Medical Management of Klinefelter Syndrome XXY in Adults

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On behalf of Dr. Adrian Dobs M.D. M.H.S
Objective

- Historical background
- What is Klinefelter syndrome?
- How common is Klinefelter syndrome in adulthood?
- Clinical Picture
  - Neuropsychiatric aspect
  - Metabolic syndrome/diabetes/Obesity
  - Cardiovascular risk
  - Bone disease
  - Cancer
  - Other comorbidities
- Treatment
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- **Treatment**
Historical Context

• Described in 1942 by Harry Klinefelter
  – Characterized by gynecomastia (enlargement of the chest), lack of facial and body hair, small testicles, and infertility

• Defined in 1959 by Patricia Jacobs as being associated with an extra X chromosome

Metaphase Plate Showing 47 Chromosomes
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What is Klinefelter Syndrome (KS)?

23 pairs of chromosomes in each cell, including **1 pair of sex chromosomes**

Female (46XX)  
Male (46XY)

KS most commonly due to extra X chromosome, resulting in **47XXY** karyotype
- Extra X chromosome is from mother 50% and from father 50% of time
- Variations including mosaicism with 46XY, or other karyotypes (ex: 48,XXXY)

**Klinefelter Syndrome:**

Risk factors: advanced maternal and paternal age
How Does Klinefelter Syndrome Affect Hormones?

**NORMAL**
- Brain
- Gonadotropin hormones (LH/FSH)
- Testicles
  - Testosterone
  - Sperm

**KLINEFELTHER**
- Brain
- Gonadotropin hormones (LH/FSH)
- Testicles
  - Testosterone
  - Sperm

Red X indicates absence or reduction in production.
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Epidemiology

- Prevalence 1/500-1/1000
  - 0.1-0.2% of newborns (prenatal diagnosis)
  - 3-4% of infertile men (most common cause of infertility)
  - 10-12% of males with azoospermia (no sperm production)
- < 10% diagnosed before puberty
- Underdiagnosed: only 25%
- Late diagnosis: usually mid 30s during fertility evaluation
• Overall, the diagnosis of Klinefelter syndrome is delayed and is likely underdiagnosed in men

• Regardless of timing of diagnosis, important to be aware of the types of conditions men with Klinefelter syndrome are at risk of developing and how we can best prevent and treat these complications
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CLINICAL PICTURE

Cardiovascular Risk

Neuropsychiatric Aspect

Osteoporosis

Normal bone

Osteoporosis

CANCER

METABOLIC SYNDROME

Insulin Resistance

High Blood Pressure

High Triglyceride Levels

Low HDL Cholesterol
# Clinical Features of Klinefelter Syndrome

<table>
<thead>
<tr>
<th>Features</th>
<th>Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>Infertility (adults)</td>
<td>91-99</td>
</tr>
<tr>
<td>Small testes</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Azoospermia (adults)</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Learning disabilities (children)</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Delay of speech development (children)</td>
<td>40</td>
</tr>
<tr>
<td>Psychiatric disturbances (children)</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal obesity (adults)</td>
<td>50</td>
</tr>
<tr>
<td>Metabolic syndrome (adults)</td>
<td>46</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>10-39</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>5-40</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>10</td>
</tr>
<tr>
<td>Fractures</td>
<td>Increased risk (2-40 fold)</td>
</tr>
<tr>
<td>Breast cancer (adults)</td>
<td>Increased risk (50 fold)</td>
</tr>
<tr>
<td>Mediastinal cancers (children)</td>
<td>Increased risk (500 fold)</td>
</tr>
<tr>
<td>Increased gonadotropin levels</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Decreased T levels</td>
<td>63-85</td>
</tr>
<tr>
<td>Mitral Valve prolapse</td>
<td>0-55</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>~18</td>
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</tbody>
</table>
NEUROPSYCHIATRIC ASPECTS
Neuropsychiatric Aspects

• The relationship between aneuploidy, T deficit and the risk of neuropsychiatric disorders is still not clear

• Usually intelligence Quotient (IQ) shows normal score in KS, however there are 2 patterns:
  - Verbal IQ (VIQ) < Performance IQ (PIQ): ↑autism
  - PIQ < VIQ: ↑schizotypal traits (magical thinking, delusional ideation and eccentric behavior)
Neuropsychiatric Aspects

- Functional impairment (language)
- Psychosis (schizophrenia, conduct disorder, ADHD, autism)
- Anxiety/depression

Possible causes:
- Significant differences in brain structure and volume
- Genetics/Extra X chromosome
- Hormones
Wide spectrum of possible psychiatric manifestations

Not clear if T replacement helps (conflicting results)

Very important to have psychology involved in the multidisciplinary team
METABOLIC SYNDROME, DIABETES AND OBESITY
Metabolic Syndrome

Syndrome characterized by at least 3 of the following 5 criteria:

- Diabetes
- High blood pressure
- Low HDL-Cholesterol
- High Triglycerides
- Insulin Resistance
- Hypertension
Metabolic Syndrome

Syndrome characterized by at least 3 of the following 5 criteria:
- Diabetes
- High blood pressure
- Why does it matter?

• 5 times more likely to develop diabetes
• Twice as likely to develop heart disease
• Even 1 risk factor increases risk of heart disease
• Other risk factors also increase likelihood of heart disease such as high LDL (bad cholesterol) and smoking
Diabetes Mellitus

Disease in which blood sugar levels too high

• Insulin brings sugars down
• Type 1 diabetes: body does not make insulin
• Type 2 diabetes (more common): body resistant to insulin
• Too much sugar in the blood over the long-term can lead to:
  – Heart disease, stroke, amputations, and complications in the eyes, kidneys, and nerves
• Diagnosis: blood test
  – Hemoglobin A1C, fasting glucose, oral glucose tolerance test
Increased Risk of Metabolic Syndrome and Diabetes in KS

- 48% KS subjects
- 10% Control subjects

Classification of patients:
- Green: Diabetes
- Dark green: IFG
- Dotted green: DM or IFG
- Yellow: Metabolic syndrome

Percentage affected graph shows a significant increase in metabolic syndrome and diabetes in KS subjects compared to control subjects.
Increased Risk of Metabolic Syndrome and Diabetes in KS

- 50% of men with KS have abdominal obesity
- Men with KS have higher fat % at same BMI
- Strongest predictor of metabolic syndrome is fat, especially truncal fat ("apple shape") and not T level
- Frequency of type 2 DM in KS 10-39%
- Type 1 DM less common
Metabolic Syndrome, Obesity and Diabetes: Summary and Implications

- Well-described risk in men with KS
  - \(^{\uparrow}\) fat / \(^{\downarrow}\) muscle (even at the same weight)
  - Metabolic syndrome
  - Diabetes mellitus

- Concern for increased risk of complications including heart disease
Reducing the Risk of Metabolic Syndrome and Diabetes in KS

• Healthy lifestyle:
  – Diet and exercise
  – Avoid smoking

• Screening:
  – Physical exam: changes in body composition may prompt consideration of testosterone treatment
  – Cholesterol panel
  – Screening for diabetes: hemoglobin A1C, oral glucose tolerance test, fasting glucose
Reducing the Risk of Metabolic Syndrome and Diabetes in KS

• T replacement only partially improved metabolic syndrome and body composition

• Likely genetic factors affecting metabolic parameters and not only hormones
### Increased Mortality in KS

- **Median Loss of Life 1.5-2 Years**

  Median survival age of men with KS 71.4 vs. 73.5 years

- **Unclear what other factors may also be involved**

<table>
<thead>
<tr>
<th>Cause/disease</th>
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<tbody>
<tr>
<td>Lung cancer</td>
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<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Circulatory disease</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
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<tr>
<td>Intestinal thrombosis</td>
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CARDIOVASCULAR RISK
Cardiovascular (CV) Risk

• Ischemic heart disease
• Peripheral vascular disease
• Pulmonary embolism (clot in lung)
• Intestinal thrombosis (clot in guts)
• Strokes (bleeding or clots or AVM)
Cardiovascular Congenital Anomalies

• Mitral valve prolapse >↑ risk of sudden death
• Reduced artery diameter
• Other defects reported
Testosterone replacement for CV abnormalities

• Cardiovascular abnormalities are not reversed by T replacement
• Likely genetic factors as well
• Timing of T replacement to prevent CV abnormalities not known
How do we screen?
Some groups suggest echocardiography (heart echo) to detect these abnormalities

How do we reduce CV risk?
Aggressive CV risk modification
BONE DISEASE
Osteopenia/Osteoporosis

- Defined by measurement of bone mineral density (BMD)
  - Most commonly using dual-energy X-ray absorptiometry (DEXA) (Z-and T-scores)
Osteopenia/Osteoporosis

- osteopenia/osteoporosis $\rightarrow$ fractures $\rightarrow$ morbidity with hip fractures $\rightarrow$ mortality

  - Not uniformly shown in all studies, but decreased bone mass in 25–48% of cases
    - Osteoporosis in 6–15%

- Annual decrease in bone mineral density (BMD) rate approximately 1% at the lumbar spine and femoral neck
Possible Mechanisms Contributing to Reduced Bone Mass

- Unfavorable fat/muscle ratio, low physical activity
- Low vitamin D levels
- Low testosterone levels
- Multiple other factors (including but not limited to genetics, other hormonal factors)
Low T Levels Causing Osteoporosis

- Normal BMD in childhood and early puberty
  - T deficiency begins at least in adolescence/young adulthood
  - However, T levels not uniformly correlated with BMD

- Some studies have shown no improvement in BMD with T replacement
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What does this mean?

Unclear if testosterone reverses bone abnormalities, but adequacy and timing of initiating T is important (adolescence to early adulthood)
Bone Health: Summary and Implications

Increased osteopenia/osteoporosis

– Multiple risk factors, including (not limited to):
  • Low testosterone (adequacy, timing)
  • Low vitamin D
  • Increased fat relative to muscle

– Screening:
  • History and physical:
    – Diet (including calcium intake)
    – Screening for fractures either by history or on exam
  • DEXA (to test for bone mineral density)
  • Vitamin D level in the appropriate circumstances
Reducing the Risk of Bone Disease in KS

**DEXA Screening**

- **Normal BMD/Normal T**: Monitor T annually and DXA every 2-5 yrs
- **Normal BMD/Low T**: Start T, monitor DXA/labs every 2-5 yrs
- **Low BMD/Normal T**: Address risk factors, calcium/vitamin D, ?Bisphosphonates/?T treatment, DXA/labs every 1-2 years
- **Low BMD/Low T**: Address risk factors, calcium/vitamin D, T treatment/consider bisphosphonates, DXA/labs every 1-2 years
CANCER
Cancer Risk

• ↑ incidence of certain cancers: breast, lung, and non-Hodgkin lymphoma
• Different studies showed different rates
• Breast cancer risk seems to be 20-30 times higher than expected but still lower than risk in women
• Other studies found increased risk of mediastinal tumors in ages 15-30
Cancer Risk: Screening

• Breast cancer
  – Physical exam: examination of the breasts and axilla (underarm)
    • Painless lump, nipple retraction, bleeding from the nipple, lymph node abnormality

• Mediastinal tumors
  – History and physical: unexplained respiratory (breathing) complaints, precocious (early) puberty should prompt X-ray

• Lung cancer, other cancers
  • Avoid smoking
OTHER MEDICAL CONDITIONS
Other Medical Conditions

- Infertility
- Thromboembolism (clots in the blood/lungs)
- Sexual dysfunction
- Autoimmune disease (thyroid disease, lupus)
- Varicose veins
- Caries (dental cavities)
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TESTOSTERONE (T) REPLACEMENT
Who Should Receive Testosterone (T)?

Hypogonadal symptomatic men:
- Induce and maintain secondary sexual characteristics
- Sexual function
- Sense of well-being
- Bone mineral density/metabolic health
Who Should Receive Testosterone (T)?

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When should T be initiated in KS:

- Controversial

- Probably in **adolescence**, when gonadotropins (FSH/LH) rise even with normal T level
Caution Starting Testosterone

- Breast or prostate cancer
- Palpable prostate nodule or induration
- PSA >4 ng/ml in average risk men
- PSA >3 ng/ml in high risk men:
  - African-Americans
  - First-degree relatives with prostate cancer
- Hematocrit > 48%
- Severe uncontrolled lower urinary tract symptoms
- Uncontrolled or poorly controlled heart failure
Options for Testosterone Replacement

- Intramuscular T (injection)
- T gel
- T patches
- T pellets (implantable)
- Buccal T
- Nasal T gel
- Oral T (FDA approved May 2019)
<table>
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<tr>
<th>Formulation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable T esters</td>
<td>Relatively inexpensive</td>
<td>Fluctuations in T levels, mood and libido, More erythrocytosis</td>
</tr>
<tr>
<td></td>
<td>Flexible dose (if self-administered)</td>
<td></td>
</tr>
<tr>
<td>T gel</td>
<td>Flexible dose, easy, good tolerability</td>
<td>Skin-to-skin contact with women and children</td>
</tr>
<tr>
<td>T patch</td>
<td>Easy</td>
<td>Skin reaction at application site</td>
</tr>
<tr>
<td>T Pellet</td>
<td>Infrequent administration (3-6 months)</td>
<td>Infection, Expulsion of pellet</td>
</tr>
<tr>
<td>Buccal T</td>
<td>Convenience</td>
<td>Irritation of gums in 16%, Alteration in taste</td>
</tr>
<tr>
<td>Nasal T gel</td>
<td>Rapid absorption</td>
<td>Multiple daily dosing, Nasal side effects</td>
</tr>
<tr>
<td>Oral T (approved)</td>
<td>Easy</td>
<td>Headache, nausea, ↓HDL, ↑BP</td>
</tr>
</tbody>
</table>
# Monitoring After Testosterone Initiation

<table>
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<tr>
<th>Test</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone levels</td>
<td>Goal mid-normal range&lt;br&gt;Aim for level of 350-700 ng/dl (1 week s/p injection or 2-8 hr after transdermal)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>&gt;54% → stop until Hct decreases to safe level; evaluate for hypoxia and sleep apnea and initiate therapy at a reduced dose</td>
</tr>
<tr>
<td>PSA</td>
<td>Urology consultation&lt;br&gt;PSA increases &gt;1.4 ng/mL within 12 months&lt;br&gt;PSA &gt; 4 ng/mL at any time&lt;br&gt;PSA velocity (rise speed) &gt;0.4 ng/mL per year&lt;br&gt;Detection of prostate abnormality on exam&lt;br&gt;Substantial worsening of LUTS</td>
</tr>
<tr>
<td>Bone density test</td>
<td>1-2 years after testosterone initiation in men with osteoporosis or low trauma fracture</td>
</tr>
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Acknowledgements

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