

High Prevalence of cardiometabolic risk features in adolescents with 47,XXY/Klinefelter Syndrome - Davis et al.

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Adapted by Jennifer K Ramsdell

Guide to reading this adaptation:

This is an adaptation of a research paper. It includes information pertaining to children and men with 47,XXY/Klinefelter Syndrome, and other sex chromosome trisomies. This is a shortened version of the original paper, edited for clarity, readability, and relevancy to the XXY community. Page numbers noted in this adaptation correspond to the research paper.

Introduction

Klinefelter syndrome (KS) occurs in 1:600 males. These males are born with an additional X chromosome, most often appearing as 47,XXY. While there seems to be a variety of neurodevelopmental and physical features associated with KS, almost all males with KS have small testes and an impaired ability to produce mature sperm.

Past studies have found that men with KS have a higher rate of having, and dying from cardiovascular disease (CVD) and type 2 diabetes (T2D). Metabolic syndrome describes a set of features that can create an elevated risk of developing CVD and T2D, including:

- ◆ Central adiposity - the accumulation of fat in the lower torso around the abdominal area
- ◆ Elevated blood glucose
- ◆ High triglycerides
- ◆ Low density lipoprotein cholesterol
- ◆ hypertension

If at least 3 of these features are present, metabolic syndrome can be diagnosed, though there's no definition for what it means to be diagnosed in youth. Those with KS seem to be more susceptible to the cardiometabolic (CM) risks than others carrying certain genetic conditions, with some studies reporting that up to 50% of adults with KS meet the criteria for metabolic syndrome diagnosis.

Hypogonadism is likely a contributor to central adiposity and CM risks in individuals with KS. While there has been some evidence that suggests testosterone replacement therapy (TRT) has improved the CM outcome in hypogonadal men, the research for individuals with KS has been

mixed, with some studies showing that TRT led to changes in body composition, but not changes in insulin sensitivity. Studies suggest that poor CM conditions are difficult to reverse in adulthood, which is why it is necessary to start screening for CM conditions in younger boys.

Why conduct this study?

There's not much research available on children with KS, but research suggests CM differences do begin early for boys with KS, including adiposity and insulin resistance. Previous research did not investigate whether these CM differences were caused by hypogonadism, obesity, or something else, but androgen treatment in these young boys did make a measurable difference, particularly on adiposity. Additionally, this previous research suggests that energy metabolism is measurable in boys with KS at a young age, and may be influenced with treatment.

This study was conducted because there has been no previous research of CM risk factors done in adolescents with KS, though there is ample research on adults with KS and emerging research on infants and prepubertal children. It is important to understand CM dysfunction throughout the entire lifespan of individuals with KS in order to create preventative and early intervention strategies. Additionally, the researchers wonder what role testosterone plays in CM in young people with KS. They compared prevalence of CM risk features in pubertal adolescents with KS to healthy control subjects, and then they also examined the difference between individuals with KS who were on TRT and those who weren't on testosterone.

The Study

One hundred boys aged 10-18 participated in the study. There were 50 participants with KS who had confirmed nonmosaic karyotype 47,XXY. They were recruited from the eXtraordinary Kids Clinic at Children's Hospital Colorado, national advertisements to clinicians caring for patients with KS, and community advocacy groups like Association for X and Y Syndromes (AXYS). The control group of 50 boys without KS were recruited from the local community.

Within the KS group, 48% had been diagnosed with KS postnatally around 8.5 years old, for reasons including developmental delays, learning disabilities and/or behavioral concerns, pubertal microorchidism (abnormally small testes), tall stature, and epilepsy evaluation. Nearly half the individuals with KS were on TRT at varying dosages and durations of treatment.

All participants had a physical exam by a physician to determine what stage of puberty they were in, and had their height, waist circumference, and blood pressure measured. Blood was drawn in the morning before they had eaten (when possible) and included measurements of serum total testosterone, liver enzymes, and a cholesterol panel. 30 participants from the KS group and all control participants had a fasting blood glucose and hemoglobin A1c measured.

According to the researchers, there is no clear definition of metabolic syndrome for youth, so these researchers determined that they would judge CM risk factors based on:

- ◆ Elevated triglycerides (greater than or equal to 100 mg/dl)
- ◆ Low HDL cholesterol (less than 50 mg/dl for boys younger than 14 years old and less than 45 mg/dl for boys 15-19 years old)
- ◆ Elevated fasting blood glucose (greater than or equal to 110 mg/dl)
- ◆ Elevated waist circumference (greater than 75th percentile for age and sex)
- ◆ Elevated systolic blood pressure (greater than 90th percentile for age, sex, and height)

The researchers' primary focus was looking at the data for the presence of 3 or more CM features. They then looked for the presence or absence of each CM feature. Finally, they compared the participants with KS who were on TRT to those who were not, to see similarities and differences in their CM features.

Results

In the KS group, 96% of boys had at least one CM risk feature and 30% of participants had 3 or more CM risk features, compared to 12% of boys in the control group. Adolescents with KS were more likely to have high triglycerides and low HDL, and triglycerides and waist circumference were significantly higher in the boys with KS. Additionally, while fasting glucose was not higher in the boys with KS, the HbA1C was significantly higher, which indicates chronically higher blood glucose.

While BMI was in the normal range for nearly all participants, researchers found that participants on both sides with higher BMI were more likely to have three or more CM risk factors; a higher BMI was also linked to a larger waist circumference in both participants with KS, and the control group. Notably, for the boys with KS, BMI was linked with their systolic blood pressure and triglycerides.

In the analysis of CM risk features in adolescents with KS, those who had received TRT were half as likely to have the presence of three or more CM risk features, compared to those who had not had TRT. Those boys who had TRT had significantly lower HDL cholesterol and lower systolic blood pressure. Because of the small sample size more research needs to be done to reach true conclusions about the benefits of TRT in combating CM risk features.

Conclusion/More Research Needed

The results of this study agree with the previous studies on cardiometabolic health in boys and adult men with KS. The results of this study suggest that poor CM health begins early in life for boys with KS and increases with age, therefore it is important to counsel for CM risk and evaluate the risk factors in adolescents in KS, even if BMI is in normal range.

Researchers can only hypothesize for now about how abdominal adiposity may lead to insulin resistance and increased rates of cardiometabolic features in individuals with KS. Insulin resistance is widely reported with KS.

More research is needed to determine if and how testosterone deficiency may increase the chances of CM features in individuals with KS. While there seems to be a link between hypogonadism and cardiometabolic dysfunction, hypogonadism does not explain the full picture of poor CM health in boys with KS. There has not been a long term study conducted that assesses CM health with TRT and other interventions in individuals with KS. All boys with KS may benefit from healthy lifestyle habits including a well-rounded diet and daily moderate-to-vigorous physical activity should be emphasized.

