Chapter 7: Endocrine Disorders

Introduction

Good to Know

The **endocrine system** produces hormones that allow our bodies to develop and function.

This system consists of glands in the head, neck, and abdomen that release many different types of hormones into the bloodstream.

These hormones perform a variety of functions in the body, from regulating blood sugar levels after meals to triggering physical changes during puberty.

Both Fanconi anemia (FA) and its treatment can harm the endocrine system. About 8 of every 10 children and adults with FA have at least one endocrine abnormality [1-9].

These abnormalities can affect the body in a variety of ways, delaying puberty in one person, for example, while causing diabetes, brittle bones, or short body height in another.

A complete list of concerns related to the endocrine system is shown below:

- *Short stature*
- *Challenges related to weight and nutrition*
- *Abnormal glucose or insulin metabolism (often contributing to pre-diabetes or diabetes)*
- *Underactive thyroid gland (known as hypothyroidism)*
- *Insufficient production of growth hormone (GH) or other pituitary hormones*
- *Pubertal delay, underactive testes or ovaries (known as hypogonadism), and infertility*
- *Low bone mineral density (often contributing to osteoporosis, or brittle bones)*

Because endocrine abnormalities influence so many aspects of growth and development, the endocrine clinical care team should include an **endocrinologist** or **pediatric endocrinologist**, a **dietician**, and for females a **gynecologist** or a **reproductive endocrinologist.** The endocrine team should work in close collaboration with other FA specialists to provide comprehensive care.

Height

Short stature is a common characteristic of patients with FA. More than half (60%) of children and adults with FA are shorter than all but 2.5% of their healthy peers. In scientific terms, this means the average person with FA is two standard deviation (SD) units, or -2 SD, shorter than the average in the general population [7] (Table 1). The average height of adult women with FA is about 150 cm (4 feet, 11 inches), while the average adult man with FA is 161 cm (5 feet, 3.5 inches). In children considered "short" by FA standards (at least shorter than 2 SD below the average in the general population, or < -2 SD), body heights ranged from 7.8 SD to 2 SD shorter than the average in their healthy peers (median, about -3.4 SD) [1, 2, 7]. However, a number of individuals with FA have normal height, and about 1 of every 10 patients is taller than the average in the general population [7].

Table 1. Average height of patients with FA, by research center.

	Number of Patients	Average Height SD	Range of Height SD
NY (1)	54	-2.4	-6.3 to +0.8
NIH (2)	45	-2.1	-7.8 to +0.8
CCHMC (7)	120	-2.1	-5.4 to +1.8
Overall	**219**	**-2.2**	**-7.8 to +1.8**

Abbreviations: New York Center, NY; National Institutes of Health, NIH; Cincinnati Children's Hospital Medical Center, CCHMC; height Z-score in standard deviation units from the mean for age and gender, HtSD

In patients with FA, short stature can be traced back to a number of factors:

- ***Endocrine abnormalities***
  People with FA who have hormone deficiencies tend to be shorter than the average of people with FA who have normal hormone levels, with average differences of -1 SD in children and -1.7 SD in adults [1, 7]. Adult heights may be even shorter in children with untreated GH deficiencies or

hypothyroidism. However, it is important to note that endocrine defects are not the only possible reasons for short stature. Even FA patients with healthy hormone levels tend to be shorter than average for the general population, with about half of them being within the height range considered normal. Conversely, some patients with FA are very short despite having normal hormone levels. As a result, hormonal replacement therapy does not always result in normal growth.

- ***Genetic mutations***
  Certain genetic mutations are strong predictors of short stature in patients with FA, independent of hormone levels. For example, a subset of patients with the IVS4 A to T mutation of *FANCC* have an average height of -4.3 SD; these patients are significantly shorter than FA patients with other mutations [(1)]. In contrast, patients in the FA-A complementation group have heights similar to the other complementation groups as a whole [(7)].

- ***Parental heights***
  Height is an inherited trait, and parental heights may be used to predict the adult heights of their children. However, this prediction may not be helpful in patients with FA because FA children are shorter than average despite their parents' heights being similar to that of the general population [(7)]. Therefore, predicted adult heights may not be accurate in patients with FA because short stature is influenced by additional factors.

- ***Birth size***
  Average birth weight in infants with FA is at the lower end of the normal range, typically about 1.8 SD less than average for the general population. Approximately half of all children with FA are considered small for gestational age (SGA) at birth, with length or weight about 2 SD less than average [(7)]. In the general population, about 90% of children who are considered SGA at birth catch up to the normal range for height. In contrast, only about one-quarter of FA children who are considered SGA at birth catch up to the normal range [(7)]. In a series of FA patients studied at Cincinnati Children's Hospital Medical Center, the median height of children considered SGA at birth was -2.6 SD, while the median height of children considered appropriate for gestational age (AGA) at birth was -2.0 SD [(7)].

- ***Poor nutrition***
  Being underweight is linked with short stature in patients with FA [7], and suboptimal nutrition may also predispose children to stunted growth, or growth failure.

- ***Transplant status and medications***
  It remains unclear whether the transplant process directly affects the growth of patients with FA. However, medications such as androgens and corticosteroids, which are used to treat FA patients, may affect growth and bone maturation, and impair adult height. Some medications or irradiation used during hematopoietic stem cell transplantation (HSCT) may affect thyroid or gonadal function, which in turn may negatively impact growth and adult height. These factors are discussed in more detail later in the chapter. In addition, total body, abdominal, or thoracic irradiation used in preparation for HSCT may directly influence the growth of the spinal cord.

Evaluation of growth

Regular screening: Growth should be closely followed in children with FA. Accurately measuring height with the use of a stadiometer (the ruler and sliding paddle mounted on the wall—not the weight scale—of most doctors' offices) is important, and height should be plotted on a growth chart. Children with FA who consistently fall low on the growth chart (with heights ≤ -2 SD compared with the average in the general population) or children with FA whose height gradually falls to a lower percentage on the growth chart, indicating a decline in annual growth velocity, should be evaluated by a pediatric endocrinologist. Endocrine evaluation should include a full assessment of growth and thyroid hormones, as well as pubertal status (Table 2). Nutritional and medical causes for poor growth should be identified in children with FA as early as possible.

Targeted testing for patients with abnormal growth: Determining the patient's bone age (BA) is part of a standard endocrine evaluation for short stature, and involves a radiograph of the left hand and wrist. Bone age may need to be reassessed every 1 to 2 years in short children. The results of BA assessments are sometimes used in height prediction algorithms, wherein if BA appears younger than the patient's actual age, the height prediction algorithm may suggest that adult height will be more favorable as the child has more "room to grow". This prediction assumes that the child will continue to experience healthy growth, optimal nutrition, normal hormone secretion, and normal timing of puberty; however, these assumptions are not necessarily correct in FA patients. Androgen therapy may accelerate BA, while hypothyroidism,

GH deficiency, hypogonadism, and corticosteroid therapy may delay BA. Therefore, estimates of adult height based on BA may lead to over-optimistic height predictions in patients with FA. Adult height predictions should be re-evaluated after a decrease in the growth velocity or following initiation of androgen therapy and after HSCT [10].

In addition to tracking the patient's bone age, GH secretion can be indirectly evaluated by measuring insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) levels. Levels of these proteins may be used to screen patients with short stature or growth failure. A thorough evaluation for GH deficiency by stimulation testing and MRI of the pituitary gland may be performed in consultation with a pediatric endocrinologist.

Recommendations for therapy

Treatment for growth failure or short stature requires identifying the underlying cause. Healthy nutrition is important for maintaining optimal growth and dietary changes may be indicated. In that case, if the dietary changes aren't enough, hormone replacement therapy may be needed. Replacement of specific hormone deficiencies is discussed later in this chapter.

Table 2. Endocrine screening recommendations for patients with FA.

	Annual screenings for all patients	Detailed testing for selected patients
Growth	• Plot patient's height and weight on a growth chart	If patient exhibits signs of growth failure: • Test levels of IGF-1, IGFBP3 • Obtain a bone age radiograph • Test levels of FT4/TSH • If patient has suspected GHD: • Perform GH stimulation tests • Obtain a pituitary MRI if evidence of pituitary hormone deficiency
Thyroid Activity	• Plot patient's height and weight on a growth chart • Perform early morning TSH and FT4 tests	If patient has suspected central hypothyroidism: • Determine the ratio of 0800h TSH to afternoon TSH
Cortisol Levels		Perform low dose ACTH stimulation test if evidence of: • Any other pituitary hormone deficiency • A pituitary abnormality on MRI
Glucose, Insulin, and Metabolism	• Consider fasting glucose and insulin testing; 2-hr post-prandial glucose and insulin tests • Measure HbA1c (after HSCT) • Consider fasting lipid profile in patients older than 10 years	If patient is overweight/obese/has hyperlipidemia: • Perform a 2-hour OGTT test • If patient previously had an abnormal OGTT but does not have diabetes: • Repeat OGTT yearly
Puberty and Gonadal Function	• Perform pubertal staging of pubic hair and either breasts (girls) or testes (boys) during physical examination • Assess menstrual history and clinical evidence of hypogonadism in post-pubertal patients	If patient has early/delayed puberty or suspected hypogonadism: • Obtain a bone age radiograph • Test LH, FSH, estradiol, or testosterone levels
Bone Mineral Density	• Assess the patient's dietary calcium and vitamin D intake • Measure 25OH-vitamin D level	Consider DXA scan to evaluate BMD: • Every 5 years starting at age 14 • Before HSCT and 1 year after HSCT • Repeat in 1 year if patient has low BMD • Repeat every 2 years if patient has hypogonadism or premature ovarian failure, or as in line above.

Abbreviations: Thyrotropin, TSH; free thyroxine, FT4; insulin-like growth factor, IGF-I; IGF binding protein 3, IGFBP3; growth hormone, GH; magnetic resonance imaging, MRI; hematopoietic stem cell transplant, HSCT; glycosylated hemoglobin, HgbA1c; luteinizing

hormone, LH; follicle-stimulating hormone, FSH; 25-hydroxy-vitamin D level, 25OH-vitamin D; dual X-ray absorptiometry, DXA; standard deviation units (Z-score) from the mean (SD); bone mineral density, BMD; adrenocorticotropic hormone, ACTH; two-hour oral glucose tolerance test, OGTT

Weight and Nutrition

Good to Know

Body mass index (BMI) reveals whether your body weight is healthy, given your height.

Here's what the numbers mean in adults:
Healthy weight: BMI 18.5 to 25
Overweight: BMI greater than 25
Obese: BMI greater than 30

Approximately half of FA children are born SGA [7]. In a series of patients studied at Cincinnati Children's Hospital Medical Center, infants with FA who were considered SGA were not only shorter but were also thinner than infants considered to fall within normal parameters at birth. Specifically, the average body mass index (BMI) was -1.3 SD in infants considered SGA, compared with -0.5 SD in infants considered to fall in the average range [7].

The BMIs of children and adults with FA are generally similar to the non-FA population, with average BMIs of -0.2 SD in children and -0.95 SD in adults. However, about one-quarter to one-third of all patients with FA are thin or underweight, while a few are overweight [2, 7]. The frequency of overweight in children with FA is similar to that in the general population, with a range of 11% to 27% depending on the group of patients studied [2, 7].

In some cases, being underweight may stem from the nutritional and gastroenterological problems common in patients with FA. Some children may have a smaller than expected appetite; others have trouble absorbing nutrients from food. In addition, illnesses like those that affect FA patients can raise caloric requirements. Glucose intolerance and insulin deficiency may also contribute to poor weight gain.

Excess weight gain, on the other hand, may reflect lifestyle factors and a genetic predisposition to obesity.

Evaluation of under- or overweight patients

Body weight should be assessed at least annually; more frequently if there is concern about failure to thrive or excessive weight gain relative to standard norms. If there are concerns related to body weight, a registered dietitian should assess the patient's nutritional intake. In addition, the primary care provider should thoroughly evaluate the patient for underlying medical conditions, concurrent medications, specific hormone-related conditions, and related co-morbidities.

Recommendations for intervention

Healthy dietary intake should be encouraged, including sufficient calcium and vitamin D from foods or supplements. Input from a registered dietician may be needed. The underlying causes of under- or overweight should be addressed, including treatment of endocrine disorders. Related co-morbidities due to obesity should be prevented and treated, as discussed later in this chapter in the sections on abnormal glucose metabolism, lipid abnormalities, and metabolic syndrome.

Table 3. Endocrine disorders in children and adolescents with FA, by research center.*

Research Center	Average Patient Weight	Thyroid Activity	Growth Hormone	Glucose/ Insulin Levels	Onset of Puberty	Bone Mineral Density
NY (1)	Of 54 patients studied, including a few adults, the average BMI was lower (-1.3 SD ± 0.2) than the average in the general population.	Of 53 patients, about one-third (36%) had low thyroid activity.	Of 48 patients, nearly half (44%) had low levels of GH.	Of 40 patients, 20% had impaired glucose tolerance, 5% had diabetes, and 72% had higher than normal levels of insulin.	Not studied.	Not studied.
NIH (2)	When 24 patients were compared with the general population, about 1 in 5 (21%) had BMI greater than 85th percentile.	Of 20 patients, 1 in 5 (20%) had low thyroid levels.	Of 14 patients with suspected GHD#, half (50%) had low levels of GH. Of 24 patients with GHD or suspected GHD#, MRI revealed a midline defect in almost 1 in 5 patients (17%).	Of 24 patients, 4% had diabetes, 17% had insulin resistance, and 29% had dyslipidemia (unhealthy levels of cholesterol and triglycerides).	Of 14 males, about two-thirds (64%) had small testes. Of 17 females, more than 1 in 10 (12%) had delayed menarche, starting their periods later in life than their healthy peers.	Not studied.
CCHMC (3-5, 7, 9)	One third of patients (33%) studied had BMIs lower than average in the general population (< -1.8 SD). Far fewer patients (11%) had BMIs greater than average in the general population (> +1.8 SD).	Of 70 patients, about two-thirds (61%) had low thyroid levels.	Of 32 patients, about 1 in 10 (12%) had low levels of GH. Of 11 patients, almost half (45%) had small pituitary glands on MRI.	Of 47 patients, 68% had hyperglycemia, or high blood sugar. Of 39 patients, 34% had high insulin levels. Of 24 patients, 17% had dyslipidemia (unhealthy cholesterol and triglyceride levels).	Of 22 males, most (86%) had small gonads. Of 7 females, 14% had delayed menarche, and 13% had high FSH levels.	Of 29 patients, only 3% had low bone mineral density.
U of M (6, 8)				Of 17 patients, 6% had impaired fasting blood sugar, 24% had low first-phase insulin release, 17% had increased first-phase insulin release and high fasting insulin, and 8% had impaired glucose tolerance.		Of 49 patients, about half (52%) had low bone mineral density following HSCT.

* Different studies used different biochemical criteria.
# Suspected GHD was defined by growth failure, low levels of IGF-1, and/or low levels of IGFBP-3.
Abbreviations: New York Presbyterian Hospital-Cornell University Medical Center, NY; National Institutes of Health, NIH; Cincinnati Children's Hospital Medical Center, CCHMC; University of Minnesota, U of M; body mass index Z-score in standard deviation units from the mean for age and gender, BMI SD; hematopoietic stem cell transplantation, HSCT

Abnormal Glucose or Insulin Metabolism

Glucose elevation/delayed insulin secretion

Diabetes mellitus occurs more commonly in patients with FA than in the general population [11]; moreover, patients with FA have a relatively high incidence of high blood sugars, also known as impaired glucose tolerance. One study detected diabetes in approximately 8% of patients with FA, while an additional 27% to 68% of these patients had impaired glucose tolerance (Tables 3 and 4) [1, 2, 4, 6, 7]. In addition, as many as 72% of patients with FA had elevated insulin levels 1 to 2 hours after eating. Interestingly, insulin levels were low 10 to 45 minutes after an oral glucose test, suggesting slow initial insulin secretion, but became elevated 60 to 120 minutes after the test [4, 6]. Although the elevated levels suggest that insulin resistance may contribute to diabetes in patients with FA, these findings also support the possibility that insulin-producing cells known as beta cells (β-cells) do not function properly in these patients, which could impair first-phase insulin secretion [4, 6]. So the diabetes in FA is not typical for either Type 1 or Type 2 diabetes.

Good to Know

The foods and drinks you consume are broken down into sugars—such as **glucose**—that enter your blood and fuel your body.

- Patients with **impaired glucose tolerance** have trouble breaking down the sugars found in their diets, but they do not yet have diabetes.
- Impaired glucose tolerance is sometimes a warning sign that the patient may eventually develop diabetes

The cause of impaired first phase insulin secretion in patients with FA is unknown, but could stem from possible damage inflicted by enhanced reactive oxygen species (ROS) on the β-cells that secrete insulin or, alternatively, from iron overload in heavily transfused patients. Several medications used in the treatment of FA, particularly androgens and corticosteroids, are known to alter

glucose metabolism. Androgen treatment can significantly elevate both blood sugar and insulin levels [1]. Chronic steroid therapy also predisposes patients to insulin resistance and high blood sugar, known as hyperglycemia [12-14]. The guidelines regarding glucocorticoid use in FA should be the same as in any other subject: use the lowest possible dose of medication.

Screening for abnormal glucose and insulin metabolism

All patients should be screened for abnormalities related to glucose and insulin homeostasis upon diagnosis with FA and, if possible, every year thereafter (see Table 2). Patients can be screened for glucose tolerance by measuring blood sugar and insulin concentrations after fasting for 8 hours, and by measuring post-prandial blood sugar and insulin concentrations 2 hours after a meal. The danger of measuring only serum glucose values, or relying solely on fasting values, is that some patients may be overlooked—particularly those with impaired glucose tolerance whose blood sugar and insulin levels are normal after fasting but elevated 2 hours after a meal. Glycosylated hemoglobin (HbA1c) and fructosamine levels may be deceptively normal, presumably due to impaired glycosylation or to elevated levels of fetal hemoglobin in patients with bone marrow failure [7], and therefore are not helpful in FA patients prior to HSCT. HbA1c scores may provide more useful information after HSCT compared to before HSCT.

In patients who have suspected endocrine abnormalities and possess risk factors such as overweight/obesity or hyperlipidemia, a more detailed evaluation is needed in consultation with an endocrinologist. This evaluation should include a 2-hour oral glucose tolerance test (OGTT, 1.75 g glucose/kg body weight, maximum dose 75 g glucose). Some clinical centers obtain serum samples to measure blood sugar and insulin levels every 30 minutes during a 2-hour OGTT. Patients with abnormal OGTTs must be followed at least annually with repeat testing. The prevalence of diabetes mellitus in patients with FA increases with age and disease progression, and the majority of FA patients may be at risk.

Treatment of blood sugar and insulin abnormalities

Diet
All persons diagnosed with FA—regardless of OGTT results— should be placed on a healthy diet that avoids excessive consumption of concentrated sweets such as juices, soda, and candy. A registered dietician can provide valuable guidance, particularly by helping the patient distinguish unhealthy "simple" carbohydrates (such as candy) from healthier "complex" carbohydrates (such as whole grain breads). It is important to encourage adequate caloric consumption and regular exercise.

Diabetes medications
Patients who have FA and diabetes should be treated by an endocrinologist. Insulin or oral medications should be tailored to the cause of diabetes, just as in the general population, with the goal of improving blood sugar control without causing low blood sugar, or hypoglycemia.

- *Treatment of hyperglycemia without obvious diabetes:*
  It remains unclear whether FA patients with normal fasting blood sugar but impaired glucose tolerance should be treated with insulin. Administration of short-acting insulin with meals may be more beneficial than metformin, due to the abnormal pattern of insulin release in patients with FA. Some practitioners recommend treatment with short-acting insulin at mealtime, to help the body process carbohydrates, if post-prandial blood sugar is consistently higher than 180 mg/dL.

- *Insulin therapy during HSCT:*
  During HSCT, many children with FA require insulin therapy to treat the high blood sugar, or hyperglycemia, that is often triggered by steroid therapy. A combination of long-acting and short-acting insulin may be required for adequate blood sugar control. The duration of therapy may vary depending on the duration, dose, and type of transplant medications used—particularly for corticosteroids, tacrolimus, sirolimus, or similar medications.

- *Isolated hyperinsulinemia:*
  Some practitioners have begun using oral diabetes medications such as metformin to treat otherwise normal children and adolescents with FA who occasionally have high levels of insulin, known as isolated hyperinsulinemia, but do not have glucose impairments. In overweight patients with FA, metformin may indeed be the best first choice. Patients who are treated with metformin should be monitored closely for side effects, as there have been no long-term studies on the risks or benefits of metformin in patients with FA.

Dyslipidemia, Obesity, and Metabolic Abnormalities

The scientific literature includes lipid test results from 29 patients with FA. Of these patients, about half (55%) had unhealthy levels of cholesterol and triglycerides, a condition known as dyslipidemia. Of these patients, 21% had elevated levels of LDL, 31% had low levels of HDL, and 10% had elevated triglycerides [2]. An abnormal lipid profile was observed in nearly half (40%) of patients with hyperglycemia or insulin resistance. Of the patients with FA and diabetes, 75% were overweight or obese. Adults with FA and diabetes tended to be overweight or obese, compared with those without these metabolic abnormalities. About 1 in 5 (21%) adults with FA were diagnosed with metabolic syndrome, a condition in which patients are overweight/obese, have dyslipidemia, and develop resistance to the effects of insulin. Half of the 24 children tested had at least one metabolic abnormality, including 4 children with insulin resistance, 1 with diabetes, and 7 with dyslipidemia [2]. FA patients are at risk for metabolic syndrome, so we recommend a healthy diet and a regular exercise regimen, and careful screening for blood pressure and lipid abnormalities.

Good to Know

Cholesterol comes in two forms:

- **LDL** is a "bad" cholesterol that builds up on the walls of arteries;
- **HDL** is a "good" cholesterol that scours these build ups from the artery wall to prevent heart attacks and stroke.

Triglycerides are the building blocks of fats and oils.

A person with **dyslipidemia** has unhealthy levels of cholesterol and triglycerides.

Hypothyroidism

Many children with FA have mildly abnormal levels of serum thyroid hormones—that is, hormones secreted from the thyroid gland into the bloodstream—including borderline low levels of thyroxine (T4) or free T4 (FT4), or borderline high levels of thyroid-stimulating hormone (TSH) (Tables 3 and 4) [1, 2, 5, 7]. This combination of test results is consistent with mild hypothyroidism, or low thyroid activity. Mild hypothyroidism can occur either

because the thyroid gland is abnormal and cannot make enough T4 hormone (known as primary hypothyroidism) or because the thyroid gland is normal but the pituitary gland does not make enough TSH to stimulate the thyroid (known as central hypothyroidism).

About 60% of individuals with FA have thyroid function tests that suggest primary hypothyroidism. The mechanism of hypothyroidism in patients with FA remains unclear, but there is no indication that the primary hypothyroidism stems from an autoimmune process, in which the body mounts an immune attack against itself. Therefore, the thyroid appears to fail for other, yet-to-be-determined reasons in patients with FA. Hypothetically, some thyroid cells may die because of unrepaired DNA damage stemming from oxidative injury. One study described reduced thyroid hormone binding in persons with FA [(1)]. Although reduced thyroid hormone binding is often not clinically significant, it can make total T4 levels appear low and falsely suggest hypothyroidism without causing TSH elevation. Thyroid hormone binding globulin (TBG)-bound T4 (but not other bound forms) was lowest in individuals receiving androgen therapy [(1)], suggesting the need to use Free T4 and TSH as the most important tests.

Thyroid evaluation

Thyroid function should be evaluated by obtaining an early morning (e.g., 8:00 am) blood sample and measuring free T4 and TSH levels. All patients with FA should undergo screening for hypothyroidism once a year or more often if clinically indicated, for example, if the patient shows signs of growth failure (Table 2). Central hypothyroidism is suggested by low levels of free T4 and by a TSH ratio of less than 1.3 at 8:00 am compared to afternoon TSH [(16)]. Patients who are diagnosed with central hypothyroidism should undergo evaluation for other pituitary hormone deficiencies; specifically, the physician should rule out central adrenal insufficiency and consider ordering a pituitary MRI.

Recommendations for treating hypothyroidism

Hypothyroidism should be treated promptly, particularly in children younger than 3 years of age. Thyroid hormone replacement treatment should be initiated just as in non-FA patients, based on low thyroid hormone levels: specifically, a free T4 level below the laboratory reference range and/or a TSH level above the reference range. Thyroid hormone therapy should strive to reduce TSH levels to the range of 0.5 to 2 mU/L in patients with primary hypothyroidism. In central hypothyroidism, therapy should aim to raise free T4 levels to just above the middle of the normal range.

There is ongoing controversy about the use of TSH levels greater than 3 mU/L as a threshold for the treatment of mild hypothyroidism [15]. Some endocrinologists may use a TSH level of 3 mU/L, or even 4.5 to 5 mU/L, as the upper limit of a normal TSH level in healthy individuals. However, treatment, especially in adults, is often not considered necessary unless TSH levels are persistently 10 mU/L or higher, or unless free T4 levels are low [16-18]. Among pediatric endocrinologists, some use the above approach, while others prefer to treat mildly elevated TSH levels in the hopes of improving their patients' growth [15].

In one study, 8 children with FA were treated for 7 months with thyroid hormone and for 7 months with placebo; the treatment and placebo phases occurred in random order. Children grew significantly better on thyroid hormone than on placebo, and parents felt that their children had better energy levels during the thyroid hormone phase [5]. This study suggests that children with FA who have short stature and borderline results on thyroid function tests may benefit from using thyroid hormone therapy; however, it should be noted that a small number of patients were studied and the effects were not conclusively proven.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) has been described in case reports of a few patients with FA [19-23]. In one study, more than half (54%) of patients younger than 20 years failed to produce growth hormone (GH) in response to clonidine, a medication known to stimulate GH. Similarly, most patients (72%) failed to raise GH levels in response to another GH stimulator, arginine. Using a more stringent criterion for diagnosing GHD (specifically, peak GH levels ≤ 5 mcg/L), but without priming the patients in advance, 12% of 32 children tested had GHD [7]. Growth hormone deficiency was more common in patients who had undergone HSCT (25%) than in patients who did not have HSCT (8%) [7]. The processes that underlie secretion of GH may be abnormal in children with FA during spontaneous overnight GH secretion studies [1], although these results are sometimes difficult to interpret because of the significant overlap with values observed in children without GHD [7]. Taken together, these test results suggest that while few children with FA have GHD, others may have an underactive hypothalamus, leading to "partial" GH deficiency or, alternatively, to neurosecretory GH deficiency. In these individuals, GH and insulin-like growth factor I (IGF-I) values may not be as severely affected as the patient's height.

Evaluation for GHD

Screening for GHD in a child with poor growth can be performed by drawing a blood sample and measuring IGF-I and IGFBP3 levels (Table 2). If IGF-I and IGFBP3 values are below -2 SD for the patient's age, evaluation should include standard GH stimulation testing. One caveat is that IGF-1 is known to be a poor marker of GHD in thin individuals or in those who have received total body or cranial irradiation. Sex steroid priming should be considered prior to GH stimulation testing in pre-pubertal girls age 10 and older, and in pre-pubertal boys age 11 and older or who are in stage 2 of puberty [24, 25]. Evaluation of GH secretion in a slowly growing child should be done through the use of two standard GH stimulation tests, including clonidine (150 mcg/m^2, maximum dose 300 mcg), arginine (0.5 g/kg, maximum dose 20 g), or glucagon (0.3 mg/kg, maximum dose 1 mg) [25-27]. Peak GH levels are considered normal if they rise to 10 ng/mL or greater [28]. Patients diagnosed with GHD should be evaluated for central hypothyroidism, central adrenal insufficiency (as discussed below), and should also undergo an MRI scan of the pituitary gland.

Recommendations for treatment

Patients with GHD can be treated with recombinant human GH therapy. A short child with FA is a candidate for treatment with GH if GHD has been convincingly documented by the child's short stature, slower than normal growth rate, and low GH peak on a stimulation test. Physicians should counsel FA families about the risks and benefits of therapy. To date, there is no clear consensus on the safety of GH therapy in FA patients. Though having FA is not an absolute contraindication to GH treatment, there is some controversy surrounding the use of GH in patients without GHD. It should be recognized that in some instances, treatment with GH may be instituted in the absence of GHD if deemed appropriate by the patient care team, either before or after HSCT. In the absence of safety data, GH therapy in FA patients should be titrated to achieve IGF-I concentrations in the mid-to-normal range for the patient's age (i.e., between 0 and 1 SD). Therapy should be discontinued immediately if routine hematological examination reveals clonal hematopoietic stem cell proliferation. Growth hormone therapy should be temporarily discontinued immediately prior to HSCT and for at least 6 months after HSCT, as well as during critical illness [29].

Although no studies have examined the effectiveness of GH treatment in children with FA after HSCT, significant growth responses to GH therapy have

been observed in some patients with FA (Petryk, Polgreen, Miller, MacMillan, Wagner, unpublished data). In studies of patients without FA, the response to GH treatment after HSCT has varied [30-33]. Ongoing use of glucocorticoids after HSCT may limit the patient's growth response. In a study that included HSCT recipients, GH treatment was associated with significantly improved adult height (on average, patients treated with GH grew about 4 to 5 cm taller than untreated children) [34] and did not increase the risks of recurrent leukemia, secondary malignancies, or diabetes in post-HSCT patients treated with GH compared with those who were not treated. A beneficial effect of GH treatment on growth rate after HSCT has also been reported by others [35, 36].

Patients with FA are inherently at an increased risk of cancer, particularly for acute leukemia prior to HSCT as well as malignancies of the head and neck and gynecological cancers [37-39]. At this time, there is no evidence that this risk is enhanced in FA patients treated with GH. Patient registries have provided useful safety and efficacy data on the use of GH in the general population and in cancer survivors, but have included few patients with FA [40-46]. A large study of 13,539 cancer survivors, including 361 patients treated with GH, did not find an increased risk of cancer recurrence in GH-treated survivors [47]. However, the risk of a second neoplasm, mostly solid tumors, was slightly increased in survivors treated with GH.

Despite these possible risks, it should be noted that severe short stature may have a negative impact on the patient's quality of life and daily functioning. Families should be counseled regarding the predicted adult heights of their children, the effects of available treatment modalities on growth rate, and the potential risks and benefits of GH treatment—with the caveat that there is no clinical information about the long-term safety of GH therapy in patients with FA.

Cortisol Sufficiency

Good to Know

- **Cortisol** is a steroid produced by the body that plays important roles in stress response, immunity, metabolism of nutrients, and other processes.
- Cortisol levels ebb and flow in response to the body's **circadian rhythm**. Levels are lowest when you fall asleep, highest just after you wake, and gradually decline until the following night.

Most FA patients have normal circadian cortisol levels and experience normal responses to treatment with adrenocorticotrophic hormone (ACTH). ACTH stimulation testing has been normal even in patients with reported pituitary stalk interruption syndrome (PSIS) and multiple pituitary hormone deficiencies [2]. However, cortisol sufficiency should be evaluated in young children with FA who have poor growth and who require major surgery because of possible central hypothalamic dysfunction, even in the absence of a detectible midline central nervous system defect [3, 20]. Finally, ACTH stimulation testing is recommended to rule out central adrenal insufficiency if the patient has other pituitary hormone deficiencies.

Multiple Pituitary Hormone Deficiencies

In previous studies, MRI scans of the brain and pituitary gland have suggested that the pituitary gland is smaller and has a thinner stalk in patients with FA compared with age-matched children without FA [[3], unpublished data NIH]. Four patients with FA at the National Institutes of Health (NIH) had an abnormal brain MRI with midline defects ranging from absent corpus callosum and septum pellucidum to septo-optic dysplasia. In addition, 1 patient was noted to have a thickened pituitary stalk while 2 patients had pituitary stalk interruption syndrome (PSIS) [[2], unpublished data NIH]. This syndrome has previously been reported in 8 other patients with FA [23, 48-50], and was associated with permanent GHD and severe growth failure. Specifically, the average height SD of all the children with PSIS at diagnosis was -4.6, with a range of -3.7 to -5.7. These patients were also at risk for multiple pituitary hormone deficiencies: 5 of 10 patients with FA and PSIS had hypothyroidism, 1 of 10 patients had hypogonadotrophic hypogonadism, and the remaining 4 patients were too young to evaluate. Furthermore, 5 of 6 male patients had cryptorchidism, in which one or both testicles fail to descend, and 4 of 6 male

patients had microphallus (an abnormally small penis). Together, these findings suggest that in addition to GHD, the male patients had hypogonadotrophic hypogonadism, a condition in which the testes produce lower than normal amounts of sex hormones due to an underlying problem with the pituitary gland or hypothalamus.

Based on the available evidence, a brain MRI with emphasis on the pituitary/hypothalamic area should be obtained in any FA patient who has one or more pituitary hormone deficiencies, including GHD, central hypothyroidism, or ACTH deficiency. Serum IGF-1 testing has been proposed as a screening test, as all patients with PSIS and GHD had a low IGF-1 [48]. Serial endocrine testing is essential in patients with PSIS, because pituitary hormone deficiencies may evolve over time.

Puberty, Hypogonadism, and Fertility

Early onset of puberty

Children and adolescents with FA may enter puberty earlier than their healthy peers. If puberty starts too early or progresses too quickly, it may limit the number of years a child can grow and thus compromise adult height. A child with FA who experiences an early onset of puberty and has short stature may benefit from gonadotropin-releasing hormone agonist therapy. A previous study suggests this therapy can delay puberty to increase the patient's adult height by an average of 4 to 5 cm after 4 years of therapy [51].

Good to Know

- **Puberty** normally begins around age 10 in girls, and around age 11 in boys.
- Puberty is considered **delayed** if no physical changes have occurred by age 14 in boys, or by age 13 in girls. Additionally, puberty is considered delayed in girls if menstrual cycles have not yet begun by age 16 or 3 years after developing breast buds.

Delayed puberty

More commonly, children with FA enter puberty later than their healthy peers. While delayed puberty is fairly common, its underlying cause is not well understood. There may be blunted and/or prolonged gonadotropin [primarily luteinizing hormone (LH)] responses to stimulation, suggesting abnormal regulation of the hypothalamic and pituitary glands. Chronic illness is also associated with delayed pubertal maturation. Total body irradiation and some chemotherapy agents used during HSCT may also affect gonadal function.

Evaluation for pubertal disorders

In patients with FA, the onset, pubertal stage, and tempo of progression of puberty should be monitored during annual physical examinations. Physical exams should include Tanner staging of pubic hair, and assessments of breast development in girls and testicular size in boys (Table 2). Assessment of bone maturation can be useful in adolescent children who experience delayed or abnormal progression of puberty, while measuring the concentrations of certain hormones—particularly LH, FSH, estradiol, or testosterone—can be useful in adolescents and in adults who develop symptoms of hypogonadism, a condition in which the testes or ovaries produce insufficient amounts of hormones.

Recommendations for treatment of delayed puberty

A boy who shows no signs of puberty by age 14 years should be evaluated for possible causes of delayed puberty. After evaluation, low-dose testosterone therapy can be initiated according to the child's height and growth potential. Young boys with confirmed hypogonadism can be treated using topical gel preparations or by injections of testosterone started at an appropriately low dose and gradually increased over several years to adult replacement levels. It is important to avoid rapid increases in testosterone levels in adolescents to ensure continued height gain and avoid premature fusion of the growth plates. Bone age should be monitored during therapy.

Similarly, a girl with FA who shows no signs of puberty by age 13 years should receive a full hormonal work up. After evaluation, low-dose estrogen therapy may be started and slowly titrated under the care of the pediatric endocrinologist or adolescent gynecologist, taking into account the child's height and potential for growth. It is important to avoid rapid increase in estradiol levels in adolescents to ensure continuing height gain and to avoid premature fusion of the growth plates. Bone age should be monitored during therapy. Estrogen therapy will increase bone mineralization, optimize the child's growth rate, and achieve breast development. Progesterone (i.e., medroxyprogesterone, 10 mg by mouth daily for 10 days) should be added when breakthrough bleeding occurs or after 2 years of estrogen replacement therapy.

Estrogen therapy is not needed if a girl has normal pubertal development or is having normal menstrual cycles, even if there is evidence of ovarian hormone deficiency. In patients with FA, there is no medical contraindication to the use of oral contraceptive pills.

Hypogonadism

Hypogonadism is very common in adults with FA. In addition, hypogenitalism with small testes and penis size affects two-thirds (64%) of men with FA, while premature ovarian failure affects most (77%) females with FA [2]. In another study, almost half (40%) of adults with FA had evidence of hypogonadism [7]. Both hypergonadotropic (either testicular or ovarian) hypogonadism [50] and hypogonadotropic (specific to the hypothalamic-pituitary glands) hypogonadism have been reported in patients with FA. Gonadal function may be affected by several factors, including FA itself, SGA status at birth, gonadotropin deficiency, cryptorchidism, and/or the conditioning regimen used for HSCT, including radiation and chemotherapy [48].

Genital Tract Abnormalities

Developmental anomalies of the genital tract are more frequent in patients with FA than in the general population. Boys may be born with undescended testicles and hypospadias, a condition where the urethra opens on the underside of the penis. Many boys with FA have small testes for their age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis. Girls with FA may be at higher risk for certain reproductive malformations, including a smaller than normal uterus, half-uterus, or uterus that does not open into the vagina [52].

Fertility

Patients with FA often experience fertility problems, with males often being infertile and females often having premature menopause in their 20s or 30s, although rare pregnancies have been documented as described in *Chapter 6* [52]. Contraception should always be used when pregnancy is not desired. Infertility may stem from a number of different factors, including a reduced sperm count in men, treatments for HSCT, and the type of genetic mutation underlying FA. Gonadotropin-releasing hormone has been shown to acutely upregulate the expression of *FANCA* mRNA and protein, suggesting that *FANCA* plays a regulatory role in gonadal function [53]. Disruption of *Fanca* in mice is associated with hypogonadism and a reduction in fertility [54]. Animal studies have also shown that the *Fancc* protein is required for the proliferation of primordial germ cells [55]. In addition, radiation or chemotherapy with HSCT may contribute to decreased fertility after HSCT. Cryopreservation of embryos or sperm is being investigated as a reproductive option. Future studies are needed to more fully address the fertility issues in patients with FA.

Bone Mineral Density

Good to Know

- Someone with **osteopenia** has lower-than-normal bone density. Osteopenia often leads to osteoporosis.
- A person with **osteoporosis** has brittle bones that break easily. This occurs when minerals and protein are depleted from the bones.

Bone mineral density (BMD) in FA has been reported in a few studies with differing conclusions. An earlier report described osteopenia or osteoporosis in 12 of 13 adults with FA, but the BMD was not corrected for the short stature commonly observed in individuals with FA [(2)]. In contrast, another report showed that BMD is normal in children and adolescents with FA, if adjustments are made for height. In 34 children and 3 adults with FA (including roughly equal numbers of patients with prior HSCT and no HSCT), lumbar spine BMD Z-scores adjusted for height age were in the normal range [(9)]. In 9 children and adolescents with FA who were followed at the NIH (half of whom had undergone HSCT) (unpublished data), height-adjusted lumbar spine BMD Z-scores were completely normal, according to an online BMD Z-score calculator [(56)]. We recommend that the BMD of children with FA be adjusted for height and that Z-scores be calculated. An online calculator (http://www.bmdcspublic.com/zscore.htm) may be used to calculate the height-adjusted Z-score in children with FA. There is limited information as to whether BMD in adults with FA should be adjusted for height, and few studies have examined the correlation of height-adjusted BMD and fracture risk.

Bone mineral density may decrease after HSCT in many patients including those with FA, but the underlying reasons for this remain unclear. In a study of 49 children, including 12 with FA, BMD decreased during the first year after HSCT, with the most significant bone loss occurring by 6 months [(57)]. The effects of HSCT on BMD in children with FA were similar to those in children without FA. The average areal lumbar BMD Z-score declined 0.5 SD units during the first 6 months after HSCT, and the number of patients with a Z-score below −1 increased from 34% at baseline to 52% 1 year after HSCT [(8)]. The reduction in lumbar BMD at 6 months correlated with the cumulative dose of glucocorticoids [(57)]. While BMD remained within normal limits, the average height-adjusted lumbar BMD Z-score was lower in patients who had undergone prior HSCT (-0.9) compared with those who had not had prior HSCT (-0.3) [(9)].

Long-term prospective studies are needed to examine the mechanisms underlying decreased BMD following HSCT in FA children.

In adults, HSCT is associated with decreased bone formation and increased resorption, and similar mechanisms may apply in children [58]. Medications used during HSCT, such as glucocorticoid therapy, may also contribute to low BMD. Long-term prospective studies should explore whether BMD declines further or recovers over time after HSCT. Hypogonadism and GHD may also predispose patients with FA to low BMD.

Screening for bone health

Dual energy absorptiometry (DXA) should be used to evaluate BMD in patients with FA before HSCT and 1 year after HSCT. The first DXA evaluation may be performed at about age 14 if the patient has not undergone HSCT, and follow-up scans should be dictated by the patient's risk factors. Patients with FA who have hypogonadism and growth hormone deficiency should be evaluated for low BMD and treated as necessary. Levels of serum calcium, magnesium, and 25-OH vitamin D levels should be measured in HSCT recipients and in patients with low BMD [59]. Patients exposed to prolonged or high doses of corticosteroids, or who have a history of fractures, immobility, hypogonadism, or hormone deficiencies should be referred to an endocrinologist.

Recommended therapies for bone health

Among other dietary recommendations, it is important to maintain adequate dietary intake of calcium and vitamin D to provide the opportunity for normal bone growth and mineralization. Supplementation should meet RDA requirements. More aggressive intervention with calcium and vitamin D replacement may be indicated if the patient's BMD is low after adjusting for height. Vitamin D levels should be targeted to achieve sufficient concentrations (>30 ng/mL) [60]. Treatment of hormone deficiency—specifically treatment of pubertal delay, hypogonadism, and GHD—is beneficial for bone mineralization.

Bisphosphonates are effective in preventing bone loss after HSCT in adults and may be effective in improving the BMD in HSCT-recipient children as well, but more studies are needed before a routine recommendation can be made regarding their use for the treatment of low BMD [61]. Experienced endocrinologists or nephrologists may consider treatment with bisphosphonates in children with FA who, after vitamin D deficiencies have been addressed, sustain two or more low-

impact fractures and have height-adjusted BMD Z-scores lower than -2 SD. Oral bisphosphonates should be used with caution as they may worsen esophageal reflux and have other potential health concerns. The risk/benefit ratio of this treatment must be evaluated by a specialist prior to treatment.

Adults with Fanconi Anemia

Endocrine results have been reported for only a small number of adults with FA [1, 2, 7, 9] (Table 4). Endocrinopathies clearly persist into adulthood, though the treatment of FA with HSCT can alter the course of disease. Early endocrine diagnosis and therapy may improve the patient's quality of life. Treatment of endocrine issues in adults with FA should be monitored by endocrinologists who care for adults, with attention to the patient's thyroid status, glucose tolerance, lipid abnormalities, maintenance of normal BMI, gonadal function, and bone mineral density.

Lipid abnormalities were frequently seen in nearly 40 patients with FA who were followed at the NIH (unpublished data). More than half of the adults had one or more of the following lipid abnormalities: total cholesterol > 200 mg/dL, HDL cholesterol < 40 mg/dL, LDL cholesterol > 129 mg/dL, or triglycerides > 150 mg/dL. Insulin resistance, as determined by the homeostatic model assessment (HOMA), and metabolic syndrome were also common in adults.

Thyroid abnormalities remain prevalent in FA patients older than 18 years, with 37% to 57% of patients having hypothyroidism. These patients typically present with either elevated TSH levels or low free T4 levels [2, 7] (Table 4). In one study, a low stimulated GH peak was observed in a small number (6 of 16) of adults with FA [2, 7]. Hypogonadism with small testes was present in at least half (50%) of men with FA, and hypogonadism was present in one-third (30%) of women with FA. As mentioned earlier in this chapter, many women with FA experience premature menopause.

One study reported decreased BMD in 12 of 13 adults with FA; of the 8 females with decreased BMD, 7 experienced premature ovarian failure and early menopause [2]. However, the BMD was not adjusted for height in this study, and the measured BMD may have underestimated the volumetric BMD in several individuals with short stature whose bones were likely smaller than those of other participants [62]. It is not clear whether BMD in adults with FA should be routinely adjusted for height. The correlation of fracture risk with height-adjusted

BMD in adults with FA is also unknown. Additionally, many FA adults have hypogonadism, other endocrine deficiencies, and HSCT—all of which may adversely affect bone health and trigger the early development of osteoporosis.

Table 4. Endocrinopathies in adults with FA*.

Research Center	No. Patients	Adult Height	Thyroid Activity	Growth Hormone	Blood Sugar/Insulin Levels	Gonadal Function	Bone Mineral Density
NIH (2)	17	On average, adults with FA were -1.9 SD shorter than average for other adults.	Of 15 patients, more than half (57%) had abnormal thyroid activity.	Of 5 patients, 3 had suspected GHD#.	Of the patients, 18% had diabetes, 35% had insulin resistance, and 21% had metabolic syndrome.	Of 4 males, half had hypo-gonadism. Of 13 females, about two-thirds (69%) had premature ovarian failure.	Of 13 patients, most (92%) had low bone mineral density.
CCHMC (7, 9)	42$	More than half (58%) of adults with FA were -1.8 SD shorter than average for other adults.	Of 27 patients, more than one-third (37%) had abnormal thyroid activity.	Of 9 patients, about one-fifth (22%) had GHD.	Of 16 patients, 2 had diabetes, one-third (30%) had hyperglycemiaand about one-fifth (19%) had dyslipidemia.	Of 25 males, nearly half (40%) had hypo-gonadism.	Of 15 patients, 13% had low bone mineral density.

* Different studies used different biochemical criteria.
$ Adults were defined as post-pubertal. Of the 42 patients in the study, 26 were 18 years or older.
Abbreviations: National Institutes of Health, NIH; Cincinnati Children's Hospital Medical Center, CCHMC
Cases of suspected GHD were defined by growth failure, low IGF-1 levels, and/or low IGFBP-3 levels.

Medications and Treatments That Affect Endocrine Function

Androgen therapy

Androgen therapy is used to improve the blood counts of patients with FA, and can cause endocrine-related side effects that need to be monitored. Androgens can improve growth rates, but often hasten the maturation of growth plates, which reduces the time available for childhood growth. Children treated with androgens may appear to be growing well, but their potential adult height may decline due to rapid skeletal maturation and premature fusion of cartilage plates at the end of long bones, known as epiphyseal fusion. Androgen use may also result in virilization in both males and females. The impact of androgen therapy on height and bone maturation should be discussed with the patient's family. Prior to beginning androgen therapy, a bone age X-ray should be performed. During androgen therapy, the patient's bone age should be reassessed periodically, and may be checked every 6-12 months.

Multiple transfusion therapy

Multiple red blood cell transfusion therapy can affect endocrine function by causing iron overload (see *Chapter 3*). The accumulation of iron in endocrine glands can affect testicular and ovarian function, contribute to diabetes, and may lead to primary hypothyroidism, hypoparathyroidism, or pituitary dysfunction.

Hematopoietic stem cell transplantation

Transplantation is inherently associated with a state of illness. Illness is not an optimal time to assess any hormone concentrations, as thyroid levels, growth, gonadal function, nutrition, and glucose regulation are often altered during this period. The treatments and irradiation used during HSCT may exacerbate the patient's underlying intrinsic risk for endocrine disorders and lead to growth failure as a consequence of GHD, primary hypothyroidism, gonadal failure, and decreased BMD. Therefore, FA patients who undergo HSCT should be closely monitored for hormonal abnormalities. Some of the guidelines are outlined in the Children's Oncology Group website on long-term follow-up, available at: http://www.survivorshipguidelines.org/.

How Specific Therapies Affect the Endocrine System: Examples

- **Busulfan** can adversely affect thyroid function [63] and sometimes growth [64, 65]. It is highly toxic to gonads and can lead to gonadal failure, particularly in females [66, 67].
- **Cyclophosphamide (Cytoxan)** has a known dose-related effect on gonadal function in both males and females, particularly when used in combination with busulfan [68-71].
- **Glucocorticoids** can lead to increased appetite, weight gain, insulin resistance, and hyperglycemia, sometimes creating the need for insulin therapy. Prolonged use of glucocorticoids may cause linear growth failure and delayed puberty. Glucocorticoids adversely affect bone mineralization [72].
- **Methotrexate** increases the risk for bone loss [73, 74].
- **Total body irradiation (TBI)** increases the risk of primary hypothyroidism [75, 76], growth impairment [64, 77], hypogonadism [71, 78], and poor bone mineralization [79, 80].
- **Metoclopramide** raises prolactin levels. This can lead to leakage of fluid from the breasts, known as galactorrhea, and alteration of thyroid function or pubertal development.
- **Anticonvulsant therapy** can alter thyroid function or thyroid dose requirements. Some anticonvulsants, such as Valproate, can lead to weight gain and altered ovarian function.

Conclusions

Endocrine problems are common in patients with FA. These patients are often—though not always—shorter than the general population. Individuals with FA may have reduced GH secretion, hypothyroidism, and abnormal glucose homeostasis with deficient pancreatic beta cell secretion of insulin and/or insulin resistance. Puberty, gonadal function, and fertility may be affected in these patients. Children with FA tend to have normal BMD. In adults it is not clear if the BMD, which is typically low, should be adjusted for height and if these measures correlate with the risk of bone fractures. However, the high incidence of endocrine dysfunction—especially hypogonadism, corticosteroid use, and HSCT—may predispose adults with FA to osteoporosis.

The origin of endocrine disorders in patients with FA remains unclear. Hypothyroidism is generally accompanied by elevated TSH levels and thus seems to arise from problems with the thyroid gland, although hypothalamic-pituitary dysregulation leads to abnormal central TSH release in some patients. Hyperglycemia/hyperinsulinemia is generally thought to arise from pancreatic beta cell dysfunction, but insulin resistance and metabolic syndrome are also common in patients with FA. In contrast, GH insufficiency probably arises from problems with the hypothalamus or pituitary gland.

Currently, a single unifying cause for all of these endocrinopathies is not known. It is possible that endocrine secretory cells are damaged by excessive reactive oxygen species, with inadequate repair mechanisms in patients with FA. In addition, treatments used in FA such as androgens, glucocorticoids, chemotherapy, or irradiation with HSCT may contribute to endocrine dysfunction.

Individuals with FA should be followed for the most common endocrine abnormalities, including growth failure, hypothyroidism, hypogonadism, and glucose/insulin abnormalities. The multidisciplinary patient care team should include an endocrinologist to initiate the work up and management of endocrine disorders.

Chapter Committee

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