resorption	Marker of bone turnover	Bone formation Conclusions:	Bone resorption Conclusions:
Sakadamis 2002 ¹²	11 adult men with DS (average age of 26.5)	12 controls	<i>none</i>	<i>none</i>	OHP:Cr	<i>none</i>	Bone <i>turnover</i> increased in DS
McKelvey 2012 ¹³	30 adults (men and women) with DS (age 19–52)	8 controls	P1NP	CTx	<i>none</i>	Decreased in DS	Similar in controls
Fowler 2012 ¹¹	Ts65Dn Mouse	Littermates without Ts65Dn triploidy	P1NP	TRAP 5b	<i>none</i>	Decreased in DS	Decreased in DS
Garcia-Hoyos 2017 ⁵	75 adults over 18 years (men and women)	76 controls	P1NP	CTx	<i>none</i>	Increased in DS	Similar to controls

P1NP: N-terminal propeptide of type 1 collagen

CTx: C-terminal telopeptide of type 1 collagen

OHP:Cr = hydroxyproline to creatinine ratio