EXPERT OPINION

Hormone therapy in Fanconi anemia

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Introduction: Fanconi anemia (FA) is a genetic condition with extreme cancer predisposition resulting from abnormalities in repair of DNA breakage and crosslinks. Children with FA develop bone marrow failure (BMF) that is treated with androgen or hematopoietic cell transplantation, and are at risk for developing acute myeloid leukemia. In adulthood, persons with FA commonly develop squamous cell carcinomas of the head, neck or gynecological tract. Endocrine problems are common in FA.

Areas covered: Chromosomal breakage may lead to apoptosis of endocrine secretory cells. About 80% of children and adults with FA have at least one endocrine abnormality, and benefit from thyroid hormone therapy and vitamin D therapy. Some benefit from growth hormone therapy. Metformin may be beneficial if overweight develops, in view of the underlying insulin deficiency in FA. Estrogen or testosterone therapy is often required to complete pubertal development.

Expert opinion: Individuals with FA should be routinely screened for endocrine abnormalities, and when found to have hormone deficiencies, they should be treated with standard endocrine therapy. Research is needed to address a number of limitations and gaps in knowledge regarding mechanisms of endocrine deficiencies, safety/efficacy of endocrine therapies, and prevention of oxidative injury to DNA.

Keywords: endocrinopathy, Fanconi anemia, growth, puberty, thyroid

Expert Opinion on Orphan Drugs [Early Online]

1. Introduction

1.1 Chromosomal breakage in FA

FA is a genetic condition with extreme cancer predisposition from chromosomal breakage, resulting from abnormalities in repair of DNA crosslinks. Inheritance is autosomal recessive, so one in four children of parents each carrying a mutation will develop FA. So far, 18 FA genes have been identified, all involved in the molecular complex that repairs DNA breakage [1]. A number of the FA genes are also breast cancer susceptibility genes (including BRCA2), and research on FA relates to cancer research in general.

1.2 Features of FA

Children with FA are often born small for gestational age. About half of them have congenital abnormalities including abnormal thumbs and radii; abnormal head, eyes, ears, heart, kidneys; café au lait spots; and short stature. Other children with FA have no congenital defects and tend to have normal growth patterns until they are noted to have BMF. Children with FA typically develop gradual BMF in childhood; then clones of abnormal cells develop in the marrow, potentially progressing to acute myeloid leukemia. Historically, children with FA died by adolescent age. Now the development of leukemia can be prevented by hematopoietic cell transplantation (HCT) when the process of BMF starts. BMF may present

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Article highlights.

- Persons with FA should be evaluated by an endocrinologist.
- Common endocrine issues in FA are hypothyroidism, hyperglycemia with insulin deficiency, small stature, and gonadal dysfunction.
- Hormone deficiencies in FA should be treated with standard endocrine therapy.

This box summarizes key points contained in the article.

with aplastic anemia, myelodysplasia syndrome, a decline in platelet count, or unexplained macrocytic red cells. In adulthood, persons with FA commonly develop squamous cell carcinomas of the head, neck, or gynecological tract. The current median lifespan in FA is ~ 33 years.

Children should be evaluated for FA if they have any of the issues listed in (**Table 1**), or if they have family history of the following: FA, abnormal thumbs, features of VACTERL or of radial ray or renal anomalies, aplastic anemia, acute myeloid leukemia, myelodysplastic syndrome, or other specific tumors (squamous cell carcinoma of the head and neck, vulvar/vaginal, cervical, or esophageal region, medulloblastoma, Wilms tumor, neuroblastoma, retinoblastoma) [1-3].

1.3 Endocrinology of FA

About 80% of children and adults with FA have at least one endocrine abnormality [1,4,5]. Hypothetically, some endocrine cells may die because of unrepaired DNA damage from oxidative injury. FA proteins are directly involved with the machinery of cellular defense and the modulation of oxidative stress [6,7]. Endocrine deficiency in the FA population may result from DNA damage from excessive reactive oxygen species leading to cell death and loss of endocrine cell mass and secretory ability. Typically, children with FA do not grow to the height expected given the heights of their parents. Short stature may result from reduced growth hormone (GH) secretion, hypothyroidism, or abnormal glucose homeostasis with inadequate insulin secretion (as insulin is required for normal growth). Timing of onset and progression of puberty, along with gonadal function and fertility, may be abnormal [4,5]. Adults with FA have been reported to have osteopenia or osteoporosis.

2. Short stature

2.1 Treatment

Treatment for growth failure or short stature requires identification of the underlying cause. The etiology of short stature in FA includes endocrine and non-endocrine causes. Among the latter are factors such as undernutrition, FA mutations, parental heights, and birth size, as well as transplant status and medications. Approximately half of FA children are born small for gestational age (SGA), with length or weight below two standard deviation units from the mean for age (SD) [5]. After SGA birth, many FA babies do not catch up into the normal range. Healthy nutrition is important for maintaining optimal growth, along with treatment of any deficiency of thyroid hormone, vitamin D, GH, or pubertal hormone.

Patients with FA who have hormone deficiencies are shorter (average height -2.2 SD) than those with normal hormone production (average heights of -1 and -1.7 SD in children and adults, respectively) [5,8]. However, FA individuals with normal hormone production still tend to be shorter than average, with only about half of them being within the normal range. Adult heights of individuals with FA range from -4SD to the population mean (average adult height in FA: men 161 cm or 5 feet 3.5 inches; women 150 cm or 4 feet 11 inches).

2.2 Screening

Growth in children with FA should be closely followed using measurements of height and weight obtained at least yearly. Nutritional and other medical causes for poor growth should be identified in children with FA as early as possible. Children with height ≤ -2SD, or who show a decline in annual growth velocity, should be evaluated by a pediatric endocrinologist. Endocrine evaluation should include assessment of growth and thyroid hormones, and pubertal status (**Table 2**). Assessment of bone age (BA) is part of a standard endocrine evaluation for short stature. Androgen therapy may accelerate bone maturation, whereas hypothyroidism, GH deficiency (GHD), hypogonadism, and corticosteroid therapy are associated with delayed BA.

3. Undernutrition

3.1 Treatment

Healthy dietary intake should be encouraged, including sufficient calories, calcium and vitamin D. Underlying causes of poor weight gain should be addressed, including treatment of endocrine disorders.

3.2 Screening

Weight should be assessed at least yearly and more frequently if there is evidence of failure to thrive relative to standard norms. If there are concerns, nutritional intake should be assessed by a registered dietician. Underlying medical conditions, concurrent medications, specific hormone-related conditions and related co-morbidities should be evaluated.

4. Hypothyroidism

4.1 Treatment

Hypothyroidism should be treated promptly, particularly in children younger than 3 years of age. Thyroid hormone replacement treatment should be started if free thyroxine (T4) is below the laboratory reference range and/or if thyroid-stimulating hormone (TSH) is above the reference range (**Table 3**). In primary hypothyroidism, target for thyroid hormone therapy should be TSH in the range of 0.5 – 2 mU/L. In central

Table 1. Patients who should be evaluated for FA.

Characteristic/ body Part	Specific feature
Height	Short stature, microsomia
Skin	Café au lait spots, skin pigmentation (hyper, hypo)
Upper Limbs	
Radius:	Absent, hypoplastic, absent or weak pulse
Thumb:	Absent, hypoplastic, bifid, duplicated, rudimentary, attached by thread, triphalangeal, long, low set, digitized
Thenar-eminence:	Flat, absent
Hand:	Absent first metacarpal, clinodactyly, polydactyly
Ulna:	Short, dysplastic
Head	Microcephaly, hydrocephaly
Face	Triangular, birdlike, dysmorphic, mid-face hypoplasia
Neck	Sprengel, Klippel-Feil, short, low hairline, web
Spine	Spina bifida, scoliosis, hemivertebrae, coccygeal aplasia
Eyes	Strabismus, epicanthal folds, hypotelorism, hypertelorism, cataracts, ptosis
Renal	Horseshoe, ectopic, pelvic, hypoplastic, dysplastic, absent, hydronephrosis, hydroureter
Gonads	
Male	Hypogenitalia, undescended testis, hypospadias, micropenis, absent testis, infertility
Female	Hypogenitalia, bicornuate uterus, malposition, small ovaries, late menarche, early menopause, infertility
Development	Mental retardation, developmental delay
Ears	
Deafness:	Conductive, sensorineural, mixed
Shape:	Abnormal pinna, dysplastic, atretic, narrow canal, abnormal middle ear bones
Speech	Delayed, unclear
Cardiopulmonary	Congenital heart disease: patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation, situs inversus, truncus arteriosus
Low birth weight	
Lower limbs	
Hips:	Congenital hip dislocation
Feet:	Toe syndactyly, abnormal toes, club feet
Gastrointestinal	Tracheoesophageal fistula
	Esophagus, duodenum, jejunum, imperforate anus, annular pancreas
	Malrotation
	Poor feeding
Central nervous system	
Pituitary:	Small, stalk interruption, PSIS, ectopic pituitary bright spot on MRI
Structure:	Absent corpus callosum, cerebellar hypoplasia, hydrocephalus, dilated ventricles

Adapted from reference [1-3].

hypothyroidism, target for thyroid hormone therapy should be a free T4 just above the middle of the normal range (whereas TSH typically will be suppressed on therapy).

There is potential growth benefit in FA with the use of levothyroxine if TSH > 3 mU/L, as shown by a prior study [9]. Eight children with FA were treated in random order for 7 months with thyroid hormone, compared to 7 months with placebo. 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 [10]. Thus, children with FA who have short stature and borderline thyroid function tests may benefit from using thyroid hormone therapy.

4.2 Screening

Thyroid function should be evaluated by obtaining an early morning (e.g., 8 am) blood sample for free T4 and a TSH level. All FA patients should undergo screening for hypothyroidism yearly or more frequently if clinically indicated (example, growth failure, or children under age 3 years) (**Table 2**). Central hypothyroidism is suggested by a low free T4 and a ratio of TSH at 0800h to TSH after 1000h of < 1.3 [10]. If central hypothyroidism is identified, patients should undergo evaluation for ACTH deficiency, and pituitary MRI should be done.

5. Growth hormone deficiency

5.1 Treatment

Guidelines for GH therapy in the general population have been published [11,12]. GHD can be treated with recombinant human GH therapy (**Table 3**). In spite of the risk for cancer inherent in FA, a short child with FA can be treated with GH if they have been convincingly documented to have GHD (short stature, growth rate below normal, and low GH peak on stimulation testing). Severe short stature may have a negative impact on a child's quality of life and daily

Table 2. Endocrine recommendations for annual endocrine screening in patients with FA.

Parameters	Annual screening	Additional tests
Growth, weight	Height and weight plotted on growth chart	For growth failure –IGF-I, IGFBP3 –BA radiograph –Free T4/TSH For suspected GHD: –GH stimulation tests –MRI pituitary if evidence of any pituitary hormone deficiency
Glucose, insulin and metabolism	Fasting & 2-h post-prandial glucose and insulin HbA1c (after HCT) Fasting lipid profile (after age 10y)	If overweight/obese or hyperlipidemia –2 h OGTT testing if previous abnormal OGTT but not diabetic –Repeat OGTT yearly
Thyroid	Height and weight plotted on growth chart Early morning TSH, FT4 yearly	For suspected central hypothyroidism: –Ratio of 0800h TSH to afternoon TSH
Cortisol		ACTH stimulation testing if evidence of any other pituitary hormone deficiency, or pituitary abnormality on MRI.
Puberty and gonadal function	Pubertal staging of pubic hair, and breasts (girls) or testes (boys) during physical examination Assess menstrual history and clinical evidence for hypogonadism in post-pubertal individuals	If early/delayed puberty or suspected hypogonadism: –BA radiograph –LH and FSH –estradiol and AMH in females –testosterone and inhibin-B in males
Bone mineral	Assess dietary calcium and vitamin D intake Measure 25OH-vitamin D	DXA scan for BMD: –every 5 years starting at age 14 years –Pre-HCT and one year after HCT –Repeat in a year if diagnosed low BMD –Every 2 years if hypogonadism or premature ovarian failure

Adapted from reference [1].

25OH-vitamin D: 25-hydroxy-vitamin D level; ACTH: Adrenocorticotropic hormone; AMH: Anti-Mullerian hormone; BA: Bone age; BMD: Bone mineral density; DXA: Dual x-ray absorptiometry; FSH: Follicle-stimulating hormone; FT4: Free thyroxine; GH: Growth hormone; HCT: Hematopoietic cell transplant; HgbA1c: Glycosylated hemoglobin; IGF-I: Insulin-like growth factor; IGFBP3: IGF-binding protein 3; LH: Luteinizing hormone; SD: Standard deviation units (Z-score) from the mean; TSH: Thyrotropin.

functioning. However, treatment with GH in FA in the absence of GHD is controversial, and there is no consensus on the safety of GH therapy in FA patients.

Families with FA should be counseled about predicted adult heights, effects of GH hormone therapy on the growth rate, and potential risks and benefits of GH treatment. Only one small study has been published on the efficacy of GH treatment in FA and GHD after HCT [13]. GH treatment resulted in a significant increase in the growth rate in three of the four patients. The mean increase in height was 0.9 ± 0.6 SDS. There were no adverse events from GH.

There continue to be concerns about long-term safety after GH therapy during childhood, even in children with a normal medical history. The majority of reports are reassuring; however a few reports have raised concerns about GH therapy having effects on tumor growth [14-21], or on vascular health including heart disease and stroke [22-24], with greater concerns in patients treated with higher GH doses. However, several studies have suggested that any association of GH therapy with stroke risk may be incorrect [18,25-29]. Overall, "there are real risks to taking GH…we must ensure that there are sound reasons for treatment with GH and that the benefits outweigh the risks" [30].

If the decision is made to use GH therapy in FA patients who have GHD, the GH dose should be titrated to achieve insulin-like growth factor-I (IGF-I) concentrations in the mid-normal range for age (between 0 and +1 SD). IGF-I is generated in tissues in response to GH levels. GH therapy should be discontinued immediately if routine hematological examination reveals clonal hematopoietic stem cell proliferation.

5.2 Screening

Screening for GHD in a short child with a slow growth rate includes measurement of IGF-I and IGF-binding protein 3 (IGFBP3) levels (**Table 2**). If IGF-I and IGFBP3 values are below the mean for age by more than one SD, evaluation should include standard GH stimulation testing [31]. Of note, IGF-I is known to be a poor marker of GHD in individuals who have received total body or cranial irradiation. Sex steroid priming should be included as preparation prior to GH stimulation testing in pre-pubertal girls age 10 years and older, or in pre-pubertal or early pubertal boys age 11 years and older [32]. Evaluation of GH secretory ability usually includes clonidine (150 mcg/m^2, maximum dose 300 mcg) and arginine (0.5 g/kg, maximum dose 20 g), or glucagon (0.3 mg/kg, maximum dose 1 mg) [32-34]. GH peak is

Table 3. Hormone treatment in patients with FA.

Hormone	Dosing	Monitoring	Potential side effects
Thyroid hormone (levothyroxine)	Infant–10 – 12 mcg/kg/d Age 3 – 13y–3 mcg/kg/d 14+y–1.5 – 2 mcg/kg/d	TSH & FT4 every 3m TSH every 6m TSH every 6 – 12 m	If dose high–tachycardia
Growth hormone (somatotropin)	0.2 – 0.3 mg/kg/wk divided into dose/d	IGF-I & IGFBP3 every 3 – 6 m	Bruising, hyperglycemia, slipped capital femoral epiphysis, unknown effect on cancer risk
Hydrocortisone	HC–10 mg/m2/d divided into 2 – 3 doses/d Triple dose for illness	None	If dose high– excess weight, poor growth, osteopenia, cataracts
Insulin	0.3 – 1.5 unit/kg/d (half, as long-acting/d; half, divided pre-meals, short-acting)	4 to 10 blood sugars/d fasting, pre-meals, at bedtime	Bruising, if dose high–hypoglycemia
Metformin	Start dose slowly: age 7 – 12 y–250 mg twice daily (not FDA-approved) age > 12y–1000 mg twice daily	Blood sugar fasting & pre and 2h after dinner weekly	Abdominal pain, diarrhea
Gonadotropin-releasing hormone agonist (GnRHa)	3m form–11.25 mg every 3m	Pubertal staging every 6m Bone age x-ray yearly	Hot flashes, delay in bone mineral accrual
Testosterone	IM–start 40 – 50 mg/m2/m Adult dose 150 – 200 mg every 2 weeks Gel transdermal–start 0.5g/d; adult 5 g/d	Clinical Serum testosterone	If dose high–high hemoglobin, rapid bone maturation, decreased adult height
Estradiol	PO–start 5 mcg/d Patch–12.5 mcg 2X/wk Adult–standard OCP	None	If dose high–nausea, rapid bone maturation, decreased adult height
Progesterone	Start after spotting– 10 mg po/d for 10d every 3 m	None	none
Vitamin D	RDA 1000 units daily If 25OHD < 25, start 50,000 units weekly for 3 m	Serum 25OHD	If level high–hypercalcemia, hypercalciuria
Bisphosphonates	Pamidronate 1 mg/kg IV over 3 h, every 3 m	Repeat DXA after 1y	Fever, hypocalcemia, tetany (endocrinologist supervision)

25OHD: 25 hydroxy- vitamin D; 2X: Twice; d: Day; DXA: Dual photon x-ray absorptiometry; FT4: Free T4; h: Hour; IM: Intramuscular; IGFBP3: IGF-binding protein; IV: Intravascular; mcg/kg/d: Micrograms per kilogram per day; mg: Milligrams; m2: Meter squared or body surface area; m: Month; po: Oral; RDA: Recommended daily allowance; wk: Week; y: Year.

considered a normal stimulated response if it rises to a value of 10 ng/ml or greater by radioimmunoassay [35]. Patients identified to have GHD should undergo evaluation also for central hypothyroidism, central adrenocorticotropin (ACTH) insufficiency, and also should undergo MRI scan with pituitary imaging.

6. Pituitary hormone deficiencies

6.1 Treatment

Appropriate hypothalamic-pituitary hormone treatment should be instituted in patients diagnosed with pituitary abnormalities, including those with precocious puberty or deficiencies of thyroid hormone, GH, hydrocortisone, or pubertal hormones (**Table 3**).

6.2 Screening

Screening should be performed annually for thyroid function, and as clinically appropriate for GH secretion and gonadal function (**Table 2**). As children with FA have the possibility of hypothalamic dysfunction, even in the absence of a detectible midline central nervous system defect, cortisol sufficiency should be evaluated in young FA children who have poor growth and who will require major surgery [36,37]. ACTH stimulation testing also is recommended to exclude the presence of ACTH insufficiency if other pituitary hormone deficiencies are present. Of note, pituitary hormone deficiencies may evolve over time, so yearly hormone screening is necessary.

MRI of the brain and pituitary shows that often the pituitary is smaller with a thinner stalk in some patients with FA compared to that of age-matched children without FA [36]. MRI imaging may show PSIS (pituitary stalk interruption syndrome) [38]. A brain MRI with emphasis on the pituitary/hypothalamic area should be obtained in any FA patient with growth failure, height of -3 SD or shorter, or with one or more pituitary hormone deficiencies, including GHD, central hypothyroidism, or ACTH deficiency.

7. Dyslipidemia and obesity

A healthy diet and exercise regimen should be emphasized. Fasting lipid profile should be considered on an annual basis in patients > 10 years (**Table 2**). Screening should also include blood pressure measurement.

8. Abnormal glucose or insulin metabolism

8.1 Treatment

Children and adults with FA tend to have hyperglycemia, especially after eating. Impaired early insulin secretion in patients with FA may result from damage to DNA from enhanced reactive oxygen species (ROS) action in the β-cells (which secrete insulin), or from iron overload in heavily transfused patients. Androgen treatment used in FA can lead to significant rise in both glucose and insulin levels [8]. Chronic steroid therapy also predisposes to insulin resistance and hyperglycemia [7,39,40]. As in other children, glucocorticoid use in FA should be limited to the minimum necessary.

A low glycemic index diet is useful for control of the serum glucose, because of the sluggish insulin secretion in FA in response to a glucose load. Patients diagnosed with FA–regardless of oral glucose tolerance test (OGTT) results–should be placed on a healthy diet that avoids concentrated sweets and excessive sugar intake. This recommendation applies only to concentrated sweets (e.g., juices, soda, and candy) and not all forms of carbohydrate. It is important to ensure adequate caloric consumption and regular exercise. Obtaining assessment and recommendations from a registered dietician can be helpful.

During HCT, many children with FA require insulin therapy for hyperglycemia related to steroid therapy (**Table 3**). A combination of long-acting and short-acting insulin may be required for adequate glucose control. The duration of therapy may vary depending on the duration, dose and type of transplant medications used (corticosteroids, tacrolimus, sirolimus, etc). FA patients treated with insulin for their diabetes should be followed by an endocrinologist. The goal for insulin therapy is improved glucose control without hypoglycemia. Treatment with short-acting insulin at mealtime (carbohydrate coverage), without long-acting insulin, can be considered if post-prandial glucose is consistently > 180 mg/dL. Whether FA patients with normal fasting glucose but impaired glucose tolerance should be treated with insulin is less clear. Use of short-acting insulin with meals may be more beneficial than metformin, due to the sluggish insulin release in response to carbohydrate intake in FA. However, metformin may be beneficial in FA individuals who have hyperinsulinemia related to being overweight (**Table 3**). Such use in FA should be accompanied by increased surveillance, as potential risk for side effects is not known. There are no long-term data on the risks or benefits of metformin in FA patients.

8.2 Screening

All FA patients should be tested for abnormalities of glucose and insulin homeostasis upon diagnosis of FA and, then screened yearly (**Table 2**). Screening for glucose tolerance can be performed with fasting glucose and insulin, plus a single post-prandial sample (2 h after a meal) for glucose and insulin concentrations. Obtaining only fasting serum glucose values may miss identifying patients with impaired glucose tolerance. Glycosylated hemoglobin (HbA1c) and fructosamine are not helpful in FA patients prior to HCT, presumably due to impaired glycosylation or elevated levels of fetal hemoglobin in those with BMF [5]. HbA1c may be more useful as a screen after HCT.

In those with suspected abnormalities, a 2-h OGTT (1.75 gm/kg, maximum dose 75 gm) should be performed with samples for both glucose and insulin levels every 30 min. Abnormal OGTT results should be repeated yearly. The prevalence of diabetes mellitus in FA is age- and disease progression-dependent. The majority of FA patients may be at risk.

9. Puberty, hypogonadism, and fertility

9.1 Treatment

In the child with FA who has early onset of puberty and short stature, use of gonadotropin releasing hormone agonist therapy can delay puberty to achieve an average of a 4 – 5 cm increase in adult height over 4 years of therapy [41] (**Table 3**).

Causes of delayed puberty in FA include chronic illness, poor weight gain, or GH or thyroid hormone deficiency. In addition, total body irradiation and some chemotherapy agents used with HCT may affect gonadal function and may contribute to decreased fertility after HCT. Adult FA patients have a high incidence of hypogonadism. Delayed puberty can be treated using sex steroid therapy. However, avoiding rapid increase in sex hormone levels is important in short adolescents, both boys and girls, in order to avoid premature fusion of the growth plates.

In a boy with no signs of puberty by age 14 years, low dose testosterone therapy can be initiated, taking into account height and growth potential (**Table 3**). Treatment modality can include topical gel preparations or injections of testosterone started at an appropriate low dose and gradually titrated up over several years to adult replacement levels.

In a girl with FA who has no signs of puberty by age 13 years, low-dose estrogen therapy may be started and slowly titrated under the care of the pediatric endocrinologist or adolescent gynecologist, taking into account height and potential for growth (**Table 3**). Estrogen therapy will increase bone mineralization, optimize growth rate, and achieve breast development. Progesterone should be added when breakthrough bleeding occurs or after 2 years of estrogen replacement (**Table 3**). 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 [elevated follicle-stimulating hormone (FSH) or low anti-mullerian hormone (AMH)]. In FA, there is no medical contraindication to the use of oral contraceptive pills.

9.2 Screening

Onset of puberty, pubertal stage, and tempo of progression of puberty should be monitored by yearly physical examination including assessment of Tanner staging of pubic hair, breast development (in girls) and testicular size (in boys) (**Table 2**). Assessment of bone maturation (BA) can be useful in adolescent children who have delayed or abnormal progression of puberty, whereas hormone concentrations (LH or luteinizing hormone, FSH, estradiol, and AMH in females; LH, FSH, testosterone, and inhibin B in males) can be useful in adolescents and in adults with symptoms of hypogonadism.

10. Bone mineral density

10.1 Treatment

Among other dietary recommendations, it is important to maintain adequate dietary intake of calcium and vitamin D in order to offer opportunity for normal growth and mineralization of bone, especially if bone mineral density (BMD) is low after adjustment for height (**Table 3**). Vitamin D levels should be targeted to achieve vitamin D sufficiency (> 30 ng/ml) [42]. Treatment of hormone deficiency, specifically treatment of pubertal delay, hypogonadism, and GHD, can also be beneficial for bone mineralization. HCT is associated with decreased bone formation and increased bone resorpsion [43]. Medications used during HCT, such as glucocorticoid therapy, may also contribute to low BMD.

An experienced endocrinologist or nephrologist may consider treatment with bisphosphonates (after addressing vitamin D deficiency) (**Table 3**). Indications for bisphosphonate therapy include height-adjusted BMD Z-score lower than -2.0 SD with clinically significant fractures defined as a long bone fracture of the lower extremities, vertebral compression fracture, or two or more long bone fractures of the upper extremities [44-46]. The risk/benefit ratio [47] must be evaluated by specialists prior to treatment.

10.2 Screening

Children with FA should have a vitamin D measurement annually, along with providing history of their dietary intake of vitamin D and calcium (**Table 2**). Serum calcium, phosphorus, magnesium and 25-OH vitamin D levels should be evaluated in HCT recipients and in patients with low BMD [48]. Dual energy absorptiometry (DXA) evaluation of BMD is recommended before HCT and 1 year after HCT. DXA evaluation may begin at about age 14 years if there has been no HCT, with follow-up scans dictated by risk factors. BMD measurement by DXA in children with FA should be adjusted for height and BMD Z-scores calculated. The calculator at this website http://www.bmdcspublic.com/zscore.htm [49] can be used to calculate height-adjusted Z-score in children with FA. FA patients with history of prolonged or high doses of corticosteroids, history of fractures, immobility, hypogonadism, or GHD should also have evaluation for low BMD.

11. Summary

Endocrine problems are common in FA. Persons with FA are usually shorter than the general population and do not grow to their target heights. However, some persons with FA have normal height. Individuals with FA may have hypothyroidism, reduced GH secretion, and hyperglycemia. Puberty, gonadal function and fertility may be abnormal. Children with FA usually have BMD Z-scores within the expected range for age when adjusted for their short stature, but lower than average. The high incidence of endocrine dysfunction, especially hypogonadism, corticosteroid use, and HCT itself may predispose to development of osteoporosis.

The etiology of endocrinopathies in FA is unclear. Hypothyroidism is generally accompanied by elevated TSH levels and, therefore, appears to be of thyroidal (i.e., peripheral) origin, although hypothalamic-pituitary dysregulation leading to abnormal central TSH release may also be present. Hyperglycemia/hyperinsulinemia is generally considered to be related to pancreatic beta cell dysfunction, but insulin resistance and metabolic syndrome are also common. In contrast, GH insufficiency is probably of hypothalamic or pituitary (i.e., central) origin. Currently, a single unifying cause for all of these endocrinopathies is not known. It is possible that in FA endocrine secretory cells are damaged by excessive reactive oxygen species, with inadequate repair mechanisms leading to cell death. In addition, treatments used in FA such as androgens, glucocorticoids, chemotherapy or irradiation with HCT contribute to endocrine dysfunction.

Individuals with FA should be routinely screened for endocrine abnormalities. The multidisciplinary patient care team should include an endocrinologist to initiate the work up and management of endocrinopathies, a dietician, a gynecologist, and a reproductive endocrinologist when appropriate. The endocrine team should work in close collaboration with other FA specialists to provide comprehensive care for individuals with FA.

12. Expert opinion

12.1 Key findings and weakness of research in field?

The pattern of potential endocrine deficiencies in children and adolescents with FA has been well-described. However, not as much is known about gonadal function in adolescents, or about endocrine function in adults with FA. Mechanisms underlying development of hormone deficiencies have only just begun to be investigated *in vitro* and in animal studies.

Table 4. Persistent questions for future research.

Short stature
- What is a "normal" growth pattern for FA children before HCT?
- What is the impact of short stature on adult quality of life?
- How are endocrine deficiencies associated with FA gene mutations?

Thyroid
- What are the mechanisms underlying the development of hypothyroidism in FA?
- Are there growth benefits for initiating thyroid hormone treatment using a lower TSH cutoff?
- Are there benefits to thyroid hormone replacement in FA adults who have mild TSH elevation (e.g., on lipid profile)?

Growth Hormone
- What are the efficacy and safety issues of GH treatment in FA?
- What is the appropriate timing for initiation of GH treatment?
- Can the response to a GH stimulation test predict growth response to GH treatment?
- Should GH treatment be used in FA (either before or after HCT) for severe short stature, regardless of results of GH stimulation tests?
- What should be the cutoff value for height SD score when considering GH therapy?
- What are the effects of GH treatment on body composition and glucose/insulin metabolism in FA?
- Should adults with FA be tested for GHD and should GH therapy be initiated in adult GHD?
- Does FA mutation correlate with response to GH therapy?
- Does GH treatment in FA increase cancer risk?

Pituitary
- What is the occurrence of ACTH deficiency in FA?
- What is the occurrence of multiple pituitary hormone deficiency in FA?
- What is the occurrence of pituitary structural abnormalities in FA?
- Are pituitary hormone deficiencies in FA congenital or progressive?
- Does the conformation of the pituitary change over time?
- What is the correlation between small pituitary, or pituitary stalk interruption syndrome, on MRI and clinical phenotype?

Nutrition/Abnormal glucose
- Are there age-specific optimal dietary guidelines for FA?
- Can age-specific nutrition prevent/mitigate glucose intolerance?
- What are the relative benefits of low glycemic index, complex carbohydrates, mixed composition of meals?
- Do specific insulin or glucose levels during OGTT or a mixed meal tolerance test predict progression to overt diabetes in FA and thus identify patients who might benefit from intervention?
- When (at what age or at what evidence of glucose intolerance) and in whom to initiate insulin therapy?
- What is the efficacy of insulin therapy in FA in improving weight and linear growth rate?
- What are the safety issues and efficacy of insulin sensitizers in FA persons with abnormal glucose tolerance or insulin resistance?

Dyslipidemia, obesity
- What is the relationship between leptin levels and BMI in FA?
- What is optimal therapy for elevated BMI in FA?
- What is the prevalence of metabolic syndrome in FA?
- What are the lipid patterns in FA and age of onset of dyslipidemia?
- Are lipid abnormalities more common in FA adults who have uncorrected or undiagnosed endocrine deficiencies such as gonadal insufficiency, GHD, or thyroid hormone deficiency?
- What is optimal therapy for dyslipidemia in FA?
- What is the long-term cardiovascular risk in FA?
- What is the role of oxidative stress and lipid peroxidation in metabolic syndrome in FA?
- What are the factors that contribute to development of metabolic syndrome in FA?
- What is the association between FA molecular mutations and impairment of insulin secretion/action?

Puberty
- What is the mechanism underlying the frequent occurrence of small testes in FA males, even from infancy?
- Does the normal physiologic puberty of infancy occur in FA babies?
- How do LH and FSH levels change with age in babies and children with FA?
- What is the role of the physiologic puberty of infancy in later gonadal function in FA?
- What is the pattern of progression of gonadal function in FA during adolescence in males and in females?
- What is the risk for decreased gonadal function and premature ovarian failure in women with FA?
- How does gonadal function, fertility, and gonadal hormone production progress in adults with FA?
- How to optimally monitor gonadal function in adult men and women with FA?
- When should men with FA have testing done to quantitate their sperm count and morphology?
- What factors affect fertility in adults with FA?
- What is the optimal testing for infertility in FA males?
- What is the phenotype and health of infants born to FA individuals?
- What issues are important related to ethics of fertility in FA adults?

BMD: Bone mineral density; GHD: GH deficiency.

Table 4. Persistent questions for future research (continued).

Bone Mineral
• What are the mechanisms for decreased BMD following HCT in FA children?
• What is the optimal way to adjust for areal BMD in short stature in FA?
• What is the time-course of BMD change over time in persons with FA?
• Is BMD low in adults with FA and does it decline over time. If yes, what are the factors affecting BMD in FA?
• What is the true fracture risk in adults with FA (hip and vertebral collapse)?
• How does fracture risk correlate with measures of BMD in FA adults?
• What are the factors potentially contributing to low BMD in FA adults?

BMD: Bone mineral density; GHD: GH deficiency.

12.2 Potential of field, ultimate goals of field?

Investigation into regulation of repair of chromosomal breakage has implications far beyond FA, having relevance for all cancer research.

In addition, research in the field of endocrine function in FA has the potential to enhance quality of life for individuals with FA.

12.3 What research is needed to accomplish this goal?

Research is needed to identify optimal timing of endocrine screening and optimal endocrine replacement therapy. Research is also needed into prevention of development of endocrine dysfunction.

12.4 Where is the field going in the future?

Future research will evaluate interventions to reduce oxidative injury and as a result, prolong not only endocrine function but also prolong normal bone marrow function and reduce cancer risk.

12.5 Which area of research is of great interest?

Aside from bone marrow transplantation or gene therapy, intervention to reduce oxidative injury has great potential to reduce morbidity in persons with FA.

12.6 How will this impact management and treatment of patients?

Progress in this area could benefit not only individuals with FA, but also other persons with elevated cancer risk.

12.7 Additional comments

I believe that optimizing nutrition is critical as a first-line therapy, because health, hormones, and growth are compromised by malnutrition.

Overall, standard endocrine therapies (thyroid hormone, vitamin D, pubertal hormone replacement, metformin, insulin) should be used for diagnosed endocrine deficiencies in FA, even though FA is a rare genetic syndrome associated with a cancer predisposition. The important issue is to monitor closely for outcomes and potential side effects after instituting therapy.

Sex steroid therapy to permit pubertal development should not be added until the child is tall enough.

I propose that insulin could be used at mealtimes to reduce glucose excursions even in the absence of diabetes, in view of the sluggish insulin response to glucose load in FA. Such intensive insulin therapy might make the child more anabolic and contribute to improved muscle mass and faster linear growth rate.

I propose that GH therapy for short stature associated with GHD could be used when IGF-I is low, in the presence of an adequately nourished state, in order to bring the IGF-I into the mid-normal range. IGF-I should not be pushed by GH therapy above the mid-normal range.

I believe that thyroid hormone therapy should be used in FA children who have TSH above 3 mIU/L, as it is a benign therapy that may enhance growth rate if the child is well-nourished.

Long-term risk of hormone treatment in persons with FA is unknown; therefore continued surveillance is needed. FA individuals are inherently at a life-long increased risk for malignancy, including head and neck and gynecological cancers, and acute leukemia particularly prior to HCT [50-52]. Although HCT reduces the risk of leukemia, all individuals with FA remain at increased risk of solid tumors. Questions which could stimulate new research are given in (**Table 4**). Although knowledge about endocrine issues and endocrine therapy in FA has advanced significantly, new knowledge generates new questions.

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Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Fanconi Anemia: Guidelines for Diagnosis and Management. In: Hays L, Frohnmayer D, Frohnmayer L, Guinan E, Kennedy T, 4th Edition. Fanconi Anemia Research Fund, Inc, Eugene, 2014. Available from: http://fanconi.org

•• **Comprehensive handbook for physicians and families dealing with all aspects of FA, including endocrine aspects.**

2. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev 2010;24(3):101-22

3. Parikh S, Bessler M. Recent insights into inherited bone marrow failure syndromes. Curr Opin Pediatr 2012;24(1):23-32

4. Petryk A, Kanakatti Shankar R, et al. Endocrine disorders in Fanconi anemia: recommendations for screening and treatment. J Clin Endocrinol Metab 2015;100(3):803-11

•• **Summary of the most recent research related to endocrine care of FA.**

5. Rose SR, Myers KC, Rutter MM, et al. Endocrine phenotype of children and adults with Fanconi anemia. Pediatr Blood Cancer 2012;59(4):690-6

6. Li J, Sipple J, Maynard S, et al. Fanconi anemia links reactive oxygen species to insulin resistance and obesity. Antioxid Redox Signal 2012;17(8):1083-98

• **Evidence that oxidative injury alters endocrine cell function in an animal model of FA.**

7. Pagano G, Youssoufian H. Fanconi anaemia proteins: major roles in cell protection against oxidative damage. Bioessays 2003;25(6):589-95

8. Wajnrajch MP, Gertner JM, Huma Z, et al. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. Pediatrics 2001;107(4):744-54

9. Rose SR. Improved diagnosis of mild hypothyroidism using time-of-day normal ranges for thyrotropin. J Pediatr 2010;157(4):662-7

•• **Evidence basis for improved testing for thyroid function, recognizing that 0800h TSH is significantly higher than TSH obtained after 1000h in the morning.**

10. Eyal O, Blum S, Mueller R, et al. Improved growth velocity during thyroid hormone therapy in children with Fanconi anemia and borderline thyroid function. Pediatr Blood Cancer 2008;51(5):652-6

11. Cook DM, Rose SR. A review of guidelines for use of growth hormone in pediatric and transition patients. Pituitary 2012;15(3):301-10

• **Description of the USA Food and Drug Administration approved guidelines for growth hormone use.**

12. Wilson TA, Rose SR, Cohen P, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003;143(4):415-21

13. Forlenza GP, Polgreen LE, Miller BS, et al. Growth hormone treatment of patients with Fanconi anemia after hematopoietic cell transplantation. Pediatr Blood Cancer 2014;61(6):1142-3

14. Kemp SF, Kuntze J, Attie KM, et al. Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature. J Clin Endocrinol Metab 2005;90(9):5247-53

15. Quigley CA, Gill AM, Crowe BJ, et al. Safety of growth hormone treatment in pediatric patients with idiopathic short stature. J Clin Endocrinol Metab 2005;90(9):5188-96

16. Patterson BC, Chen Y, Sklar CA, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 2014;99(6):2030-7

•• **Safety of childhood GH therapy in the Childhood Cancer Survivor Study showing no statistically increased risk for second neoplasia associated with GH exposure, as time goes out from the diagnosis of cancer.**

17. Pekic S, Popovic V. GH therapy and cancer risk in hypopituitarism: What we know from human studies. Eur J Endocrinol 2013;169(5):R89-97

18. Hartman ML, Xu R, Crowe BJ, et al. Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. J Clin Endocrinol Metab 2013;98(3):980-8

• **GH therapy of GHD adults led to no increase in occurance of death, cancer, brain tumor, recurrence, diabetes, or cardiovascular events.**

19. Mackenzie S, Craven T, Gattamaneni HR, et al. Long-term safety of growth hormone replacement after CNS irradiation. J Clin Endocrinol Metab 2011;96(9):2756-61

• **Study showed no increased risk for recurrent or secondary neoplasms during 14 years of follow up in brain tumor survivors who received GH therapy.**

20. Bell J, Parker KL, Swinford RD, et al. Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 2010;95(1):167-77

21. Longmore DK, Conwell LS, Burke JR, et al. Post-transplant lymphoproliferative disorder: no relationship to recombinant human growth hormone use in Australian and New Zealand pediatric kidney transplant recipients. Pediatr Transplant 2013;17(8):731-6

22. Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. Neurol 2014;83(9):780-6

23. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: Preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012;97(2):416-25

24. Erfurth EM. Update in mortality in GH-treated patients. J Clin Endocrinol Metab 2013;98(11):4219-26

25. Sävendahl L, Maes M, Albertsson-Wikland K, et al. Long-term

mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: Preliminary report of 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 2012;97(2):E213-17

26. van Bunderen CC, van Varsseveld NC, Erfurth EM, et al. Efficacy and safety of growth hormone treatment in adults with growth hormone deficiency: A systematic review of studies on morbidity. Clin Endocrinol (Oxf) 2014;81(1):1-14

27. Hindmarsh PC, Peters CJ. Growth hormone treatment and stroke: Should we be concerned? A case for cohort studies. Clin Endocrinol (Oxf) 2014;[Epub ahead of print]

28. Malozowski S. Reports of increased mortality and GH: Will this affect current clinical practice? J Clin Endocrinol Metab 2012;97(2):380-3

29. Ichord RN. Adult stroke risk after growth hormone treatment in childhood: First do no harm. Neurol 2014;83(9):776-7

30. Spencer D. Long-term risk of stroke in children treated with growth hormone for short stature: Looking at the big picture. Neurol 2014;83(9):e103-5

• **Editorial that puts the issues of GH therapy and risk for stroke into perspective.**

31. Nunez SB, Municchi G, Barnes KM, Rose SR. Insulin-like growth factor-1 (IGF-I) and IGF-binding protein-3 concentrations compared to stimulated and night growth hormone in the evaluation of short children: A clinical research center study. J Clin Endocrinol Metab 1996;81(5):1927-32

32. Martinez AS, Domene HM, Ropelato MG, et al. Estrogen priming effect on growth hormone (GH) provocative test: A useful tool for the diagnosis of GH deficiency. J Clin Endocrinol Metab 2000;85(11):4168-72

33. Petryk A, Baker KS, Frohnert B, et al. Blunted response to a growth hormone stimulation test is associated with unfavorable cardiovascular risk factor profile in childhood cancer survivors. Pediatr Blood Cancer 2013;60(3):467-73

34. Kargi AY, Merriam GR. Testing for growth hormone deficiency in adults: doing without growth hormone-releasing hormone. Curr Opinion Endocrinol Diabetes Obes 2012;19(4):300-5

35. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 2000;85(11):3990-3

36. Sherafat-Kazemzadeh R, Mehta SN, Care MM, et al. Small pituitary size in children with Fanconi anemia. Pediatr Blood Cancer 2007;49(2):166-70

37. Aynsley-Green A, Zachmann M, Werder EA, et al. Endocrine studies in Fanconi's anaemia. Report of 4 cases. Arch Dis Child 1978;53(2):126-31

38. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. J Clin Endocrinol Metab 2007;92(7):2624-31

39. Lenzen S, Drinkgern J, Tiedge M. Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. Free Rad Biol Med 1996;20(3):463-6

40. Sigfrid LA, Cunningham JM, Beeharry N, et al. Antioxidant enzyme activity and mRNA expression in the islets of Langerhans from the BB/S rat model of type 1 diabetes and an insulin-producing cell line. J Mol Med (Berl) 2004;82(5):325-35

41. Yanovski JA, Rose SR, Municchi G, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. N Engl J Med 2003;348(10):908-17

• **Placebo-controlled study of GnRHa in children with short stature and early puberty showing that such therapy for four years improves adult height by 4 to 5 cm.**

42. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96(7):1911-30

•• **Guidelines for screening 25-hydroxy-vitamin D levels and recommendations for vitamin D supplementation.**

43. Dvorak CC, Gracia CR, Sanders JE, et al. NCI, NHLBI/PBMTC first international conference on late effects after pediatric hematopoietic cell transplantation: endocrine challenges-thyroid dysfunction, growth impairment, bone health, & reproductive risks. Biol Blood Marrow Transplant 2011;17:1725-38

•• **Consensus conference reviewing gaps in knowledge about pediatric endocrine function after HCT and proposing future research.**

44. Ward L, Tricco AC, Phuong P, et al. Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Cochrane Database Syst Rev 2007;CD005324

45. Baim S, Leonard MB, Bianchi ML, et al. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. J Clin Densitom 2008;11(1):6-21

46. Gordon CM, Bachrach LK, Carpenter TO, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: The 2007 ISCD Pediatric Official Positions. J Clin Densitom 2008;11(1):43-58

47. Ward LM, Petryk A, Gordon CM. Use of bisphosphonates in the treatment of pediatric osteoporosis. Int J Clin Rheumatol 2009;4:657-72

48. Pulsipher MA, Skinner R, McDonald GB, et al. National cancer institute, national heart, lung and blood institute/pediatric blood and marrow transplantation consortium first international consensus conference on late effects after pediatric hematopoietic cell transplantation: The need for pediatric-specific long-term follow-up guidelines. Biol Blood Marrow Transplant 2012;18(3):334-47

•• **Consensus conference providing screening guidelines for pediatric patients after HCT for general health issues plus screening for disorders of thyroid, growth, bone mineral, and puberty.**

49. Available from: http://www.bmdcspublic.com/zscore.htm

50. Swift M. Fanconi's anaemia in the genetics of neoplasia. Nature 1971;230(5293):370-3

51. Auerbach AD, Allen RG. Leukemia and preleukemia in fanconi anemia patients. a review of the literature and report of the international fanconi anemia registry. Cancer Genet Cytogenet 1991;51(1):1-12

52. Butturini A, Gale RP, Verlander PC, et al. Hematologic abnormalities in fanconi anemia: an international fanconi anemia registry study. Blood 1994;84(5):1650-5

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