ENDOCRINE DISORDERS IN FANCONI ANEMIA

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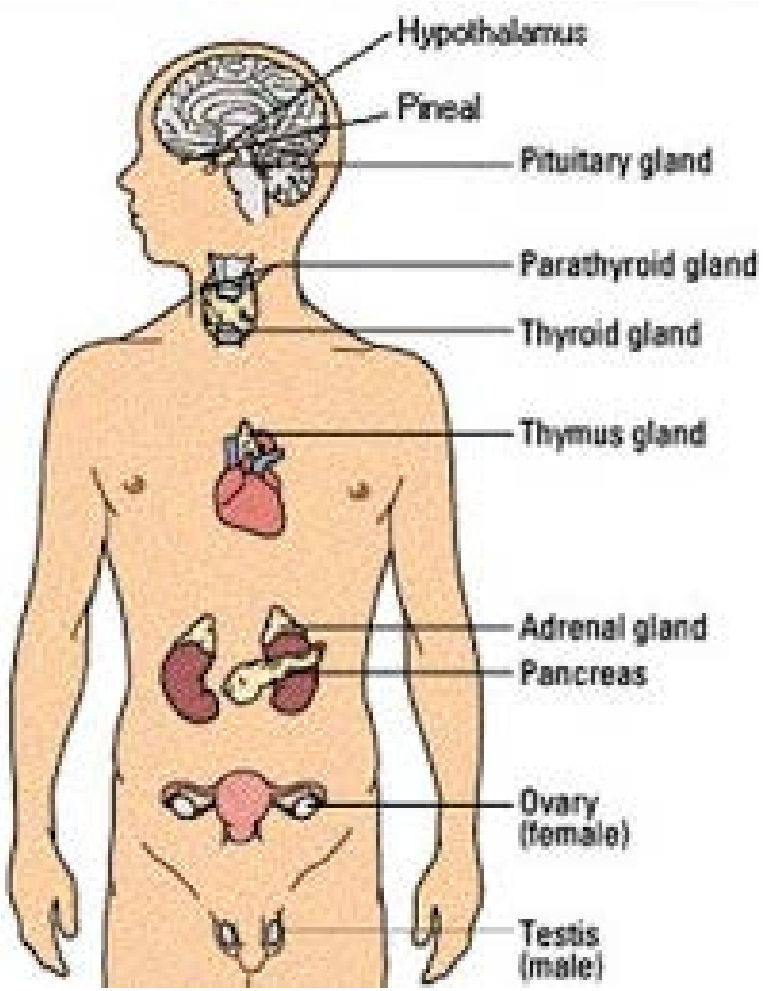
Endocrine System



- Endocrine glands release “hormones” into the blood stream- act at target sites
- Hormones control
  - Growth
  - Metabolism
  - Blood sugar
  - Puberty
  - Fertility
  - Bone health
  - Stress response

Common Endocrine Issues in FA

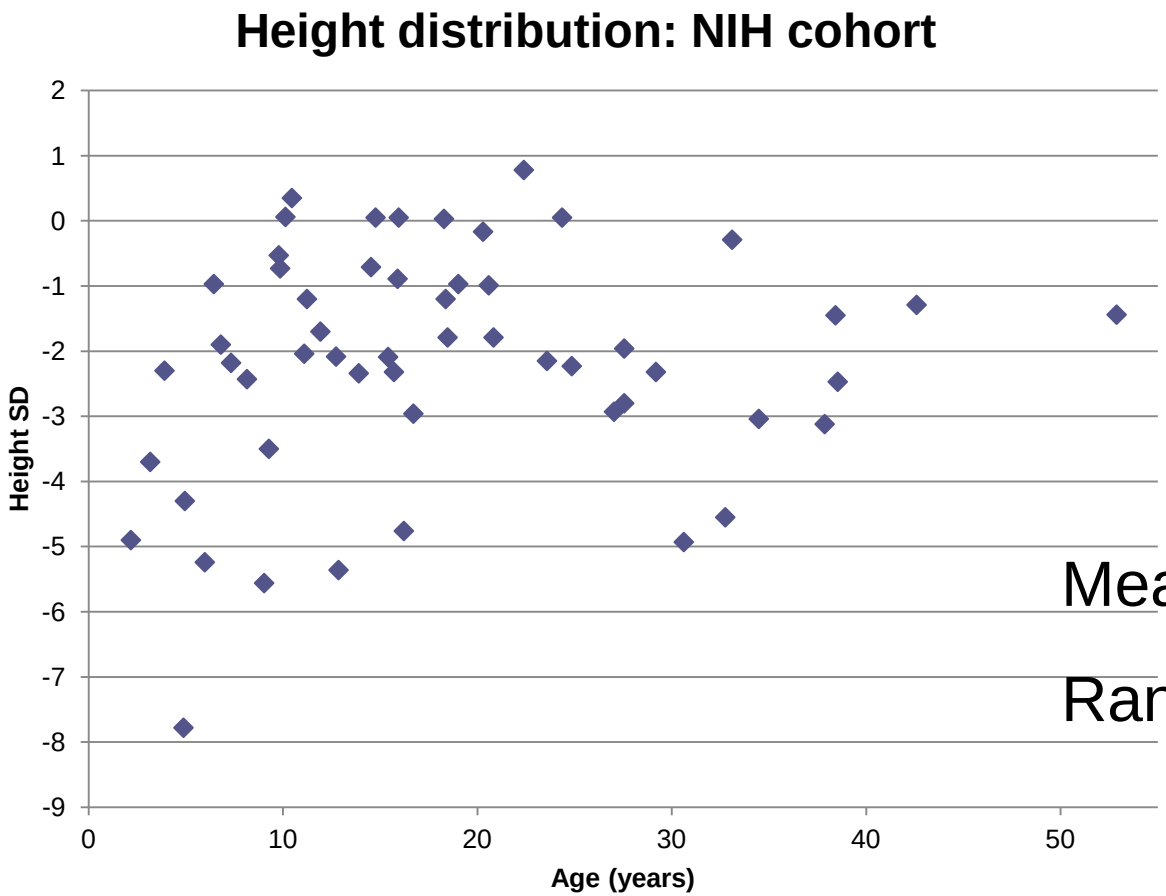
- **Growth**
  - Short stature
  - Low birth weight
  - Poor weight gain
  - Overweight/obesity
- **Metabolism**
  - Insulin resistance
  - Insulin secretion defects
  - Glucose intolerance
  - Diabetes
- **Thyroid problems**
  - Hypothyroidism
- **Puberty & Fertility issues**
  - Delayed maturation
  - Early puberty
  - Decreased sperm count
  - Premature ovarian failure
- **Bone health**
  - Low bone mineral density
  - Osteoporosis

Growth in FA

- 60% of individuals have heights < -2 SD (i.e. they are shorter than 97.5% of the general population)
- Average adult height
  - 4’ 11” in women
  - 5’ 3” in men
- 10% of individuals have above-average heights compared to the general population.

Wajnrajch MP et al. Pediatrics 2001; Giri N et al. JCEM 2007; Rose SR et al. Pediatr Blood Cancer 2012

Height Distribution in FA



N=54

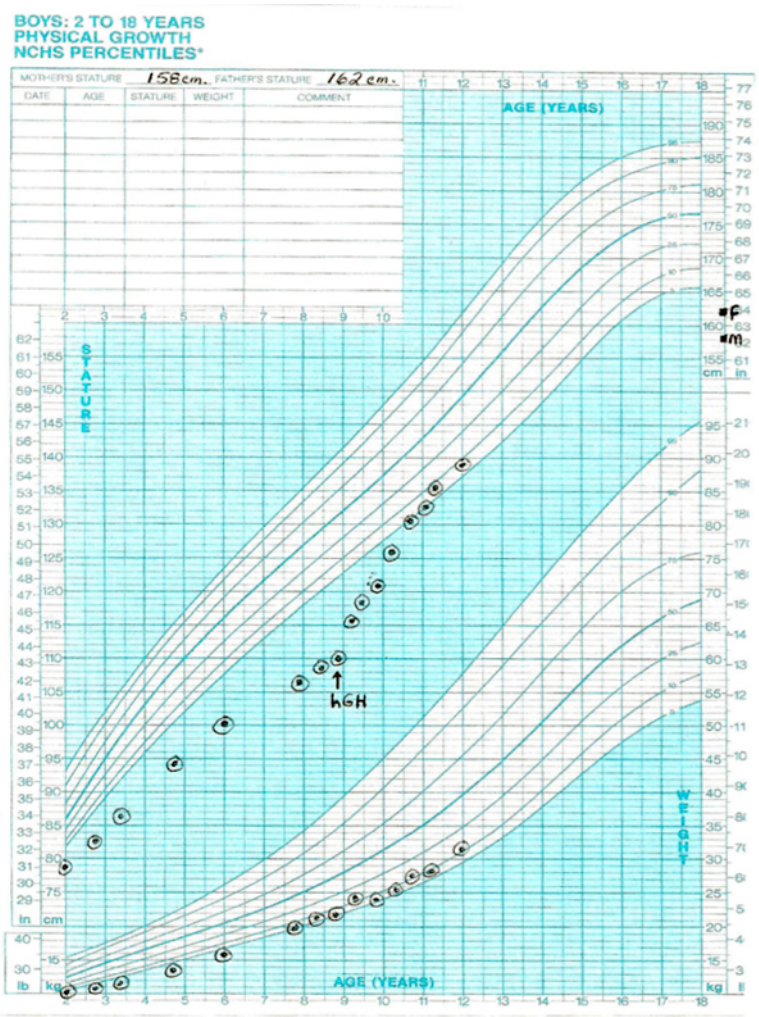
Mean height SD= -2.2

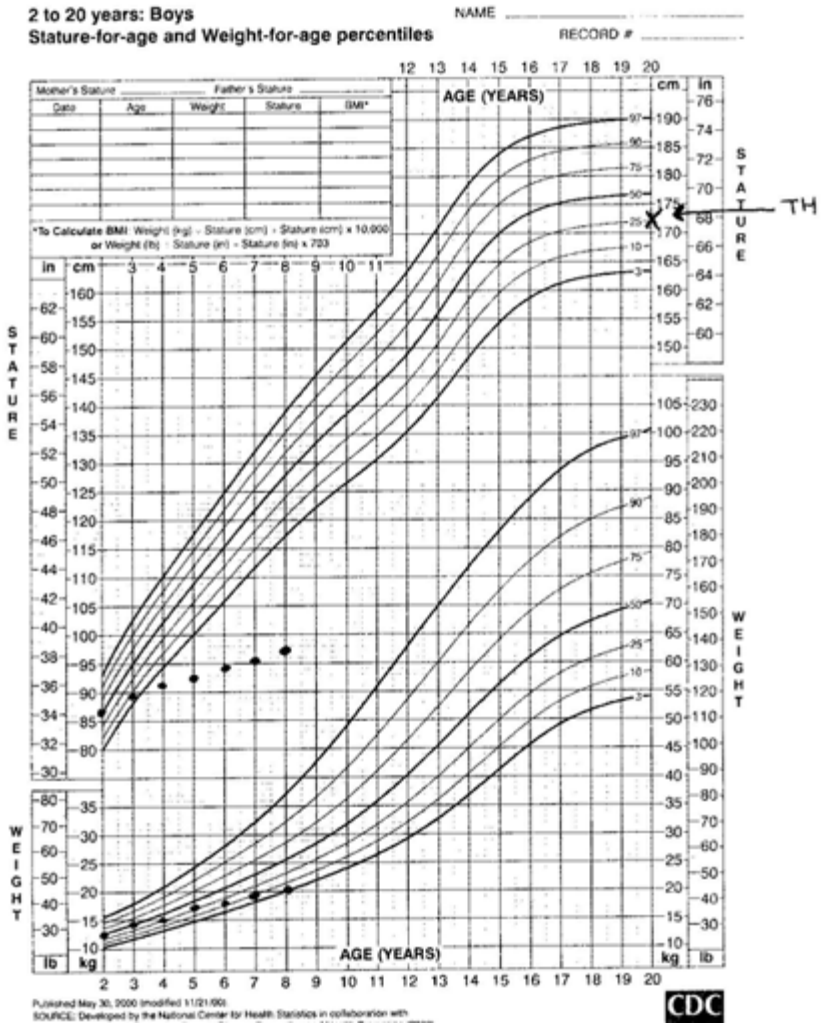
Range: 0.8 to -7.8 SD

Predisposing factors for short stature

- Family background and parent heights
- Mutation causing FA (e.g: IVS4 mutation of FANCC)
- Birth weight
- Nutrition status
- Presence of untreated endocrine abnormalities (growth hormone deficiency, hypothyroidism or early puberty)
- Medications: androgens, corticosteroids

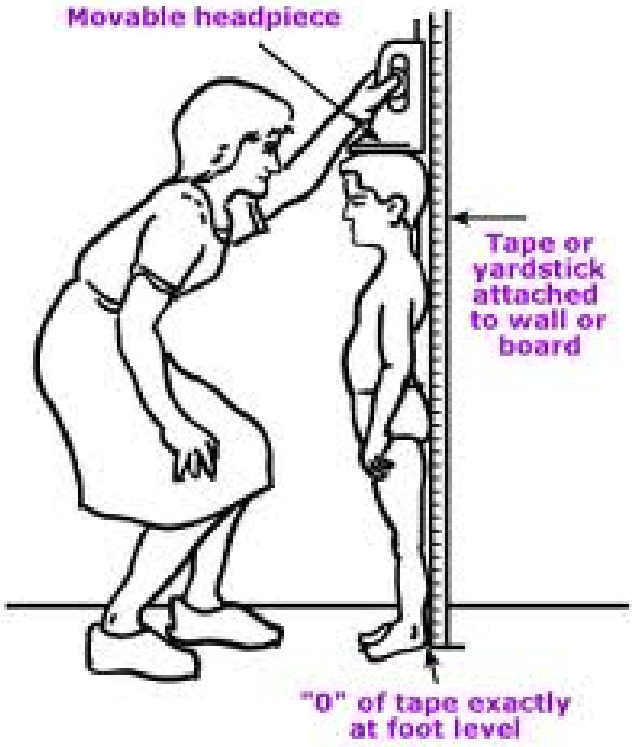
Examples of poor growth





Monitoring growth in FA

- Accurate measurement of height using a stadiometer annually and plotted on growth chart
- Needs endocrine work-up if :
  - Slow growth or Falling off Percentiles on growth chart
  - Short stature (< 3%ile on growth chart)
  - Growth hormone secretion may need to be evaluated



Treatment of short stature in FA

- Cause of poor growth must be determined and treated accordingly
- Nutrition and weight gain must be optimized
- Growth hormone therapy may be used if documented growth hormone deficiency (GHD)
- In short FA children without GHD, the efficacy and risks of growth hormone therapy are unknown.
- No long term clinical safety data on growth hormone therapy in FA

Weight issues in FA

- Half the children with FA are born “Small for Gestational Age (SGA)
  - Only 25% of them “catch up”
- 25-33% of children with FA are ‘underweight’
- 11-37% are ‘overweight’
- Issues with malabsorption, gastro-intestinal problems, chronic illness and hormone deficiencies interfere with adequate nutrition and weight gain

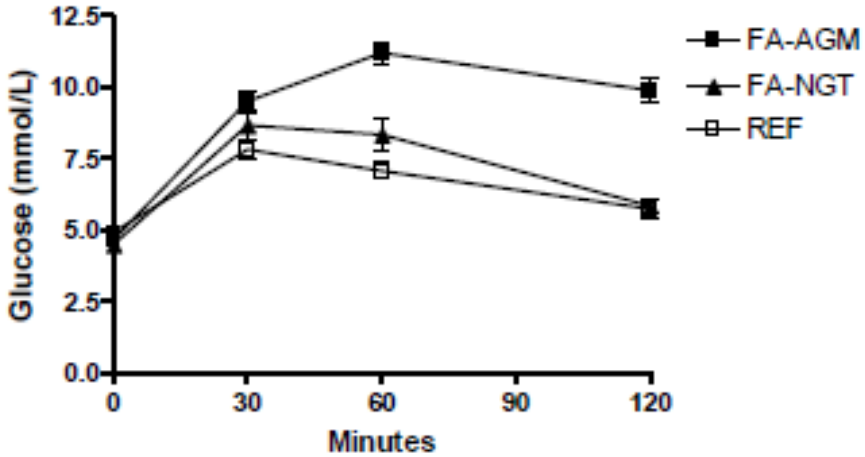
Rose SR et al. Pediatr Blood Cancer 2012

Metabolic abnormalities in FA

- Insulin resistance: 50% of adults; 38% children
- Metabolic syndrome: 18% of adults
- Diabetes: 9% of adults
  - Diabetes type: First phase insulin secretion defects as well as resistance to insulin are seen in FA
  - Medications- (steroids) also contribute
- Lipid Abnormalities: 59% of adults;19% children

NIH, unpublished data

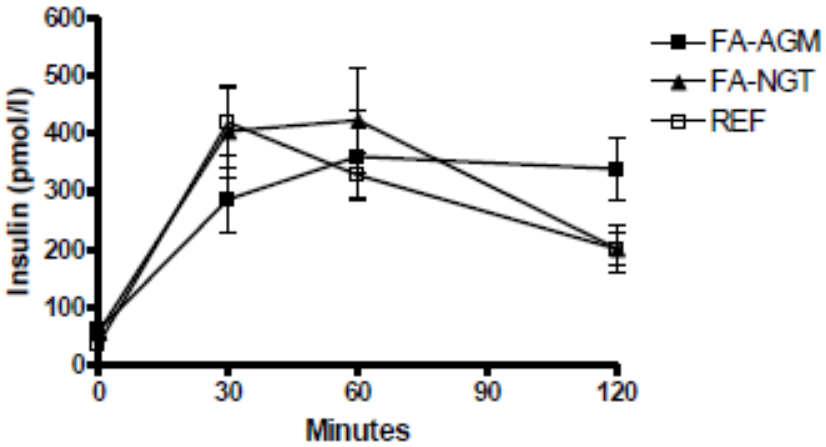
Abnormal Glucose/Insulin in FA

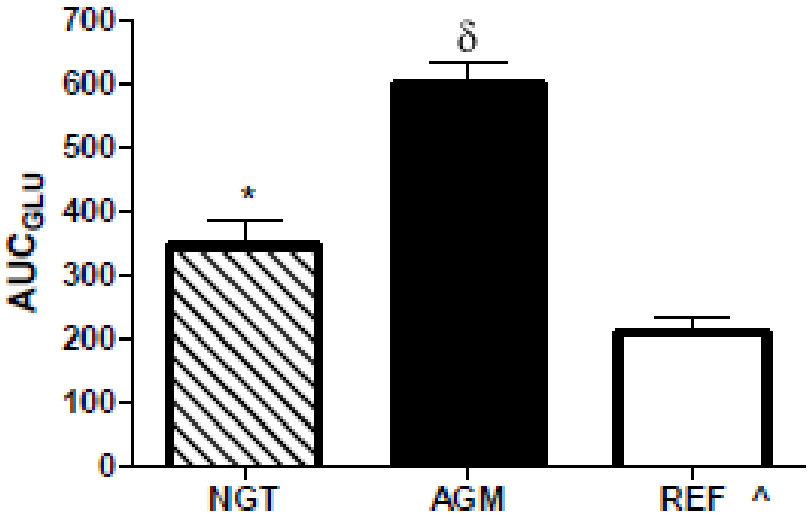


N= 39 children with FA

AGM (46%): abnormal glucose metabolism- defined as impaired fasting glucose, glucose intolerance or diabetes

NGT: normal glucose tolerance



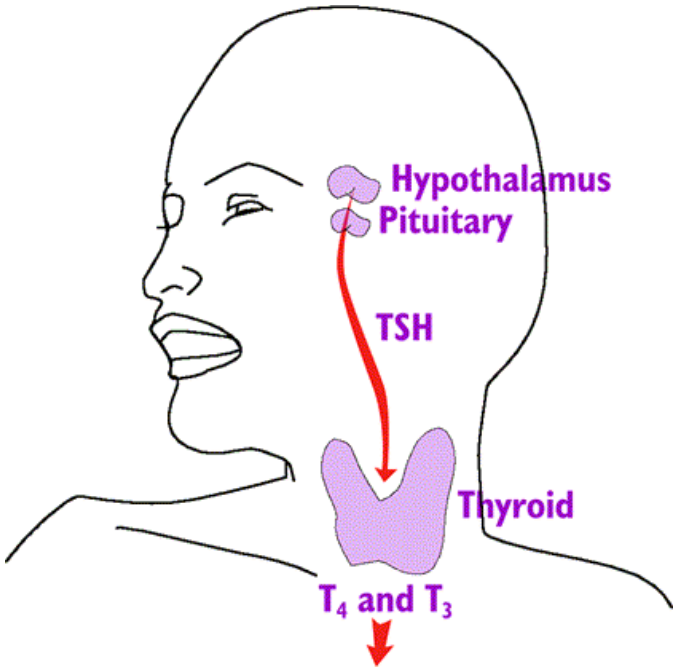


Elder DA et al. Pediatr Blood Cancer 2008;51: 256-260

Thyroid problems in FA

- Pituitary or central problem:
  - Low free T4 but low/normal TSH
- ‘Primary’ thyroid gland problem
  - Low thyroid hormone and high TSH
- Often mildly abnormal
- 37-60% of FA patients with reported dysfunction

NIH, NY data 36-37%; CCHMC 60%

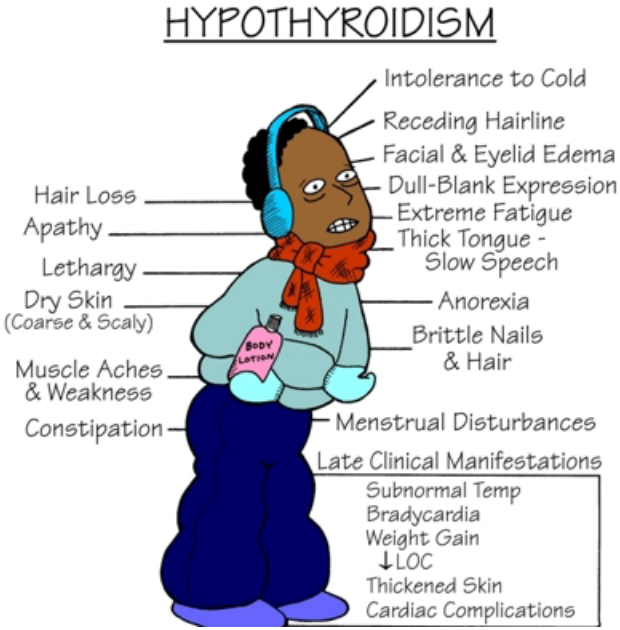


Feedback regulation of thyroid hormone

TSH: thyroid stimulating hormone
Thyroid hormone: T4 (bound to protein) or “free” T4

Symptoms and Treatment of Hypothyroidism

- An underactive gland results in hypothyroidism
  - Fatigue
  - Weight gain
  - Slow growth
  - Dry skin
  - Thinning Hair
  - Constipation



- Treatment: Levothyroxine

  Goal of therapy:

  - TSH <2 mcU/L (primary)
  - Free T4 upper half of normal range (central)
  - Borderline thyroid studies: treatment may improve growth

Puberty

- Puberty may be early or delayed in FA
- Early or precocious puberty is
  - Breast development before age 8 in girls
  - Testicular development before age 9 in boys
- Delayed puberty is
  - No breast development by age 14 in girls or no periods by age 16 years, despite breast development
  - No signs of testicular development by age 14 in boys

Management of Puberty Problems

- Onset and progression of puberty should be monitored by annual physical examination
- Refer to endocrinology
  - maturation occurs early or
  - no signs of sexual development by 14 years of age.
- Early puberty can limit height growth
- Late puberty may be a sign of hormone deficiency and can impact bone mineral density
- Medications may be used to suppress early puberty or hormone therapy may be used if delayed

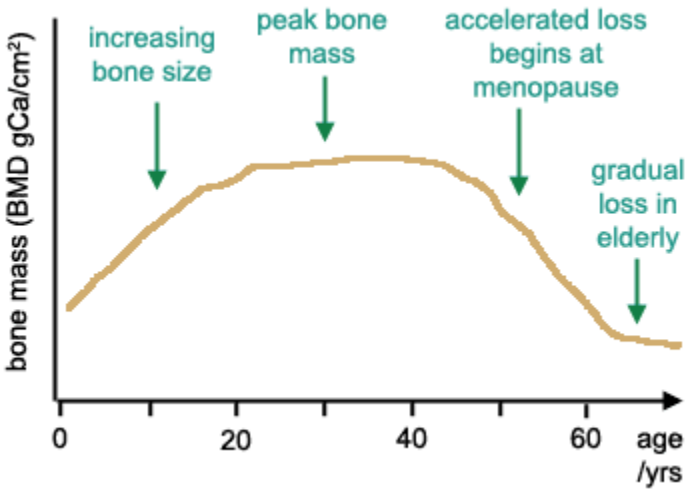
Fertility and Reproductive Function

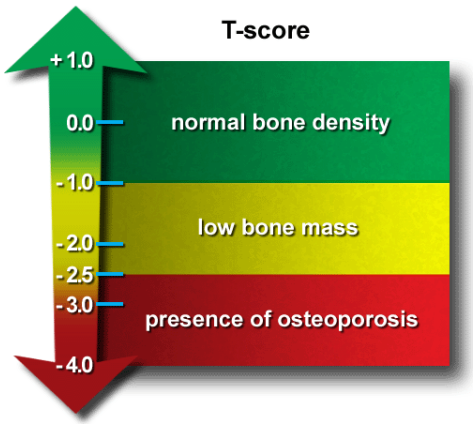
- Adult FA patients have decreased reproductive function
  - 64% of men with FA had small testes and penis and reduced sperm count
  - 77% of women with FA had premature menopause
  - Infertility is common but not well understood
  - Cryptorchidism, hypospadias and structural abnormalities of uterus may be seen
- Pituitary hormone deficiencies and chemotherapy during transplant may also affect fertility

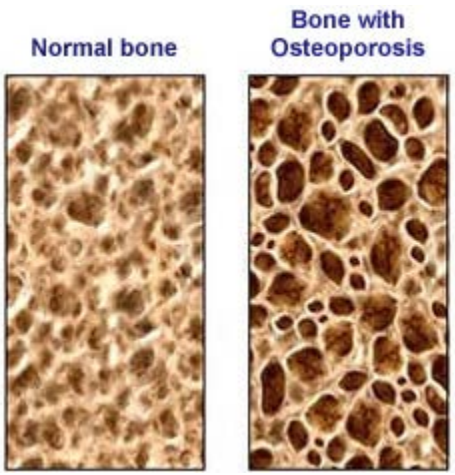
Giri N et al. JCEM 2007;

Bone health

- Peak bone mass is achieved in the 20's followed by gradual loss of bone mineral density
- More pronounced loss in post menopausal women
- In adults osteoporosis is defined as a BMD <-2.5 SD compared to BMD of sex-matched healthy young adults







Measurement of BMD

- Dual energy X-ray absorptiometry (DXA) is used to evaluate BMD
- In children, the DXA result must be reported as a Z-score (compared to age and sex-matched standard) and should be adjusted for height.
- Height-adjusted BMD is normal in children with FA
- In adults with FA: 12/13 had osteopenia or osteoporosis (unadjusted for stature)
- Factors contributing to low BMD in FA: hypogonadism, growth hormone deficiency, corticosteroid therapy, HCT

Giri N et al. JCEM 2007; Rose SR et al. Pediatr Blood Cancer 2011

Prevention/Screening for low BMD

- Adequate dietary intake of calcium/vitamin D
- Encourage weight bearing exercise and healthy life style to establish good peak bone mass
- Identify and treat hormone deficiencies
- Recognize and treat early menopause
- Screening with DXA before and following transplant
- Fracture risk is unknown in FA

Summary of Endocrine Problems in FA

- Endocrine problems are common in FA and the multidisciplinary team should include an endocrinologist
- Short stature is prevalent
  - Annual height and weight measurement
  - Further evaluation if <3%ile or poor growth velocity
- Common metabolic abnormalities include glucose intolerance, insulin secretion defects, diabetes and hyperlipidemia
  - Annual screening with post prandial in addition to fasting glucose and insulin may be performed

Endocrine issues in FA

- Both central (pituitary) and primary (thyroid) hypothyroidism are common in FA
  - Annual screening is recommended with free T4 and TSH
- Puberty may be early or delayed
  - Careful physical examination for pubertal changes and monitoring of pubertal progression must be performed
- Fertility is likely impaired in both males and females and needs further study
- BMD appears normal in kids with FA but several risk factors for increased osteopenia seen in adults
  - Recommend BMD prior to HCT and annually thereafter

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