Klinefelter’s syndrome, type 2 diabetes and the metabolic syndrome: the impact of body composition

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ABSTRACT: Klinefelter’s syndrome (KS) is the most common sex-chromosome disorder in men, affecting ~1:660 men, and is a rather common cause of infertility, hypogonadism and learning disability. Traditionally, men with KS have been described as tall, slim, narrow shouldered, broad hipped, with hypergonadotropic hypogonadism and small testes. Recent studies showed an increased risk of diabetes and an unfavourable change in body composition; with accumulation of body fat and decreased muscle mass and a concomitant decrease in insulin sensitivity, muscle strength and oxygen consumption capacity. Here, we review the data on body composition, insulin resistance and metabolic syndrome in relation to testosterone in both KS patients and normal men. Treatment with testosterone in hypogonadal states (other than KS) seems to improve body composition in both clinical and experimental studies. Despite the lack of such studies in KS, we recommend testosterone treatment to KS patients with low serum testosterone or increased LH and change in body composition.

Key words: Klinefelter’s syndrome / body composition / testosterone / metabolic syndrome / diabetes

Introduction

For more than six decades (since 1942), Klinefelter’s syndrome, KS (47,XXY), has been known as a relatively common cause of infertility, hypergonadotropic hypogonadism, gynecomastia and learning disability in men (Klinefelter et al., 1942). Although being the most common sex chromosome disorder, with a prevalence of 1:660 men (Nielsen and Sillesen, 1975; Bojesen et al., 2003), knowledge concerning morbidity and mortality in KS was inadequately described until recently, when epidemiological studies from England and Denmark showed an increased morbidity and mortality due to a variety of diseases and conditions (among them diabetes; Swerdlow et al., 2001, 2005; Bojesen et al., 2004, 2006a). The classical/typical ‘textbook’ image/phenotype of a Klinefelter patient is a tall, slender man with small testes, gynecomastia, narrow shoulders, long arms and legs and with sparse body hair. Most men with KS go through life without diagnosis, and only 25% of the expected number of KS patients is diagnosed in Denmark (Bojesen et al., 2003). This proportion of diagnosed versus undiagnosed cases is likely comparable with that of other countries, which challenges our current knowledge of the KS phenotype and hampers the extrapolation hereof to the remaining group of undiagnosed KS men. In fact, most men suffering from KS (at least those we are aware of) exhibit only a few of the many phenotypic external and internal stigmata linked to KS. The only stigmata seemingly shared by virtually all adult KS are small testes, increased LH and FSH and azoospermia (Smyth and Bremner, 1998; Bojesen and Gravholt, 2007).

Here, we will challenge the stereotypic ‘classic’ phenotype of KS and show that a majority of men with KS have alterations in body composition that may lead to diabetes, dyslipidemia, metabolic syndrome, and hence an increased risk of dying from diabetes, cardiovascular or cerebrovascular disorders. We hope that a more varied view of the KS phenotype could lead to more KS patients being diagnosed in the future. To illustrate the diversity in the KS phenotype, Fig. 1 shows a rather atypical looking KS patient.

The risk of diabetes or metabolic syndrome in KS

Epidemiological studies

Epidemiological study concerning mortality in KS has been performed in Great Britain (Swerdlow et al., 2005) and in Denmark (Bojesen et al., 2004) including more than 3500 patients and 780 patients, respectively. Both showed a generally increased mortality risk with a hazard rate (HR) of 1.4–1.5 and a specifically increased risk of dying from diabetes with a standardized mortality rate of 5.8 and HR of 1.6. We also studied morbidity, based on hospital discharge diagnoses, and showed an increased risk of being discharged from hospital with
We recently described a strikingly high incidence of the metabolic syndrome and insulin resistance in 70 KS patients compared with an age matched control group. Almost half of the KS patients fulfilled the National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP)III criteria for the metabolic syndrome (2001), whereas it was true for only 10% of the control group. Curiously, there was no difference in blood pressure between the two groups. Plasma lipids including low-density lip (LDL) cholesterol were increased, whereas high-density lip (HDL) cholesterol was decreased; a lipid pattern similar to that of patients with type 2 diabetes. Significantly more KS subjects had elevated fasting plasma insulin levels, and calculation of insulin sensitivity showed a significant decrease in insulin sensitivity (Bojesen et al., 2006b). Such figures have recently been confirmed by Ishikawa et al., who in 60 KS patients found the metabolic syndrome prevalent in 34% of KS patients with increased LDL cholesterol and waist measurements and decreased HDL compared with other men with azoospermia. There were no differences in body mass index (BMI), blood pressure or fasting glucose levels between the groups (Ishikawa et al., 2008).

Combined, both epidemiological and clinical studies show clear evidence of a dramatically increased risk of diabetes and metabolic syndrome in KS.

**Figure 1** A KS patient with a rather atypical phenotype. Note the relatively large muscle mass, normal masculine body hair distribution, beard and baldness, but also the typical abdominal obesity. This patient was diagnosed at the age of 35 years, because of infertility. Height 181 cm, weight 94 kg, karyotype 47,XXY.

either the diagnosis of type 1 diabetes or type 2 diabetes, or obesity, with HR for type 1 diabetes and type 2 diabetes being 2.21 and 3.71, respectively, and HR for obesity of 3.41 (Bojesen et al., 2006a).

**Clinical studies**

An association between KS and diabetes has been reported in a number of studies during the last 40 years. In 1965, Jackson et al. (1966) examined eight KS men and found one with mild diabetes. Becker et al. (1966) described 50 KS patients and among them 5 with diabetes. Zupplinger et al. (1967) examined 24 KS patients and found frank diabetes in 2 and a diabetic glucose tolerance test in 4 additional patients. In 1969, Nielsen et al. (1969) described an increased prevalence (39%) of a diabetic oral glucose tolerance test in 31 KS patients. Pei et al. (1998) found decreased insulin sensitivity and elevated fasting insulin levels in seven KS patients and seven hypogonadotropic hypogonadal patients compared with seven normal controls. And, in a study on 13 KS patients, significantly increased fasting insulin levels were found, but with no difference in insulin sensitivity (Yasilova et al., 2005).

In a study of 24 boys with KS, Aksglaede et al. (2008) using dual energy X-ray absorptiometry (DXA) scans found an increase in height and body fat mass compared with normal boys, whereas no differences in lean body mass, weight and BMI were found. Interestingly, the increased body fat mass was present in the boys before puberty, perhaps pointing towards a possible genetic influence of body fat in KS in addition to the influence of hypogonadism later in life.

We studied 70 KS patients and 70 age-matched controls using DXA scans to measure body composition and found dramatic changes in body composition, although no significant difference in BMI was found, the truncal fat (fat on torso; 34.0% versus 17.6%, P < 0.0001) and waist measurement (109 versus 92 cm, P < 0.0001) was strikingly and significantly increased. For equivalent values of BMI among KS and controls, an excess of 8% truncal fat was found in the KS patients (Fig. 2). Leptin, a strong biomarker of the total amount of body fat, was accordingly greatly elevated. Multivariate analysis showed that the truncal obesity was the major determinant of both the presence of metabolic syndrome and decreased insulin sensitivity, even when controlling for testosterone levels (Bojesen et al., 2006b). Other studies corroborate the presence of abdominal obesity by measures of waist circumference (Ishikawa et al., 2008) or simply a notation of obesity (Becker et al., 1966). Even the illustration in the original paper by Klinefelter et al. (1942) shows that some of the originally described patients were abdominally obese (keeping in mind that obesity was less common 60 years ago).

Apart from truncal (and general) obesity and contrary to results in pubertal boys with KS (Aksglaede et al., 2008), we found adults with KS to have significant reductions in muscle mass (Bojesen et al., 2006b). In addition, we found muscle strength (unpublished data) and maximal oxygen consumption to be significantly decreased,
pointing out that the perturbations in body composition have physical consequences.

In a subset of our KS patients examined by tissue Doppler echocardiography, we found a significantly reduced systolic and diastolic function of the left ventricle in those who fulfilled the criteria for the metabolic syndrome; moreover, truncal fat was the most important negative predictor of both reduced diastolic and systolic velocities, whereas level of fasting triglycerides was the most important predictor of decreased systolic contractility (Andersen et al., 2008b). In a similar study in young normal men, systolic function was dependent on fasting blood glucose and LDL cholesterol, but not on truncal fat (Andersen et al., 2008a). These findings point towards late consequences of alterations in body composition and the presence of the metabolic syndrome on left ventricular function in KS.

**Hypogonadism and change in body composition**

Prospective studies in populations of normal men indicate that low levels of testosterone [and sex hormone-binding globulin (SHBG)] can predict future abdominal adiposity (Tsi et al., 2000), the metabolic syndrome and type 2 diabetes (Stellato et al., 2000; Tsai et al., 2000; Oh et al., 2002; Laaksonen et al., 2004). This effect is probably not direct, since two studies independently showed that measures of insulin sensitivity, hepatic glucose output and insulin secretion were independent of sex hormone levels after controlling for upper body obesity (Stellato et al., 2000; Abate et al., 2002; Tsai et al., 2004). Similarly, the significant correlations of testosterone with insulin sensitivity, measures of body fat and maximal oxygen consumption found in our KS patients disappeared in multivariate analyses, when controlling for confounders (Bojesen et al., 2006a, b).

In KS, it is intriguing to assume that hypogonadism precedes obesity, but the findings of increased body fat mass even before puberty (Aksiglaede et al., 2008), makes this assumption weaker.

Thus, the temporal occurrences of events are unknown. For instance, does the ensuing hypogonadism lead to abdominal adiposity and hence to the well-known side effects of adiposity (the metabolic syndrome and insulin resistance) or does abdominal adiposity lead to decreased testosterone production (as well as the aforementioned known effects of adiposity)?—Indeed, both scenarios may be present and take part in a self-perpetuating vicious circle. The Leydig cells may become insulin resistant as well as other cells in the body. *In vitro* studies showed a stimulatory effect of insulin on testosterone production in both rat- and mouse- Leydig cells (Lin et al., 1986; Bebakar et al., 1990); moreover, young insulin resistant men produced less testosterone when stimulated with human choriongonadotropin (hCG) compared with non-obese men (Pitteloud et al., 2005). In addition, lower levels of testosterone, free testosterone and SHBG have been found in both obese (Pasquali et al., 1991) and diabetic men (Goodman-Gruen and Barrett-Connor, 2000; Dhindsa et al., 2004). However, prospective studies have not been performed to confirm that abdominal adiposity leads to decreased testosterone production.

Taken together, these studies suggest the presence of a vicious circle, whereby increased abdominal adiposity aggravates overall and Leydig cell insulin sensitivity, eventually leading to a further deterioration of testosterone production.

Findings of increased amounts of body fat in prepubertal boys with KS point out other causes than low testosterone. Genetic (over-expression of X-bound genes, skewed X-chromosome inactivation or CAG-repeat polymorphism in the androgen receptor) and psychosocial causes are both plausible, but no studies addressing these possible relations are at hand. Apart from the association between low testosterone, body composition, the metabolic syndrome and insulin sensitivity, hypogonadism has been associated with an adverse cardiovascular risk profile, with increased C-reactive protein (CRP) and triglycerides but decreased HDL cholesterol (Laaksonen et al., 2003). Opposing, testosterone is negatively associated with adiponectin, a cardioprotective and anti-diabetic adipocytokine (Nishizawa et al., 2002). Furthermore, testosterone treatment has been shown to suppress (relatively elevated) adiponectin levels in both hypogonadal men and in castrated mice (Lanfranco et al., 2004; Page et al., 2005a, b; Xu et al., 2005). Adiponectin is closely and inversely correlated with obesity (Diez and Iglesias, 2003). In our recent study on KS patients (Bojesen et al., 2006b), we found, rather unexpectedly, normal (non-suppressed) levels of total adiponectin and normal blood pressure, albeit in the presence of a host of acknowledged cardiac risk factors (increased weight, BMI, waist circumference, LDL cholesterol, triglycerides, CRP, fasting insulin and glucose and decreased HDL cholesterol). Likewise, the high molecular weight subform of adiponectin, which is the major active form mediating insulin sensitizing effects on hepatocytes (Berg et al., 2001; Wang et al., 2006), was non-suppressed in our KS patients (Host et al., 2009).

In KS, hypogonadism is relative rather than absolute, with testosterone one typically in the low-normal or subnormal range. The non-suppressed level of adiponectin may therefore be the result of the opposing effects of (subnormal) testosterone levels and obesity. Further, it seems plausible that non-suppressed adiponectin acts in

**Figure 2** Truncal fat in correlation with BMI. KS patients (open circles) have on average ~8% more fat on the trunk compared with controls (filled circles), independent of BMI. No formal testing for differences between the two regression lines was made, but confidence intervals for the two lines were not overlapping. Truncal fat was determined by DXA scans using a Hologic 2000 (Bojesen et al., 2006a, b).
Increased mortality in both groups is supported by the finding of decreased mortality risk from increased testosterone treatment compared with placebo (Marin et al., 1992). In a study on elderly men with heart failure, testosterone treatment for 12 weeks improved muscle strength, insulin sensitivity and maximal oxygen consumption but also improved the vagally mediated arterial baroreceptor cardiac reflex sensitivity, a prognostic factor in heart failure (Caminiti et al., 2009). In our study, in 70 KS patients, we found a trend (albeit non-significant) towards a reduction in truncal fat, total cholesterol, fasting plasma glucose and leptin among those on testosterone treatment compared with those without treatment (Bojesen et al., 2006b). Although unsupported by comparable trials in KS patients, these studies suggest that testosterone treatment in hypogonadal men may reverse the unfavourable body composition, and (with less evidence) improve insulin resistance. We therefore recommend hormone replacement therapy in KS patients with low serum testosterone or increased LH, and with other signs of hypogonadism, which in our opinion, should also include increased fat mass and decreased muscle mass. The ultimate goal of course is a reduction in morbidity and mortality or at least improvement in quality of life of KS patients. Currently, no studies indicate such positive effects of testosterone treatment in KS, but future studies will hopefully address these important issues.

**Testosterone treatment and body composition**

Apart from case reports, no prospective randomized studies on the effect of testosterone treatment on insulin sensitivity, body composition or other surrogate markers of cardiovascular health in KS have been published, but other populations have been studied. Middle-aged abdominal obese men had a significant reduction in visceral adiposity and improvement in insulin sensitivity after 8 months testosterone treatment compared with placebo (Marin et al., 1992). Experimentally induced hypogonadism in 61 younger men followed by substitution with different doses of testosterone (five different dose regimens from sub- to supra-physiological doses) showed a dose-dependent increase in fat-free mass, whereas fat mass was negatively correlated with testosterone dose (Bhasin et al., 2001). Despite these changes in body composition, no difference in insulin resistance was detected between the groups (Singh et al., 2002). In another study, induction of hypogonadism in six healthy young men for 10 weeks increased fat mass, whereas lean body mass, resting energy expenditure, protein anabolism and muscle strength decreased (Mauras et al., 1998). Additionally, in much larger populations of elderly men, several placebo-controlled studies have concurrently shown testosterone treatment to increase lean body mass and to decrease fat mass (Snyder et al., 1999; Steidle et al., 2003; Wittert et al., 2003; Wang et al., 2004; Page et al., 2005a, b). In a study on elderly men with heart failure, testosterone treatment for 12 weeks improved muscle strength, insulin sensitivity and maximal oxygen consumption but also improved the vagally mediated arterial baroreceptor cardiac reflex sensitivity, a prognostic factor in heart failure (Caminiti et al., 2009). In our study, in 70 KS patients, we found a trend (albeit non-significant) towards a reduction in truncal fat, total cholesterol, fasting plasma glucose and leptin among those on testosterone treatment compared with those without treatment (Bojesen et al., 2006b). Although unsupported by comparable trials in KS patients, these studies suggest that testosterone treatment in hypogonadal men may reverse the unfavourable body composition, and (with less evidence) improve insulin resistance. We therefore recommend hormone replacement therapy in KS patients with low serum testosterone or increased LH, and with other signs of hypogonadism, which in our opinion, should also include increased fat mass and decreased muscle mass. The ultimate goal of course is a reduction in morbidity and mortality or at least improvement in quality of life of KS patients. Currently, no studies indicate such positive effects of testosterone treatment in KS, but future studies will hopefully address these important issues.

**References**


