Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2021 February 01; 28(1): 64–74. doi:10.1097/MED.0000000000000588.

Growth, Body Composition, and Endocrine Issues in Williams Syndrome

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Abstract

Purpose of Review: Williams syndrome (WS) is a multi-system disorder caused by a microdeletion on chromosome 7q. Throughout infancy, childhood, and adulthood, abnormalities in body composition and in multiple endocrine axes may arise for individuals with WS. This review describes the current literature regarding growth, body composition, and endocrine issues in WS with recommendations for surveillance and management by the endocrinologist, geneticist, or primary care physician.

Recent Findings: In addition to known abnormalities in stature, calcium metabolism, and thyroid function, individuals with WS are increasingly recognized to have low bone mineral density, increased body fat, and decreased muscle mass. Furthermore, recent literature identifies a high prevalence of diabetes and obesity starting in adolescence, and, less commonly, a lipedema phenotype in both males and females. Understanding the mechanisms by which haploinsufficiency of genes in the WS deleted region contributes to the multi-system phenotype of WS continues to evolve.

Summary: Multiple abnormalities in growth, body composition, and endocrine axes may manifest in individuals with WS. Individuals with WS should have routine surveillance for these issues in either the primary care setting or by an endocrinologist or geneticist.

Keywords

Williams syndrome; Williams-Beuren syndrome; lipedema

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Conflicts of Interest: No authors have any relevant conflicts of interest.

Introduction

Williams syndrome (WS), also referred to as Williams-Beuren syndrome, is familiar to most endocrinologists and pediatricians because the disorder was initially linked to infantile hypercalcemia. Sixty years later we appreciate that WS is a multi-system disorder. It has the potential to involve nearly any organ system and, furthermore, numerous endocrine abnormalities are now well-documented (1). And, while “hypercalcemia” continues to trigger consideration of the diagnosis of WS, it is less frequently a problem of clinical significance than several other endocrine disturbances that occur throughout the lifespan.

The estimated prevalence of WS is ~1/10,000. It occurs world-wide without racial or ethnic predilection, and both males and females are affected. The age of diagnosis is variable and depends on the constellation of features in a given individual, but the diagnosis is most often made during young childhood (2**). Some of the prominent non-endocrine features of WS include a distinct but subtle facial dysmorphology, cardiovascular abnormalities (notably vascular stenoses and hypertension), GI problems, dental anomalies, developmental delay/ intellectual disability, anxiety disorders, and ADHD. Certain medical problems can disappear over time (such as colic and failure to thrive) whereas others can appear during adolescence or adulthood (such as diabetes and lipedema).

In 1993, WS was identified to result from a small (1.5 – 1.8 million base pair) deletion on chromosome 7q, leading to loss of one copy of a stretch of 26–28 contiguous genes (3). This deletion almost always arises *de novo* in the affected individual (4). Since persons with WS are haploid (e.g., possess only a single copy rather than two copies) of each of these 26–28 genes, much of the WS phenotype results from altered gene dose. While the global function of most of these genes is known, the exact mechanism by which haploinsufficiency leads to individual WS features is not. However, animal models and human data implicate several of these genes in WS endocrine dysfunction. The multiple endocrine manifestations of WS, along with potential mechanisms and recommended surveillance and management, are summarized in Table 1.

Statural Growth

Infants with WS are more likely to be born small for gestational age (SGA) (5–8), and stature in children and adults with WS is generally below average (5, 6*, 7, 8*, 9). Estimates of height less than 3rd percentile in WS range from 28–41 percent (5, 9). On average, children with WS have decreased growth velocity during early childhood, with relative normalization during later childhood due to early pubertal timing (7, 10). The duration of the pubertal growth spurt is 1 year shorter than the average duration in the general population (7), and average adult height is up to 2 standard deviations less than the mid-parental height (5, 7). Mean adult height is reported at 152–154cm in girls and 159–165cm in boys (7, 11). Bone age in children with WS is delayed up to the age of 6–7 years, at which time it “catches up” due to earlier-than-average timing of pubertal development (7).

WS-specific growth charts are available from various cohorts and should be used to track statural growth in this population (7, 11–13). The 2020 recommendations from the American Academy of Pediatrics suggest the use of growth charts published by the Greenwood

Genetic Center in 1988; these data, however, were collected before identification of the genetic deletion causing WS (2**). Alternatively, Martin and colleagues more recently have published growth charts based on a British cohort of 169 children who underwent 861 total measurements, all of whom had genetic testing to confirm the diagnosis of WS (11). Height velocity charts have also been published based on a large cohort of children with WS in Germany (7).

Children with WS are generally thought to have normal function of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis (9). In a cohort of 102 children, Kim et al. found normal values of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3), suggesting but not definitively confirming normal function of the GH/IGF-1 axis (9). However, two smaller cohorts have reported GH deficiency (GHD) in a minority of children with WS who underwent GH stimulation testing (5, 14). To our knowledge no pituitary abnormalities have been described in association with WS, and the use of GH stimulation testing is likely accompanied by a relatively high rate of false positives as it is in the general population (15). Thus, it remains unclear whether some children with WS may have true dysfunction of the GH/IGF-1 axis. Nonetheless, recombinant human GH therapy is used in children with WS who carry a diagnosis of GHD or SGA without catch-up growth, and GH therapy is reported to improve growth velocity in this population though large studies on final height are lacking (5, 16).

Body Composition, Obesity, and Lipedema Phenotype

Infants and young children with WS grow along lower percentiles for body weight, with generally reduced fat mass and, less commonly, failure to thrive (8*, 9, 17). As individuals with WS age, however, multiple studies demonstrate a progressive increase in body mass index standard deviation score (9, 18, 19). Several series on adults with WS show that, starting as early as young adulthood, at least 50% are either overweight (body mass index [BMI] 25 – 29.9kg/m^2) or obese (BMI ≥ 30kg/m^2) (20, 21). There are several distinct features to weight gain in WS. When overall body mass (e.g., weight) increases, a less than expected increase in lean body mass is observed in adults with WS compared with matched healthy controls (18). Work to confirm this finding, and to determine if sarcopenia complicates WS, is underway. The distribution of body fat also appears distinct in adults with WS. Whereas many adults have a phenotype of generalized obesity, 25–30% of adults with WS have a lipedema phenotype, with accumulation of subcutaneous adipose tissue preferentially in the lower extremities (18, 19). Figure 1 demonstrates the lipedema phenotype in the lower extremities, along with a whole-body dual energy x-ray absorptiometry (DXA) scan, in a woman with WS (18). A characteristic of lipedema is “cuffing” or a “shoulder” at the ankles, with lower extremity fat accumulation that spares the feet, as shown in the figure. Lipedema in the general population almost exclusively affects females, starts after puberty, is accompanied by pain and easy bruising in the legs, and is of unknown etiology (22). Lipedema in the WS population preferentially affects females, though affected males are also observed, and is generally unaccompanied by pain and bruising in the legs. While the etiology of lipedema in WS is also unknown, one or more 26–28 genes deleted in WS is being investigated as a genetic modifier or risk factor.

Preventing weight gain is the best strategy to prevent the occurrence of obesity or lipedema. Lipedema is reported to be particularly refractory to weight loss strategies such as dieting and exercise. However, if lipedema is present then conservative management options should be the initial line of therapy; a more invasive therapy, tumescent liposuction, has not to our knowledge been performed to date on a WS individual with lipedema.

Pubertal Development

Both boys and girls with WS have onset of puberty 1–2 years earlier than the average onset in the general population (5, 7, 10). Accordingly, girls with WS have average onset of menarche 1–2 years earlier than the general population, and both sexes have earlier-than-average pubertal growth spurts. True precocious puberty is relatively uncommon, however, and is usually central in origin. In cohorts of girls with WS, the reported prevalence of CPP ranges from 2.9% to 18.3% (5, 9, 23). In these reports, precocity is most often characterized by thelarche between the ages of 7–8 years, and cases of CPP at very early ages are rarely described (5, 9, 23). Similarly, neither CNS pathology leading to CPP nor pathology leading to peripheral precocity are consistently described in WS; rather, the CPP is generally idiopathic in both girls and boys. Of note, women with WS may also have earlier age of menopause than in the general population, but there are not definitive published data on this question.

Early pubertal development in children with WS usually occurs in the context of relatively small stature, developmental delay, and personality characteristics such as high sociability and eagerness to please that may increase the risk of inappropriate encounters of a sexual nature and/or sexual abuse. For this reason, gonadotropin releasing hormone agonists (GnRHa) are commonly and effectively used to treat CPP in children with WS (9, 24), and have also been used to treat early pubertal development that does not meet the age definition for precocity. It is important to note that there is little direct evidence in WS that use of GnRHa increases final adult height, although Spielmann and colleagues report increased final height in 13 treated girls with CPP compared to 11 controls in an observational, non-randomized cohort (24). In children without true CPP, risks of decreased bone mineral accrual must be weighed against potential psychosocial and emotional benefits of delaying pubertal development. GnRHa are not likely to increase final height in children without true precocious puberty, and they should not be used for this reason in girls with WS and earlier-than-average pubertal development.

Thyroid Abnormalities

Abnormal thyroid function tests suggesting primary hypothyroidism are frequently observed in both children and adults with WS. Approximately 5–10% of patients are diagnosed with congenital hypothyroidism and are started on thyroid hormone supplementation. However, follow-up demonstrates that only 2–3% of patients with WS continue to carry the diagnosis of congenital hypothyroidism and require life-long supplementation (9). Far more common than overt hypothyroidism is subclinical hypothyroidism, characterized by mildly elevated thyroid stimulating hormone (TSH) in the context of a normal free thyroxine (fT4) or thyroxine (T4) level. Subclinical hypothyroidism is detected in 15–30% of patients and is most often but not exclusively seen during childhood. TSH elevations are generally mild

(<10 mIU/L) but can fluctuate over time (25). Anti-thyroid antibodies are usually negative. Autoimmune thyroiditis (Hashimoto's, or chronic lymphocytic thyroiditis) is a common disease in the general population; accordingly, some individuals with WS will present with this entity (26), presumably unrelated to having WS. Thyroid US in individuals with WS demonstrates a range of abnormalities in 1/3 to 2/3 of patients scanned (25, 27). Mild hypoplasia is most frequently seen and can be detected at any age but is more prevalent outside young childhood, possibly due to continued poor gland growth. The etiology of these thyroid abnormalities is not yet known, but deletion of one of the WS critical genes, BAZ1B, has been suggested (28*).

TSH and free T4 should be checked at diagnosis of WS and serially thereafter, with a recommended frequency of at least annually until age 3 years and at least every two years thereafter (2**). As in the general population, frank hypothyroidism should be treated with levothyroxine. To our knowledge, there is no evidence regarding risks or benefits of treating subclinical hypothyroidism in WS. In the absence of specific evidence, we apply general principles of management of subclinical hypothyroidism, which include erring on the side of levothyroxine administration when children are under 3 years of age with persistent elevations in TSH, and encouraging treatment at all ages when TSH is greater than 10 mIU/L. Fluctuation in TSH between normal and mildly elevated (<10 mIU/L) is quite common in individuals with WS, however, such that over the age of 3 years we usually repeat mildly abnormal thyroid function tests at a 6–12 month interval before deciding on treatment. Given the prevalence of autoimmune thyroiditis in the general population, anti-thyroid antibodies are useful at the first instance of abnormal TSH, or with a clear pattern of rising TSH beyond 10 mIU/L. Although thyroid ultrasound may show hypoplasia, this does not change management and should not be routinely performed unless a nodule is palpated.

Glucose Intolerance and Diabetes

WS has been shown to be associated with a high rate of impaired glucose regulation. Pober and colleagues (29) performed an oral glucose tolerance test (OGTT) on 28 WS adults and classified them as having normal glucose tolerance, impaired glucose tolerance (IGT) or diabetes according to American Diabetes Association (ADA) clinical practice guidelines (30). Abnormal glucose curves in the IGT or diabetes range was observed in 75% of these adults. Multiple subsequent studies have supported high rates of impaired glucose tolerance or diabetes in adults with WS (18, 20, 31–33). In aggregate, these studies suggest that, as in classical type 2 diabetes, WS subjects begin with impaired insulin sensitivity leading to IGT, followed by β-cell dysfunction and eventual progression to type 2 diabetes. However, unlike type 2 diabetes that tends to occur in later adulthood, typically in the context of overweight or obesity, it is not uncommon in WS for dysglycemia and insulin resistance to begin in adolescence and to occur even in lean individuals.

Seven studies have reported OGTT results in children and adults with WS (14, 18, 20, 29, 32–34). The proportion of WS subjects with diabetes and IGT for all 7 studies (N=154) are summarized in Table 2. The average age of WS subjects ranged from approximately 13 to 35 years. Diabetes and IGT were identified in 18% and 42%, respectively, representing one of the highest diabetes risk groups in human populations. It is noteworthy that the average

hemoglobin A1c levels across studies were frequently well within the normal range. Positive markers of islet autoimmunity have not been reported in patients with WS, indicating that the diabetes in WS is likely within the spectrum of type 2 diabetes. The high prevalence of early onset dysglycemia in WS points to a genetic basis, though underlying mechanisms remain elusive. Haploinsufficiency for genes mapping to the WS critical region are likely responsible for the higher risk of type 2 diabetes in WS. These include *STX-1A*, which encodes syntaxin-1A, involved in vesicle docking and function necessary for insulin secretion (35, 36), and *MLXIPL*, encoding a transcription factor called the MLX-interacting protein-like or carbohydrate-responsive element-binding protein, implicated in glucose metabolism and regulation of insulin sensitivity (37, 38).

Many individuals with WS who develop diabetes have no family history of diabetes, a normal body mass index, as well as normal or mildly elevated hemoglobin A1c levels (18, 29, 32). These findings suggest that widely used diagnostic tests and traditional risk factors for diabetes do not provide good discriminatory power for IGT or diabetes in WS. Though OGTT is the optimal screening test for diabetes in WS, we generally employ fasting glucose for annual screening, with OGTT if fasting glucose is abnormal. Screening should begin in adolescence. If a diagnosis of impaired glucose tolerance or diabetes is established, lifestyle modifications, including efforts at weight loss in those who are overweight or obese, should be the first line of therapy. Unfortunately, long-term natural history studies describing the progression of diabetes and risk of diabetes-related complications in individuals with WS are lacking, as are studies of specific pharmacological agents. In the authors' clinical experience, many individuals with WS and diabetes persist in a relatively mild phenotype, with 2-hour glucose in the diabetes range but only mild abnormalities in fasting glucose and HbA1c. Given the lack of data on natural history and outcomes, it is unclear if these individuals require pharmacological treatment to reduce the risk of diabetes-related complications, although metformin provides a low-risk option with pleiotropic benefits for those who can tolerate the treatment side effects. For those with fasting glucose and/or hemoglobin A1c in the diabetes range, glycemic management can take a patient-centered, shared-decision making approach with the goal of optimizing quality of life and preventing complications (39). Factors to consider include patient characteristics and co-morbidities, the side effect profile, tolerability, and cost of each agent, the complexity of the regimen, and the burden of self-directed care in the context of the patient's living situation and available support. Standard treatment algorithms in accordance with ADA clinical practice guidelines (30) can be followed, keeping these other considerations in mind. We do not routinely check islet auto-antibodies in individuals with WS and diabetes, but sending antibodies is reasonable in children or adolescents with WS who develop diabetes, or in adults with an atypical course of rapidly worsening glycemia with ketosis.

Calcium, Vitamin D, and Bone Health

Calcium and Vitamin D

Although hypercalcemia is a classically-reported finding in infants and young children with WS, significant elevations in calcium that require intervention are relatively uncommon. Infants and children more often demonstrate mild elevations in serum calcium (plasma

calcium is 0.1–0.5 mg/dL above pediatric-adjusted norms) that generally merit monitoring as opposed to intervention (40).

Appropriate infant and child reference ranges for serum calcium, which are higher than adult ranges, are not always included in laboratory reports but should be used in interpretation of pediatric calcium levels (41). In a large study of 232 individuals with WS ages 0–67 years, Sindhar et al. report that the true prevalence of calcium levels greater than the upper limit of age-corrected reference ranges in WS was 17% in infants and 26% in toddlers, numbers that are 40–50% less than the prevalence reported based on inappropriate, adult-based laboratory norms (40). In this cohort, only 5% of infants, 10% of toddlers, and 3.4% of children older than 2 years had what the authors defined as “actionable hypercalcemia”, e.g., calcium values at least 0.5mg/dL above age-appropriate norms. Hypercalciuria is also common in children with WS and hypercalcemia, and approximately 1/3 of children with WS and hypercalcemia > 0.5mg/dL above the upper limit of normal will demonstrate nephrocalcinosis (40). Hypercalcemia in infants and young children may also manifest with irritability, vomiting, or constipation, although the presentation is more commonly mild and asymptomatic.

Hypercalcemia may also occur in adolescents and adults with WS, although this is often secondary to another medical issue such as hyperparathyroidism and should be investigated as such (40). The etiology of hypercalcemia in WS remains uncertain and does not appear to be parathyroid hormone (PTH) dependent or a result of excessive 25-hydroxyvitamin D. Increased calcium absorption from the gut, related to haploinsufficiency of the general transcription factor II-I (GTF2I) gene in the WS deleted region, may play a role (42). Additionally, Williams syndrome transcription factor (WSTF) may act to increase $1,25(OH)_2D$ concentrations, which would act to increase intestinal calcium absorption (43).

Of note, 25-hydroxyvitamin D levels are often low in patients with WS, with three studies showing prevalence of vitamin D deficiency at or above that in the general population (18, 26, 44**). The traditional practice of avoiding multivitamins and vitamin D supplementation to prevent hypercalcemia may contribute to a high prevalence of vitamin D deficiency in this population. In fact, rickets has been reported in children with WS maintained on a diet low in calcium and vitamin D intended to prevent or treat hypercalcemia (40, 45).

Management of Calcium and Vitamin D

Routine surveillance for hypercalcemia includes measurement of serum calcium every 4–6 months before the age of 3 years, and every 1–2 years thereafter. In young children, providers should also have a low threshold for measuring calcium in the setting of symptoms such as irritability or constipation (2**). A calcium level ≤0.5mg/dL above the upper limit of the age-appropriate normal range can often be managed with observation and repeat laboratory surveillance every 1–3 months. Calcium levels >0.5mg/dL above the normal range and <11.5mg/dL should prompt additional lab assessment including blood urea nitrogen, creatinine, 25-hydroxyvitamin D, PTH, and urine calcium-to-creatinine ratio. Levels in this range can generally be managed with increased hydration and/or mild reduction in dietary calcium intake, along with frequent laboratory monitoring and prompt medical attention should an intercurrent illness put the child at risk for dehydration. Renal

ultrasound should be performed in children with WS who have persistent hypercalcemia. Among infants with persistent hypercalcemia, use of a low-calcium formula such as Calcilo® can be helpful, though long-term use should be avoided (40, 45). In cases of significant hypercalcemia (e.g., plasma calcium > 11.5mg/dL and/or symptomatic hypercalcemia), endocrinology and/or nephrology should be involved, and the same treatments used in the general population can be employed, including intravenous hydration (IV), diuretics, bisphosphonates, and glucocorticoids (46). Successful treatment of refractory hypercalcemia in WS with IV pamidronate therapy is described in multiple reports (46, 47). Of note, a smaller percentage of individuals with WS – estimated at roughly 3% (40) -- present with hypocalcemia, potentially unrelated to WS and instead associated with the causes of hypocalcemia in the general population.

The recent American Academy of Pediatrics guidelines suggest avoiding vitamin D supplementation in infants with WS, but dietary calcium should not be restricted except under medical supervision (2**). Given the high prevalence of vitamin D deficiency in WS and the issues with bone mineral density described below, routine surveillance of 25-hydroxyvitamin D levels in children and adults may be appropriate, with gentle vitamin D supplementation (cholecalciferol or ergocalciferol) to ensure that both calcium and vitamin D are in the normal range. Although data on appropriate vitamin D supplementation in WS are sparse, the general approach of using 50,000 international units weekly of ergocalciferol or cholecalciferol may prove excessive in individuals with WS.

Bone Health

Increasing evidence suggests reduced bone mineral density (BMD) in both males and females with WS. Cherniske et al. were the first to report this in their cohort of 20 adults, of whom 12 met World Health Organization criteria for either osteopenia or osteoporosis at the femoral neck and 10 met criteria at the lumbar spine (26). This has since been confirmed with DXA scan in two additional studies, both of which adjusted for height to account for the artifact of DXA measurement that results in lower BMD for relatively smaller-sized bones (18, 44**). Two additional cohorts have reported BMD in both children and adults, although both of these studies used phalangeal BMD estimates rather than conventional DXA scanning (19, 48). To date, there has not been a large analysis investigating whether reduced BMD in WS translates to an increase in fracture risk. Palmieri et al. reported 3 patients with vertebral fractures among their total cohort of 29 with WS, compared to 0 controls, but larger studies are required (44**).

The mechanisms of reduced BMD in WS are unclear, but confirmation of these findings in children suggests an issue with bone formation. In support of this, low osteocalcin levels are reported in two cohorts of adults (26, 44**) and one cohort of children (48). Markers of bone resorption are also reported to be high in adult cohorts, however, with increased urinary deoxypyridinoline in one cohort (48) and increased serum carboxyterminal cross-linking telopeptide of type I collagen (CTX) in another (44**). Lower serum phosphate levels compared to controls have been reported in two cohorts (44**, 48). Importantly, Palmieri et al. recently demonstrated frankly low serum phosphate in ten of 29 young adults with WS, in conjunction with reductions in renal tubular reabsorption of phosphate and

inappropriately normal fibroblast growth factor 23 (FGF23) levels (44**). From a genetic perspective, Frizzled-9 (FZD9) in the WS deleted region appears critical to osteoblast function (49). In addition to biochemical or genetic mechanisms, individuals with WS may have reduced physical activity compared to controls (44**), which may also limit bone density accrual.

Management of Bone Health

Low BMD in WS is newly appreciated, and unfortunately little evidence exists regarding optimal surveillance and management. In the absence of specific guidelines, we recommend a baseline DXA scan around the age of 30 years for female and male adults, or sooner in the presence of a vertebral fracture or pathologic long bone fracture, with follow-up scanning every 2–10 years based on results. Providers should keep in mind that individuals of smaller stature have slightly lower BMD scores on DXA due to an artifact of estimating volumetric BMD from a 2-dimensional scan. Additionally, use of DXA T-scores is not appropriate in young adults who have not yet reached peak bone density; rather, Z-scores are preferable for interpretation in teens and until mid-adulthood. In these younger age groups, DXA results should not be used to diagnose osteoporosis without an accompanying fracture history. There are no data on pharmacological therapies to improve BMD specifically in WS, and further research is needed. Weight bearing activity should be encouraged, both for bone density and metabolic benefits, in all adults with WS who can tolerate it, and referral to physical therapy may facilitate safe plans for physical activity in adults with physical limitations.

Conclusion

Williams syndrome has multiple endocrine manifestations that require monitoring. Although many of these are mild and can be observed without treatment, providers should be aware of best practices for managing endocrine abnormalities that may arise. Additionally, providers should counsel teens regarding the possibility of glucose intolerance and developing overweight or obesity, as well as strongly encourage a routine of regular physical activity in all individuals with WS who do not have a medical contraindication to activity. Further research is needed regarding optimal treatments for diabetes and low bone density in WS.

Acknowledgements:

We thank the many individuals with WS and their families who have entrusted us with their care in clinical and research settings and have shown incredible commitment to clinical research efforts.

Financial Support: Supported in part by P30 DK040561 to T.L.S. and grants from the Williams Syndrome Association, the Lipedema Foundation, and the George Cup to B.R.P.

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Key Points

- Routine surveillance of serum calcium and thyroid function tests are recommended in infants, children, and adults with WS.
- On average, pubertal development in WS is 1–2 years earlier than in the general population; parents should be counseled regarding this, and use of GnRH analog is appropriate in children with true precocious puberty and may be considered in children with early puberty, weighing possible risks to bone health against possible benefits.
- A large percentage of adolescents and adults with WS will develop overweight or obesity, and 25–30% will develop a lipedema phenotype characterized by abnormal subcutaneous adipose tissue deposition in the lower and/or upper extremities.
- Adolescents and adult with WS have a high prevalence of glucose intolerance or diabetes, even in the absence of overweight or obesity, and require annual surveillance of fasting glucose with oral glucose tolerance test if fasting glucose is abnormal.
- Bone mineral density appears lower in children and adults with WS, and engagement in routine physical activity is a critical recommendation both to support bone health and to prevent dysglycemia.

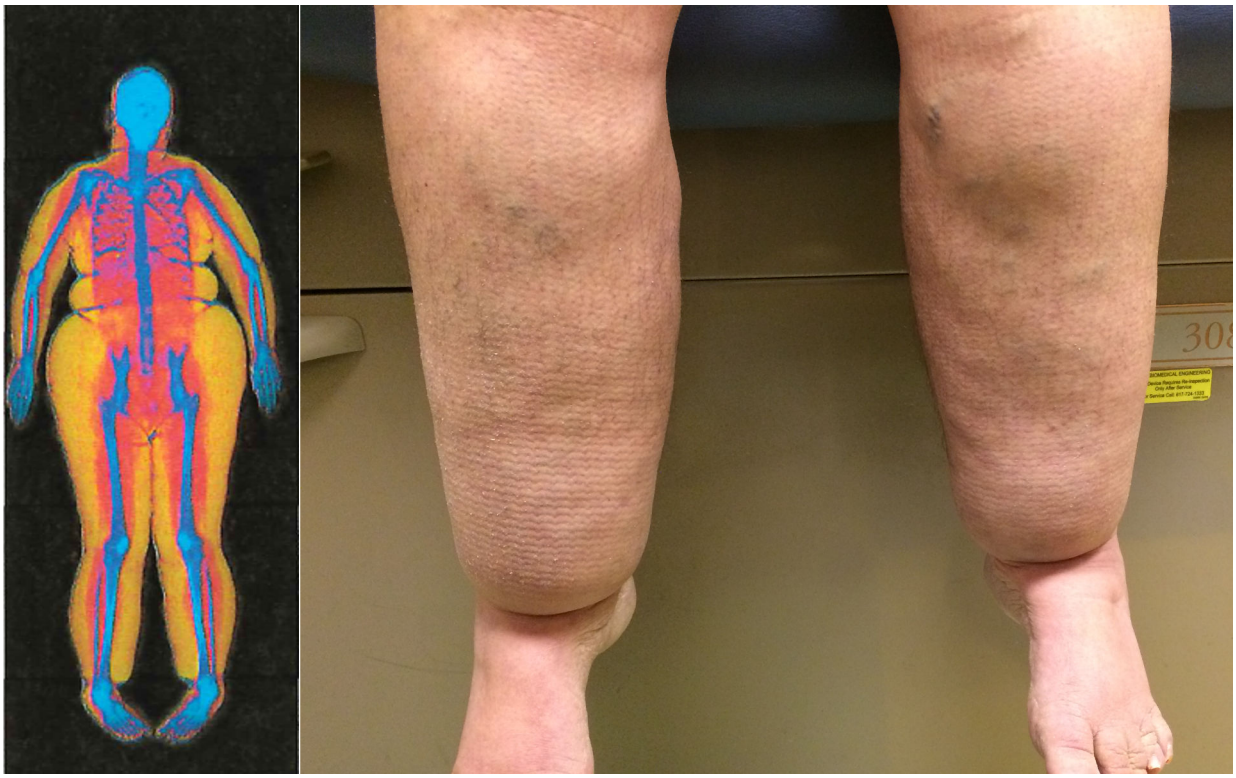

Figure 1:
Lipedema phenotype in an adult woman with WS. Left panel shows whole body dual-energy x-ray absorptiometry (DXA) scan, with yellow indicating fat mass, red indicating lean mass, and blue indicating bone mass. Right panel shows clinical photograph while seated. In both the DXA scan and the photograph, characteristic “cuffing” of subcutaneous fat is seen at the ankles, with the feet spared from fat accumulation. Reprinted with permission from Shaikh et al. (18); copyright John Wiley & Sons Ltd.

Table 1:

Summary of Endocrine Issues in WS and Recommendations for Surveillance and Management

Endocrine Issue	Presentation	Possible Mechanisms and Implicated Gene(s)	Recommendations for Clinical Management
Reduced statural growth	• Increased prevalence of SGA and/or intrauterine growth restriction (IUGR) in newborns with WS • Reduced growth velocity in early childhood • Attenuated pubertal growth spurt • Significantly reduced final adult height compared to mid-parental height in both males and females	• Likely multifactorial, including genetic causes as well as feeding difficulties often seen in infancy and early childhood	*Surveillance* • Monitor growth on WS-specific growth curve (11, 13). • Although decreased growth velocity is characteristic of young children with WS, it merits comprehensive evaluation when substantially decreased and/or when children are crossing percentiles downward on the WS growth charts. This should include evaluation of thyroid function, the GH/IGF-1 axis, and the possibility of celiac disease. *Management* • Recombinant human GH treatment may be considered for children with WS who are diagnosed with GH deficiency or who were born SGA and do not demonstrate catch-up growth by the age of 2 years. Although data are limited, it appears to increase growth velocity in children with WS.
Body composition and lipedema phenotype	• Approximately half of adults with WS demonstrate overweight or obesity. • 25–30% of adults with WS demonstrate a lipedema phenotype, predominantly in females but also occurring in males. • Reduced accrual of lean mass along with adiposity gain compared to the general population; studies to characterize possible sarcopenic obesity in this population ongoing	• Genetic etiology unclear and currently under investigation • Relatively sedentary daily routines of some individuals may contribute to obesity • Haploinsufficiency of MLXIPL (ChREBP) (50), which regulates glucose and lipid metabolism, and/or ELN (51) may play a role in lipedema phenotype, but further study is required	*Surveillance* • Height and weight should be measured every 3–6 months in young children and at least annually in older children and adults. • In adolescents and adults, annual visual inspection of fat distribution to assess for lipedema phenotype. *Management* • Prevention of obesity and lipedema phenotype with recommendations for increased physical activity and optimized nutrition • Conservative management of lipedema if it occurs; consider referral to lipedema specialist
Early pubertal development	• Pubertal development 1–2 years earlier than average for both males and females, including menarche 1–2 years earlier than average • Earlier pubertal growth spurt of shorter duration than average • True precocious puberty is uncommon and is almost always central in origin	• Unknown	*Surveillance* • Assessment of breast and genital development should be performed annually starting in early childhood. • Early pubertal onset is likely to be central in origin and should be evaluated with blood sampling for LH, FSH, and the appropriate gonadal steroid (testosterone or estrogen), ideally in the morning. • Bone age may be misleading given average delay in bone age in WS prior to mid-childhood

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Endocrine Issue	Presentation	Possible Mechanisms and Implicated Gene(s)	Recommendations for Clinical Management
			Management • GnRH agonists in true CPP • In relatively early pubertal development not meeting the definition of precocity, GnRH agonists may be appropriate given developmental delay and personality characteristics that may increase the risk of sexual abuse. In this circumstance, risks of reduced bone density accrual should be considered, and treatment should not extend beyond the age of normal pubertal development.
Abnormal thyroid function	• Sub-clinical hypothyroidism 15–30% • Congenital (or overt) hypothyroidism requiring life-long supplementation <5% • Thyroid hypoplasia (typically mild) on US • Not immune mediated in vast majority	• Mechanism responsible for thyroid dysfunction unknown • Thyroid hypoplasia has been suggested to play a causal role but may be an epiphenomenon • Deletion of BAZ1B (28) implicated in hypothyroidism	*Surveillance* • Check TSH & fT4 at time of diagnosis of WS • Repeat TSH and free T4 every 6–12 months until age 3 years, every 1–2 years thereafter *Management* • Recommend sending anti-thyroid antibodies (anti-thyroid peroxidase ± anti-thyroglobulin) once if TSH elevated to evaluate for autoimmune thyroiditis • Treat frank hypothyroidism (elevated TSH and decreased free T4) with levothyroxine • Recommend treatment with levothyroxine for individuals with TSH > 10uU/mL and normal free T4, although no WS-specific data exist • For mild elevations in TSH (<10 mIU/L) with normal free T4, no data exist, and treatment decision is provider- and family-specific. Recommend a lower threshold for treatment in children < 3 years of age. In others, serial TSH and free T4 may show normalization. • For those started on levothyroxine as infants or young children who do not demonstrate requirement for increasing levothyroxine dose as they age, a trial off levothyroxine may be appropriate after age 3–6 years
Glucose intolerance and diabetes	• Abnormal glucose tolerance is present in up to 75% of adults with WS, and diabetes is present in 9–36% of adults in reported cohorts. • Diabetes in WS also occurs outside the context of overweight or obesity • Islet autoantibodies almost always negative	• Pathophysiology seems to start with insulin resistance as early as childhood, compounded by deficits in insulin secretion • STX1A (35, 36, 52) is involved in regulating insulin secretion; haploinsufficiency may contribute to decreased insulin secretion	*Surveillance* • Fasting plasma glucose annually starting in adolescence • Recommend oral glucose tolerance test if fasting plasma glucose abnormal • Hemoglobin A1c may also be used but may be less accurate in this population; recommend correlating with fasting plasma glucose in each patient before using for surveillance *Management*

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Endocrine Issue	Presentation	Possible Mechanisms and Implicated Gene(s)	Recommendations for Clinical Management
	• Frank diabetes not generally seen in children; risk period seems to begin in adolescence and young adulthood	• MLXIPL (ChREBP) (50) is a key regulator of glucose metabolism, and haploinsufficiency may contribute to hyperglycemia and/or insulin resistance	• Nutritional counseling, including referral to a registered dietitian, and increased physical activity • Minimal evidence available in literature. From personal experience (TLS and BRP), metformin effective in many patients; insulin required in a minority. • Newer agents such as glucagon-like peptide-1 agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors may be appropriate but no data exist.
Abnormal calcium metabolism	• Mild hypercalcemia in 15–30% of infants and young children; may also occur in adulthood but with lower prevalence • Significant/"actionable" hypercalcemia in smaller percent, approximately 5–10% of infants and young children and <5% of older children and adults • Hypercalciuria often seen in conjunction with hypercalcemia • Nephrocalcinosis is a common complication in children with persistent hypercalcemia and hypercalciuria • Vitamin D deficiency is common in WS • Hypocalcemia also may occur at about the same prevalence as in the general population; no WS-specific mechanisms are known	• Uncertain; known not to be PTH-dependent • Haploinsufficiency of WSTF (43) and/or GTF2I (42) may cause increased intestinal calcium absorption	*Surveillance* • Routine surveillance with serum calcium every 4–6 months until 2 years of age and every 1–2 years thereafter (2). • Spot urine calcium-to-creatinine ratio when hypercalcemia is present (2); consider sending every 1–2 years in all children and adults • Renal ultrasound if hypercalciuria is present to assess for nephrocalcinosis *Management* • If significant hypercalcemia (>0.5mg/dL above upper limit of age-appropriate normal) present, first-line therapy should be to decrease calcium in diet and ensure ample hydration. • Calcilo® formula for infants can be an adjunct in the treatment of persistent hypercalcemia or resolving significant hypercalcemia; long-term use as the sole formula for an infant should be avoided. • Consult endocrinology and/or nephrology for calcium > 11.5mg/dL and/or symptomatic hypercalcemia • For hypercalcemia requiring inpatient treatment, IV hydration, diuretics, and bisphosphonates are effective • In the absence of hypercalcemia, do NOT restrict dietary calcium or vitamin D intake
Impaired bone mineral density	• Reduced BMD in both children and adults with WS • Unclear if this translates into increased fracture risk	• Unclear mechanism, with both impaired bone formation and increased bone resorption • Haploinsufficiency of FZD9 in the WS deleted region may cause dysfunction of osteoblasts (49)	*Surveillance* • Suggest baseline DXA scan around age 30 years, in both males and females, with repeat between 2–10 years depending on results • Cautious interpretation of areal BMD (g/cm^2) from DXA in light of short stature in most adults with WS • In children and younger adults, diagnosis of "osteoporosis" depends on combination of DXA results and fracture history; not made with DXA alone

Endocrine Issue	Presentation	Possible Mechanisms and Implicated Gene(s)	Recommendations for Clinical Management
			Management • Weight-bearing physical activity for all individuals with WS if not medically contraindicated • Ensure normal serum calcium and vitamin D levels • No WS-specific data on pharmacotherapy; osteoporosis should prompt referral to endocrinologist for management according to general guidelines

Table 2:

Classification of diabetes, normal glucose tolerance, and impaired glucose tolerance by an oral glucose tolerance test in William Syndrome subjects

Study	Mean age (SD), years	Total, N	Diabetes (N, %)	IGT (N, %)	NGT** (N, %)	Mean HbA1c (SD), %-units
Pober et al. (29)	34.9 (9.7)	28	10 (36)	11 (39)	7 (25)	5.4 (0.6)
Masserini et al. (31, 32)	29.2 (5.4)	22	2 (9)	12 (54)	8 (37)	5.4 (0.4)
Stagi et al. (33)	17*	27	3 (11)	7 (26)	17 (63)	6.3 (2.8)
Takeuchi et al. (34)	9.1*	20	4 (20)	10 (50)	6 (30)	4.8*
Lunati et al. (20)	27.3 (5.6)	31	5 (16)	13 (42)	13 (42)	5.3 (0.3)
Guven (14)	13.4*	4	0	3 (75)	1 (25)	5.5%*
Shaikh et al. (18)	28.5 (7.9)	22	3 (14)	10 (45)	9 (41)	5.6 (0.3)
Total across studies	-	154	27 (18)	66 (43)	61 (40)	-

* median value

** NGT normal glucose tolerance includes impaired fasting glucose; SD: standard deviation; NGT: normal glucose tolerance; IGT: impaired glucose tolerance; HbA1c: hemoglobin A1c