

Chapter 22

Endocrine and Skeletal Disorders

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Introduction

Prospective studies evaluating the endocrine system in individuals with dyskeratosis congenita (DC) and related Telomere Biology Disorders (TBDs) remain limited. Most knowledge regarding endocrine abnormalities is based on reports from the DC/TBDs registry maintained by Dokal et al in the United Kingdom [1] and through clinical observations of the National Cancer Institute's (NCI) prospective DC/TBDs cohort study. Endocrine disorders, such as primary hypothyroidism, growth hormone deficiency (GHD), hypogonadism, or diabetes mellitus, are not common in individuals with DC/TBDs. However, abnormalities related to the skeleton are seen with higher prevalence compared with the general population. Reported abnormal skeletal findings in patients with DC/TBDs include

avascular necrosis (AVN) of the hips and shoulders [2, 3] low bone mineral density [1] and an increased risk of fracture [4]. In addition, therapies that treat hematological manifestations of DC/TBDs, such as androgens and hematopoietic cell transplantation (HCT), may themselves lead to endocrine abnormalities, as described in this chapter (see also Chapter 10, Medical Management of Bone Marrow Failure in Telomere Biology Disorders and Chapter 13, Hematopoietic Stem Cell Transplantation).

Skeletal Complications

Epidemiology and Pathophysiology

The true prevalence of skeletal complications in individuals living with DC/TBDs is uncertain. Abnormal bone density/osteoporosis was reported in 3% of 86 participants in a multinational DC/TBD registry [5]. A 2017 study at the NCI reported that 27% of a cohort of 30 participants with DC/TBDs demonstrated low areal bone mineral density (aBMD) as assessed by dual energy X-ray absorptiometry (DXA) [6]. Avascular necrosis was reported as a feature in 3% of approximately 550 published cases of DC/TBDs in 2009 [7]. Fracture data are limited to case reports and thus no reliable estimates of prevalence are available. Many individuals with DC/TBDs (~75%) also have dental abnormalities such as shortened roots or taurodontism [8].

The pathophysiology underlying the adverse effects of DC/TBDs on bone density and strength are not well understood. Mesenchymal stem cell defects have been reported in individuals with DC/TBDs [9]. The cells responsible for bone formation (osteoblasts) and for teeth root development (cementoblasts) originate from mesenchymal stem cells (MSC), and could therefore be adversely affected by a defect in MSC availability,

longevity or function. Pre-clinical data further suggest that telomerase deficiency, a defining feature of DC/TBDs, specifically diminishes MSC differentiation into osteoblasts [10]. Additionally, the longevity and the maintenance of osteogenic potential of osteoblast lineage cells appears to be dependent upon telomerase [11, 12]. Interestingly, the activity of osteoclasts (cells responsible for bone resorption) does not appear to be significantly affected by the absence of telomerase [13]. Diminished bone formation without loss of bone resorption would be expected to lead to an imbalance in bone turnover that could adversely affect bone accrual during childhood and lead to bone loss in adults [14].

AVN occurs when the blood vessels supplying bone are compromised, leading to death of bone and bone marrow supplied by those vessels [15]. This results in pain, degenerative arthritis, and decreased function of the joint, and may require early joint replacement [15, 16]. Individuals with DC/TBDs and their parents should be educated at diagnosis regarding the early signs and symptoms of hip and shoulder AVN, since early conservative (restricted weightbearing, and antiresorptive medication, for example) and orthopedic surgical (core decompression, osteotomy, bone grafting) management may reduce disability and complications. In the presence of hip or shoulder pain in patients with DC/TBDs, physicians should perform a thorough physical exam that includes assessment of pain level, range of motion, limb length, and X-ray imaging of the affected area. Physicians should have a low threshold for skeletal imaging, as well as orthopedic referral in these patients. There are some data to suggest a potential role for bisphosphonates to slow progression of AVN or ameliorate AVN related pain in other conditions [17, 18] However, the efficacy remains uncertain and has not been specifically studied in patients with DC/TBDs [19].

Clinical Management

Because of the phenotypic variability in DC/TBDs, it is difficult to make generalizations about the timing of onset and severity of skeletal complications in this disease. Likewise, there are limited observational and interventional data in individuals with

DC/TBDs to guide the clinical monitoring and treatment of these complications when they arise. Recommendations must therefore be adapted from those established for other disorders affecting bone health in children and adults.

All individuals with DC/TBDs should be queried about their fracture history, including the number, location and mechanism of fracture(s), if present. Minimally traumatic fractures (typically defined as fall from standing height or less, at no more than a walking speed) of the spine, femur, humerus are especially concerning for an underlying impairment in bone health and should prompt consideration of further evaluation [20]. Patients who have had HCT are also at higher risk and should be considered for further bone health evaluation.

The clinical evaluation in patients determined to be at greater risk for impaired bone health should include assessment of dietary intake, weight-bearing physical activity, biochemical screening, and a DXA scan. The dietary assessment should include both macro- and micronutrient intake, with special attention to calcium and vitamin D. If possible, it is helpful to have this performed by a registered dietician or clinical nutritionist. Dietary education should be provided to patients to ensure they are meeting the age- and sex-specific recommended dietary allowance (RDA) for calcium and vitamin D [21]. Calcium and vitamin D supplementation can be considered in individuals who cannot meet the RDA from dietary sources alone. Individuals should be educated on and encouraged to meet the age-specific goals for physical activity [22]. Individuals with functional limitations may benefit from a physical therapy evaluation to help devise a safe physical activity plan.

Baseline biochemical screening should include a comprehensive metabolic panel, phosphorus, and 25-hydroxy vitamin D (25-OHD), at minimum. Vitamin D supplementation should be provided to achieve and maintain a serum 25-OHD level of at least 20 ng/mL (50 nmol/L), and preferably > 30 ng/mL (75 nmol/L) in patients with bone health risk factors [23]. Cholecalciferol (vitamin D3) is generally preferred, but ergocalciferol (vitamin D2) may also be used. The vitamin D dose to achieve sufficiency

will vary individually, typical regimens might include daily cholecalciferol of 1000 IU (25 mcg) to 4000 IU (100 mcg) or weekly ergocalciferol 50,000 IU (1250 mcg). Serum 25OHD levels should be monitored at least annually by the patient's health care team, more frequently in those being treated with high doses of vitamin D for severe vitamin D deficiency.

Determination of aBMD by (DXA) is an important component of the bone health evaluation. At present, there are limited data to inform the optimal timing for attaining first DXA in individuals with DC/TBDs. Clinical criteria [16] that suggest the need for DXA include a single long-bone or vertebral fragility fracture, multiple long bone fractures of any mechanism, chronic exposure to supra-physiologic steroids (6 months or greater), prolonged hypogonadism (in an adolescent or adult), and history/planned HCT. Older individuals with DC/TBDs but without corticosteroid exposure, fracture history, or hormone deficiency may be screened and monitored according to age-specific DXA scan screening guidelines.

DXA assessment should follow standard International Society for Clinical Densitometry guidelines, which are available for children and adults (Table 1) [24]. In children, aBMD should be assessed by Z-score, which provides a comparison to expected aBMD for a given age and sex. In older adults, T-scores are used to evaluate for the degree of bone loss compared to peak bone mass. However, in the case of younger adults, Z-scores may be preferable and allow for an assessment of disease specific effects on aBMD. Well validated fracture risk assessment tools may also be used in adults.

Table 1: Recommended Approach to DXA Assessment in Patients at Risk for Impaired Bone Health

Age	Standard Scan Sites	Alternative Scan Sites	Analysis Notes
3-5 years		• AP Lumbar spine	• Z-scores
5-18 years	• AP Lumbar spine • Whole body (less head)	• Proximal femur: consider in post-pubertal adolescents • Forearm: Consider when other sites cannot be assessed due to contracture, etc	• Z-scores, adjusted for size in short or tall individuals
≥ 18 years	• AP Lumbar spine • Proximal femur	• Forearm	• Z-scores: Pre-menopausal women and men <50 years • T-scores: Post-menopausal women and men ≥50 years

Recommendations taken from ISCD official positions (revised 2019). Selection of scan site requires availability of adequate reference data to generate Z and/or T scores for population of interest and DXA manufacturer. Recommended regions of interest include “L1-L4”, lumbar spine; subtotal (total body less head), whole body; total hip and femoral neck, proximal femur; distal 1/3 radius, forearm.

There are limitations to DXA. aBMD by DXA is an estimate of true volumetric BMD and is subject to size artifact. Specifically, BMD is underestimated in patients with small bones and overestimated in those with large bones. This is especially relevant in children with short stature or pubertal delay, which can occur in patients with DC/TBDs. As a result, aBMD Z-scores should be adjusted for size in children with short or tall stature, using an appropriate methodology for the specific DXA platform on which the scan was obtained [25-27].

The indications for the initiation of anti-osteoporosis pharmacotherapy for the treatment or to prevent osteoporosis specific to DC/TBDs is uncertain. Therefore, the standard approach used in other conditions should be applied. For children, bisphosphonates are typically not started until after first clinically significant fragility fracture, with or without low BMD, in an at-risk patient with limited expectation of spontaneous recovery [28]. In adults, bone protective therapy can be considered according to approved Food and Drug Administration or other regulatory agency

indications. Choice of agent should be individualized based upon clinical scenario and an individualized assessment of potential toxicities of respective drugs.

Growth and Growth Hormone

Short stature is reported in 12% of cases in the literature and in approximately 20% of individuals in the UK DC/TBD registry of patients with DC/TBDs [1, 3] However, the NCI cohort notes that short stature is very rare in individuals with DC/TBDs, perhaps being more common in very severely affected patients. While the precise mechanism is unknown, short stature in patients with DC/TBDs is not due to growth hormone deficiency [4]. and growth hormone therapy is not recommended unless the patient is proven to be growth hormone deficient on formal testing.

Hypogonadism

A small number of severely affected males reported decreased sperm or testosterone production, or both, a condition known as primary hypogonadism [16, 29] Animal models have demonstrated that at least one of the DC-associated gene mutations may lead to testicular atrophy in males and decreased fertility in both males and females, but this has not been duplicated in human studies [30, 31]. Physicians should check morning testosterone, LH, and FSH levels in patients with suspected hypogonadism, and have an open dialogue about both the possibility and signs and symptoms of hypogonadism.

Interventions That Affect the Endocrine System

Androgen Therapy

Patients with DC/TBDs and bone marrow failure who are not candidates for HCT may be treated with androgens [32, 33] (see also Chapter 10, Medical Management of Bone

Marrow Failure in Telomere Biology Disorders). Low peripheral blood counts respond adequately enough in approximately 50-70% of patients with DC/TBDs treated with androgens to obviate the need for transfusion [1, 34, 35]. The duration of this effect varies from patient to patient.

The androgen medications most commonly used in DC/TBDs include oxymetholone and danazol. Androgen therapy in patients with DC/TBDs can affect the endocrine system in several ways, including decreasing thyroid binding globulin (TBG), inducing rapid linear growth as well as virilization, dyslipidemia, and changes in liver structure and function. Patients with DC/TBDs treated with androgens should be evaluated frequently for abnormal cholesterol, triglycerides, liver function, and undergo imaging to assess for liver adenomas (see Chapter 10) [36]. It should be noted that patients with DC/TBDs can be more sensitive to androgens than the general population, and therefore the dose should be adjusted accordingly [16]. It is important that individuals with DC/TBDs and their families be aware of possible side effects of androgen therapy before initiation of treatment [37].

Thyroid Binding Globulin

Treatment with androgens can cause a significant decrease in liver synthesis of TBG without actually resulting in a change in thyroid function [33]. Despite a low TBG level, patients with normal thyroid glands are biochemically euthyroid with a normal serum free thyroxine (T4) and thyroid stimulating hormone (TSH) levels, and thus do not experience any clinically noticeable adverse effects [37].

Growth

Androgens stimulate osteoblasts and the production of bone matrix. As a result, pre-pubertal children receiving androgen therapy can experience premature accelerated linear growth [38, 39]. Premature skeletal maturation, with fusion of epiphyseal plates and reduced final adult height has been reported, but this effect is relatively rare, especially in patients who received androgen therapy prior to pubertal development [33,

38, 40]. Pediatric patients should undergo a baseline bone age X-ray evaluation of the left hand before initiation of androgen therapy and every 12 months while undergoing androgen treatment, until reaching final adult height. Patients receiving androgen therapy should avoid simultaneous use of growth factors like G-CSF or erythropoietin, as splenic and hepatic peliosis and splenic rupture have been reported in association with concomitant combined use [35, 38, 41].

Masculinization and Behavior Changes

Androgen therapy may lead to virilization and behavior changes, including mood swings and aggression in both female and male patients [16, 33, 42]. Females receiving androgens can develop deepening of the voice and hirsutism (excessive hair growth), while males report priapism (persistent and painful erection of the penis) [33]. The likelihood of onset and degree of virilization are directly proportional to androgen dose and duration of use [38, 42].

Lipid and Liver Abnormalities

Patients with DC/TBDs receiving androgen therapy can develop dyslipidemia and impaired liver function [16, 43]. Total cholesterol, triglycerides, and LDL (low-density lipoprotein) may be elevated, while HDL (high density lipoprotein) levels may be abnormally low [33, 43]. There is no known dose-response relationship between androgens and lipid abnormalities, but cessation of androgen therapy results in a return to pre-treatment lipid levels within a few months [38]. Liver structure and function should be evaluated with imaging at baseline prior to initiation of treatment and at regular intervals during androgen therapy, as liver adenomas and carcinomas have been observed in patients on this regimen [16].

Allogeneic Hematopoietic Cell Transplantation (HCT)

HCT is the only curative treatment for bone marrow failure in DC/TBDs; however, its conditioning regimen is associated with significant toxicity (see Chapter 13,

Hematopoietic Stem Cell Transplantation) [44, 45]. With the development of new, less toxic conditioning regimens, HCT may become a more successful treatment modality for patients with DC/TBDs [46].

HCT survivors and their physicians should be aware of an increased risk of multiple endocrinopathies, including hypothyroidism, growth failure, hypogonadism, osteoporosis, adrenal dysfunction, anterior pituitary disorders, diabetes mellitus and dyslipidemia [47]. Post-HCT screening and follow-up should be tailored to the specific conditioning regimen received by each patient.

Diabetes Mellitus

HCT survivors should have routine screening for diabetes mellitus, given higher likelihood for insulin resistance compared to healthy counterparts [47-49]. Steroid use, total body irradiation, and graft versus host disease all increase the likelihood of future risk for diabetes mellitus [47]. Therefore, HCT survivors benefit from an annual screen for insulin resistance and receive pharmacotherapy if they demonstrate glucose intolerance and diabetes mellitus [47].

Hypogonadism After HCT

Patients with DC/TBDs can experience hypogonadism as a result of alkylating chemotherapy exposure with HCT [16, 29, 46]. In males, hypogonadism can be due to Sertoli cell damage and decreased sperm production, and/or Leydig cell dysfunction resulting in low testosterone production [47]. In females, HCT can result in primary ovarian insufficiency consisting of either acute ovarian failure or premature menopause [50-52]. Reduced estrogen production leads to low libido, and vaginal changes [47]. In both males and females, clinicians and patients should have pertinent discussions regarding the impact of HCT on fertility and preservation options pre-HCT such as sperm banking in males and ovarian cryopreservation, as well as post-transplant in vitro fertilization [47, 53]. Therapy for hypogonadism should be tailored to individual patient

goals, as well as to preventing and treating other complications such as bone loss and cardiometabolic impact of sex hormone deficiency [47].

Osteoporosis

As introduced above, based upon data from other hematologic disorders treated with HCT [54-56], it is likely that patients with DC/TBDs who have undergone HCT are at increased risk of developing low BMD and osteoporosis. Steroids (both corticosteroids such as prednisone, and androgens), hypogonadism, direct damage to osteoprogenitor cells, hyperthyroidism, immobility, and calcium or vitamin D deficiency, all increase the risk of osteoporosis in HCT recipients [44]. Clinical guidelines for the management of bone health following HCT for hematologic disorders have been published for both children and adults [57, 58]. Dietary intake and physical activity should be optimized as described above. Biochemical testing is recommended at least every 6 months in the first year, and then annually thereafter. DXA is recommended prior to or at least within 3 months following transplant, with a follow up scan 12-months later. The need/timing of subsequent testing is based upon clinical course, including BMD status. Annual vertebral fracture assessment by lateral spine X-ray or DXA should be performed in patients on chronic supraphysiologic glucocorticoid doses or those with back pain. High quality clinical trial data to guide the use of bone protective agents in patients following HCT are lacking. However, expert opinion guidance has been published [58].

AVN has been reported in 4-19% of allogeneic HCT patients [47]. Given the increased risk of AVN, post-transplant patients should be educated about its signs and symptoms. Physicians should have a high index of suspicion for this complication following onset of new joint or limb pain. Patients who have received total body irradiation, those who have received corticosteroids, and those of advanced age are at particularly high risk of AVN, and should be evaluated accordingly [47, 57, 58]. The treatment approach to HCT related AVN does not differ from the standard approach described above.

Adrenal Insufficiency

All patients receiving treatment with supra-physiological doses of glucocorticoids (> 7.5 mg/d) can experience suppression of the hypothalamic pituitary axis or primary adrenal insufficiency with reduced function of the adrenal gland. These can result in fatigue and weakness [47]. Adrenal insufficiency is assessed using an ACTH (adrenocorticotropic hormone) stimulation test, but providers should be aware that even treatment with low doses of steroids can result in an abnormal stimulation test result. As a result, consultation with an endocrinologist is recommended to help address concerns and direct treatment for adrenal insufficiency in DC/TBDs patients following HCT [47].

Growth Hormone Deficiency

GH deficiency can occur following fractionated doses of 12-18 Gy when given as total body irradiation in the context of HCT [59]. Growth hormone deficiency should be suspected when there is linear growth failure (height trajectory crossing to lower percentile lines) or lack of growth acceleration during puberty, after ruling out hypogonadism, hypothyroidism, inadequate nutritional intake, or excess glucocorticoid exposure. Determination of upper to lower segment ratio using sitting height or lower segment is helpful to rule out poor spinal growth after radiation [60]. Insulin-like growth factor-I (IGF-I) levels are not always low in the context of radiation-induced GH deficiency; they should not be used to screen patients at risk [61]. When GH deficiency is suspected, a referral to a pediatric endocrinologist is indicated for further evaluation with stimulation testing.

Replacement with recombinant human GH (hGH) results in significant improvement in height in children with confirmed GH deficiency, but patients may not achieve their genetic potential due to other factors such as spinal [60] or total body irradiation [62] or scoliosis. Treatment with hGH may improve cardiovascular risk factors such as dyslipidemia and quality of life, but studies are lacking in children and results are variable and limited [63, 64].

Thyroid Disorders

Primary hypothyroidism is the most common endocrine abnormality following HCT [65]. Age under ten at the time of transplant and conditioning regimen involving total body irradiation, or chemotherapy with busulfan-cyclophosphamide, and presence of hematologic malignancy all further increase the risk of hypothyroidism among HCT survivors [47]. Therefore, individuals should have routine surveillance screens with annual thyroid function testing. Some patients may experience subclinical hypothyroidism which may resolve without any treatment, while others may require pharmacological intervention to establish biochemical euthyroidism [47].

Hyperthyroidism is rarely seen in HCT survivors, and far less common than primary hypothyroidism [47]. Patients with hyperthyroidism may experience anxiety, increased sweating, palpitations, weight loss, or diarrhea due to elevated thyroid hormone levels [47]. Symptomatic patients should have TSH, T3 and free thyroxine levels drawn, as well as assessment for thyroid antibodies [47]. Consultation with an endocrinologist is warranted for management and treatment of a symptomatic patient with hyperthyroidism.

While DC/TBDs are not associated with increased risk of thyroid cancer, radiation exposure as part of HCT conditioning regimen can lead to increased risk for thyroid nodules and thyroid malignancy in HCT survivors [47, 65]. Therefore, HCT survivors with a history of total body irradiation exposure benefit from surveillance imaging with ultrasound and identified nodules should be further evaluated with fine needle aspiration biopsy if the nodule meets threshold and criteria for biopsy [66]. Survivors with confirmed diagnosis of differentiated thyroid carcinoma by fine needle aspiration biopsy should have complete pre-operative staging of the neck with an ultrasound to assess for cervical lymph node metastasis and be referred to experienced surgeon in thyroid surgery for appropriate surgical management of the patient. Post-surgical evaluation and assessment needed for additional treatment such as radioactive iodine should be based on post-operative risk classification according to the pediatric

American Thyroid Association guidelines [67]. Patients with benign thyroid nodules should continue to have regular surveillance and undergo biopsy as needed based on imaging determination.

Table 2. Summary of reported endocrine and skeletal abnormalities in DC. Prevalences estimated from the literature and NCI DC/TBD cohort [6].

Features	Estimated Prevalence
Short stature	20%
Hypogonadism/undescended testes	6%
Growth hormone deficiency	1 patient
Low bone mineral density	3-27%
Avascular necrosis	3%
Fracture	Not systematically reported

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