

RESEARCH REVIEW

Metabolic and cardiovascular risk factors in Klinefelter syndrome

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Abstract

Klinefelter syndrome (KS), which normally presents with a 47,XXY karyotype, is the most common sex chromosome disorder in males. It is also the most common genetic cause of male infertility. KS subjects are typically tall, with small and firm testes, gynecomastia, broad hips, and sparse body hair, although a less evident presentation is also possible. KS is also characterized by a high prevalence of hypogonadism, metabolic syndrome (MetS) and cardiovascular disease. The aim of this article is to systematically review metabolic and the cardiovascular risk factors in KS patients. Hypogonadism has an important role in the pathogenesis of the changes in body composition (particularly visceral obesity) and hence of insulin resistance and MetS, but the association between KS and MetS may go beyond hypogonadism alone. From childhood, KS patients may show an increase in visceral fat with a reduction in lean body mass and an increase in glucose and impaired fat metabolism. Their increased incidence of congenital anomalies, epicardial adipose tissue, and thromboembolic disease suggests they have a higher risk of cardiovascular disease. There is conflicting evidence on the effects of testosterone therapy on body composition and metabolism.

KEYWORDS

body composition, cardiovascular risk, Klinefelter syndrome, metabolic syndrome, visceral obesity

1 | INTRODUCTION

Klinefelter syndrome (KS) was first described in 1942 as a condition characterized by gynecomastia, small testes, hyalinization of the seminiferous tubules and subsequent azoospermia (Klinefelter, Refenstien, & Albright, 1942). It is the most common sex chromosome disorder in males, with an estimated prevalence of 1 case per 660 newborns (Morris, Alberman, Scott, & Jacobs, 2008; Radicioni et al., 2010). It is commonly defined by the presence of an extra X chromosome in a male phenotype, resulting in a 47,XXY karyotype (Bojesen, Juul, & Gravholt, 2003).

The extra X chromosome is the consequence of a nondisjunction mechanism which could occur during the first or the second maternal meiotic division, or the first paternal meiotic division. A nondisjunction

event after zygote development is also possible, albeit less likely (3–10%), causing mosaicism forms (mainly 46,XY/47,XXY) (Forti, Corona, Vignozzi, Krausz, & Maggi, 2010). Higher grade aneuploidies are also possible, but should be considered and treated as different conditions (Rogol, 2020; Spaziani et al., 2018).

KS subjects are typically tall, with small and firm testes, gynecomastia, broad hips, and sparse body hair. Another phenotype, probably more prevalent than the classic presentation, involves fewer clinical features (paucisymptomatic manifestations) (Simpson et al., 2003): the lack of evident signs, combined with failure to perform a testicular examination, is the most probable reasons for underestimation of the syndrome's prevalence (Abramsky & Chapple, 1997). However, KS patients may also be characterized by other important clinical aspects, including a tendency to develop visceral obesity, dyslipidemia,

hypertension, and diabetes mellitus, and hence metabolic syndrome (MetS) (Bojesen, Host, & Gravholt, 2010). The association of KS with cardiovascular, bone, and immune disorders is another important implication (Panimolle et al., 2018; Shiraishi & Matsuyama, 2018; Tahani et al., 2018).

The aim of this review is to investigate the metabolic and the cardiovascular risk factors in patients with KS.

2 | MetS AND HYPOGONADISM

The close association between hypogonadism, truncal obesity, and MetS is well known, and testosterone deficiency is an important risk factor for the development of cardiovascular disease and diabetes mellitus (Haffner, Shaten, Stern, Smith, & Kuller, 1996; Kupelian et al., 2006). One of the first meta-analyses of the association between hypogonadism and cardiovascular disease demonstrated that low testosterone (and increased 17β -E₂) levels are independently associated with cardiovascular risk factors and with the incidence of coronary heart disease events (Corona et al., 2011). Furthermore, over a 20-year period, low levels of testosterone are projected to be involved in the development of approximately 1.3 million new cases of cardiovascular disease and 1.1 million of diabetes mellitus in the United States alone (Moskovic, Araujo, Lipshultz, & Khera, 2013).

Although not caused by an organic condition, late onset hypogonadism, currently known as functional hypogonadism, is in any case associated with various conditions such as reduced insulin sensitivity, central obesity, hypertension, muscle weakness, fatigue, and sexual dysfunction (Corona et al., 2020; Rao, Kelly, & Jones, 2013). It is well known that testosterone levels drop by about 1–2% per year in men over the age of 50 years, and that about 20% of subjects over the age of 60 have testosterone concentrations below the lower limit of normal (Harman, Metter, Tobin, Pearson, & Blackman, 2001). Importantly, Ravaglia et al. found that this increased incidence of hypogonadism runs in parallel with a rising rate of MetS, from 20% in young men to 32% in men over 60 (Ravaglia et al., 2006). In the same study, the authors showed that the mortality rate was not correlated with MetS alone, but was strongly associated with the simultaneous presence of MetS and high IL-6 levels (Ravaglia et al., 2006).

3 | MetS IN KS

As noted in the introduction, KS is an organic cause of hypogonadism and can therefore be studied as an important model of the link between low testosterone and cardiovascular and metabolic disease. It is however essential to begin by stressing an important concept that makes KS different from other genetic and nongenetic forms of hypogonadism. There is considerable evidence that hypogonadism is involved in the pathogenesis of changes in body composition, by causing the onset of visceral obesity and hence of insulin resistance and MetS. However, it is also possible that the increased visceral fat precedes the hypogonadism and that MetS may be a specific feature of

KS that is independent of the hypogonadism, probably arising from the genetic basis of the syndrome.

Epidemiological studies on morbidity and mortality in KS subjects highlighted a significant increase in hospitalizations and deaths due to diabetes mellitus and cardiovascular diseases (Bojesen, Kristensen, et al., 2006; Bojesen, Juul, Birkebaek, & Gravholt, 2006; Wang et al., 2005). Moreover, while the incidence of MetS in the general population is 10–20%, in KS subjects it is 33–46%, with an almost fivefold higher incidence of metabolic disorders (Høst et al., 2019; Ishikawa, Yamaguchi, Kondo, Takenaka, & Fujisawa, 2008).

There is a large body of anthropometric data showing important changes in body composition in KS patients, with a significant increase in total body fat mass (in particular visceral fat) and a reduction in lean body mass. Laboratory data point to increases in fasting plasma glucose (and even overt Type II diabetes mellitus), basal insulin, total and LDL cholesterol, and triglycerides, associated with a decrease in HDL cholesterol and insulin sensitivity, as measured by the HOMA index.

3.1 | Infancy and childhood

While MetS tends to increase with advancing age in the general population, its onset is both more common and more precocious in KS subjects. Epidemiological data on MetS in KS patients come from young men (mean age 35 years), usually diagnosed with KS due to infertility or sexual disorders. While it is unclear if hypogonadism is present in infants and prepubertal boys with KS, it is known that KS boys aged 4–18 years could present a higher total body fat mass, characterized by an unfavorable lean mass-fat mass ratio, compared to their age- and BMI-matched peers (Aksglaede, Molgaard, Skakkebaek, & Juul, 2008).

Another paper found that boys with KS (range 4–12.9 years) presented aspects of MetS which were not dependent on age or BMI but were instead associated with Sertoli cell dysfunction, as assessed by Inhibin B and AMH levels, and some reduction in testosterone. The study highlighted that low Inhibin B levels were associated with higher concentrations of fasting blood glucose, triglycerides, LDL cholesterol, and lower HDL cholesterol, and that AMH had a protective role on MetS onset (Davis et al., 2016).

How and to what extent testosterone replacement therapy (TRT) could restore normal body composition in infants with KS is still under debate. In a recent clinical trial, 20 KS infants aged 6–15 weeks were randomized to receive monthly intramuscular injections with testosterone cypionate 25 mg (a total of three injections) or placebo (10 subjects in each group). The TRT-treated babies showed a reduction in fat mass and an increase in fat-free mass compared with the placebo group; at the age of 5 months, adiposity in the untreated infants was 15% higher than that of typical male controls, comprised by 296 healthy infants from the Healthy Start Study (Davis, Reynolds, Dabelea, Zeitler, & Tartaglia, 2019).

Testosterone is not the only treatment studied in KS boys. A 2016 placebo-controlled study investigated the effects of 2 years' therapy with oral oxandrolone (a nonaromatizable androgen) at a dose

of 0.06 mg/kg/daily (range 1.25–3.75 mg/daily), focusing on cardiometabolic health. The treated subjects showed a significant reduction in total cholesterol and triglycerides, but unfortunately also in HDL cholesterol. There was a modest positive effect on body composition, characterized by a significant decrease in body fat. An important side effect was a not-insignificant increase in bone age, which, taken with the reduction in HDL, gives rise to strong doubts about its use (Davis et al., 2017).

3.2 | Adulthood

In one of the first milestone studies, Bojesen et al. evaluated the differences in body composition, plasma glucose, sex hormones, adipocytokines, insulin, and C-reactive protein between untreated KS patients and control subjects, and then studied the differences between KS patients under TRT and untreated patients. One of their main findings was that 44% of KS men (vs. 10% of controls) had MetS, associated with significantly lower concentrations of androgens, HDL cholesterol and insulin sensitivity and significantly higher levels of total fat mass, LDL cholesterol, triglycerides, and C-reactive protein. KS subjects who underwent TRT showed a significant drop in LDL cholesterol and adiponectin without significant changes in body composition when compared to untreated patients. The authors concluded that truncal fat, fostered by hypogonadism, is the main determinant of insulin sensitivity and MetS (Bojesen, Juul, et al., 2006; Bojesen, Kristensen, et al., 2006).

A more recent study compared 55 KS patients against a control group of 120 subjects, demonstrating a higher weight and height in the KS subjects, without any significant differences in BMI, associated with significantly lower levels of serum testosterone. Evaluation of the lipid profile indicated that triglycerides, total and LDL cholesterol levels were higher in KS patients, while HDL cholesterol was higher in the control group (with the difference only being significant for triglycerides and HDL cholesterol) (Lee, Park, Lee, & Seo, 2017).

Abdominal fat is more sensitive to catecholamines and glucocorticoid. This results in an increase in the production of free fatty acids, which play a central role in the development of MetS. Recent studies demonstrated that adipose tissue must be considered as a well-defined endocrine organ with two different components: white adipose tissues (WATs), which store lipids to allow gaps between meals, and brown adipose tissues, which burn lipids for thermogenesis (Cinti, 2018). Adipose tissue interacts with the renin–angiotensin–aldosterone system and with the production of adipokines, pro-thrombotic molecules, and pro-inflammatory cytokines, which are involved in the genesis of insulin resistance. A recent study tested the hypothesis that high-fat feeding increases afferent impulses from WATs, which reflexively elevate efferent nerve activity to the skeletal muscle and adipose tissue, thus impairing peripheral glucose uptake. This mechanism is enhanced by an increased salt intake, suggesting that it both induces and enhances insulin resistance (Cao et al., 2018, 2019).

Taking into account the NCEP-ATP II criteria for the diagnosis of MetS, KS patients usually show visceral obesity, glucose, and lipid

metabolism disturbances. However, the presence of hypertension is less common, probably due to the possible role of testosterone in blood pressure and electrolyte regulation systems such as the renin–angiotensin–aldosterone system and the vasopressin/thirst mechanism (Andersen et al., 2008).

4 | HYPOGONADISM AND MetS: WHICH CAME FIRST, THE CHICKEN OR THE EGG?

As noted above, as yet there is no consensus on whether testosterone alone is responsible for metabolic alterations in KS. The presence of metabolic disorders during infancy and childhood—a period in which the presence of overt hypogonadism is less certain—suggests that hypogonadism may not be the only link between KS and MetS. Several studies have investigated the interaction between genetic parameters and MetS. A possible role has been hypothesized for the parental origin of the extra X-chromosome, or for the X-chromosome inactivation mechanism, but no significant effects on body composition and on anthropometric data were found for either of these. In contrast, androgen receptor (AR) CAG polymorphism explains some phenotypic variations (Zitzmann, Depenbusch, Gromoll, & Nieschlag, 2004), such as arm span and height, which are positively correlated with the CAG number, and some laboratory findings, such as hematocrit and total cholesterol, which are negatively correlated with the CAG number (Bojesen, Hertz, & Gravholt, 2011). In addition, a 2015 study showed that the increased insulin resistance in KS was linked to CSF2RA gene dosage, which maps to both the X and Y chromosome (Zitzmann et al., 2015).

As noted above, the variability of AR, caused by microsatellite trinucleotide CAG repeats, has a more complex role. It is well known that AR transactivation activity is inversely associated with the number of CAG repeats (normal range 11–31). Unlike Bojesen et al., Chang et al. did not find differences in the number of CAG repeats between KS patients (whether treated or untreated) and subjects with a normal karyotype; the only confirmed association was between CAG repeats and the arm span and leg length of XXY subjects (Chang et al., 2015).

5 | ANDROGEN REPLACEMENT THERAPY AND MetS

TRT in hypogonadal subjects improves insulin sensitivity, increases lean body mass, and reduces total fatty mass. It has also been demonstrated that in hypogonadal patients with Type 2 diabetes, testosterone treatment enhances insulin sensitivity in obese but not in thin subjects, demonstrating the importance of visceral obesity in the pathogenesis of insulin resistance (Grossmann, Gianatti, & Zajac, 2010; Selvin et al., 2007). In elderly hypogonadal subjects, TRT reduces waist circumference and blood pressure and improves lipid profile. These modifications are due to inhibition of lipoprotein lipase, which consequently reduces triglyceride uptake in the visceral adipose tissue, adipogenesis, and the secretion of leptin and inflammatory

cytokines, in particular TNF and IL-1 (Lunenfeld, Mskhalaya, Kalinchenko, & Tishova, 2013; Saad, Gooren, Haider, & Yassin, 2008).

In the aforementioned 12-month randomized, double-blinded, placebo-controlled study by Høst et al., 13 KS subjects with a mean age of 34.8 years took oral TRT (160 mg/daily) or placebo for 6 months. They were then compared to 13 age- and BMI-matched healthy subjects in order to evaluate the effects of the therapy on body composition, muscle strength, maximal oxygen uptake, insulin sensitivity, and metabolism. The treated patients showed a significant reduction in subcutaneous abdominal and total body fat, but not in intraabdominal fat mass. They also showed an increase in lean body mass, physical fitness and maximal muscle strength, but these modifications were not statistically significant. There were no changes in insulin sensitivity or metabolism, probably due to the short treatment period and relatively low initial BMI of the KS subjects (Høst et al., 2019).

Another recent paper, reporting on a cross-sectional retrospective study on 81 treated and 181 untreated KS patients (mean age 40 years), found no statistically significant differences in various metabolic parameters (lipid profile and glucose-homeostasis status), but did find a significant increase in BMI in the treated group (Ehrhart, Guthrie, Qeadan, & Burge, 2018).

The aforementioned 2006 study by Bojesen et al. on 71 KS subjects, of whom 35 were taking TRT, did not find any significant variations in BMI or waist circumference, but found a slight reduction in truncal fat mass (Bojesen, Juul, et al., 2006; Bojesen, Kristensen, et al., 2006). In contrast, two other papers did not find any difference in weight, waist circumference, and BMI (Lee et al., 2017) or in weight, BMI, waist circumference, abdominal fat mass, lean body mass, and total fat mass (Chang et al., 2015).

Given all the above, although the close relationship between hypogonadism and MetS is well established, no definitive conclusions can yet be drawn on the effect of TRT on body composition and metabolic control in KS subjects. In fact, while the effects of TRT are more clear and unequivocal in general forms of hypogonadism, in KS subjects the genetic influence is far more complex and still uncertain, which may well be the reason for the conflicting results of the abovementioned studies.

6 | CARDIOVASCULAR FEATURES

6.1 | ECG and echocardiography features, congenital anomalies, cardiovascular risk

As mentioned above, KS does not affect blood pressure, and no significant changes in heart rate and ECG traces are generally described (Esposito et al., 2012). However, some changes in ventricular repolarization (corrected for heart rate [QT/QTc interval]) that can lead to cardiac arrhythmia have been detected in correlation with hypogonadism (Piccirillo et al., 2019; Salem et al., 2019). A 2015 case-control study of 62 KS subjects compared to an equal number of healthy age-matched controls found a shorter QTc interval in the KS

subjects, which became even shorter in patients under TRT. The authors concluded that genes on the X chromosome could regulate the QTc interval, and testosterone probably has a significant role in modulating the mechanism (Jørgensen et al., 2015). The same conclusion was reached by Zitzmann et al., who found a markedly shorter QTc interval in their cohort of KS patients (Zitzmann et al., 2015).

KS subjects present autonomic nervous system modifications and a consequent increase in adrenergic activity, associated with an important reduction in the density and sensitivity of the peripheral adrenergic receptors that could affect chronotropic activity and heart recovery rate (Lauer, 2009). A reduced tolerance of physical activity (due to impaired systolic function) and a pathological shift in diastolic activity, combined with an increase in the carotid intima-media thickness, has also been described, especially in subjects with marked hypogonadism and/or MetS (Aksglaede et al., 2008).

Congenital cardiovascular abnormalities are undoubtedly more common in KS subjects than in the general population, although their frequency is still not particularly high. Some cases of interatrial and interventricular defects, tetralogy of Fallot, and patent ductus arteriosus have been described. Two cases of patients with hypertrophic obstructive cardiomyopathy have been reported (Ahmed, Hafeez, Ali, & Ahmed, 2009; Yoshida et al., 1998); in the second case, this was associated with sick sinus syndrome and coronary arteriovenous fistula (Yoshida et al., 1998).

In 1984 Fricke et al. reported, for the first time, an increased incidence (55%) of mitral valve prolapse in KS, compared to an average incidence of about 6% in the general population (Fricke, Mattern, Schweikert, & Schwanitz, 1984). In this article, the prolapse was not related to the degree of chromosome aberration, however its association with a karyotype involving sex chromosome abnormalities, as also seen in other genetic hypogonadal conditions (e.g., Turner syndrome), was confirmed.

Other possible echocardiographic abnormalities in KS include interatrial septum aneurysm, seen in 5% of KS subjects. This is not usually associated with an evident shunt but is often combined with the so-called Chiari network; this embryonic remnant of the venous sinus, which appears as an accentuation of the right atrium trabeculation, is found in 37% of all KS subjects but in 70% of KS patients with interatrial septum aneurysm (Granato et al., 2019).

In their Danish register study based on hospital admission and discharge diagnoses, Bojesen et al. evaluated the comorbidities associated with KS compared to the general population. In relation to cardiovascular risk, they found that KS subjects presented a higher rate of pulmonary embolism, ischemic heart disease, peripheral vascular disease and intestinal vascular insufficiency, the latter caused by intestinal thrombosis (Bojesen, Juul, et al., 2006; Bojesen, Kristensen, et al., 2006). A similar study by Swerdlow et al. investigated the cause of mortality in KS men in Britain, using (like Bojesen) the standardized mortality ratio as the outcome measure. The results were consistent with the Danish register study except for ischemic heart disease, which was associated with a significantly decreased mortality (Swerdlow, Higgins, Schoemaker, Wright, & Jacobs, 2005).

6.2 | Epicardial adipose tissue and endothelial progenitor cells

The role of epicardial adipose tissue has regained importance in recent years as a cardiac marker of visceral adiposity, used in the evaluation of cardiovascular risk in patients with obesity and MetS (Iacobellis, Corradi, & Sharma, 2005). It is located between the ventricular myocardium and the visceral pericardial tissue (on the free surface of the right ventricle, in correspondence with the apex of the left ventricle and around the atria) (Iacobellis, Diaz, Mendez, & Goldberg, 2014; Nelson et al., 2011). Epicardial adipose tissue has interesting biochemical properties, including high release of free fatty acids, high protein content, weak oxidation capacity and low glucose use, associated with its ability to secrete adiponectin and inflammatory cytokines (e.g., TNF- α , IL-1 β , IL-6) (Iacobellis et al., 2005).

The most relevant aspect is the possible infiltration of adipocytes into the underlying myocardium: this, associated with the increased epicardial fat thickness (EFT), determines the conditions for the development of arrhythmias, due to electrical instability. Adipocytes could also stratify around the small intramyocardial coronary arteries, leading, through the secretion of pro-inflammatory adipokines, to vasculitis and/or atherosclerotic phenomena (Iacobellis et al., 2005).

The reference values for EFT are 6.5 mm for females and 7.5 mm for males (Iacobellis et al., 2005). Granato et al. reported an average EFT of 8 mm, with a maximum of $\geq 9.5\%$ (generally considered as the threshold for cardiometabolic risk) in 5% of their KS population, which consisted of 221 men with a mean age of 34.2 years. They found a strong correlation between EFT and truncal body fat. They also found that EFT was higher in hypogonadal KS patients than in nonobese controls and eugonadal KS patients, while it was similar in hypogonadal KS patients and both obese controls and KS patients under TRT, thus demonstrating that the major determinants of both EFT and truncal body fat were BMI and KS itself, independently of testosterone levels (Granato et al., 2019). These results are in line with the findings of other authors, who also affirm that cardiovascular abnormalities are not reversed by TRT (Di Mambro et al., 2010; Foresta et al., 2012).

There has been some interest in a report that a drop in the number of circulating endothelial progenitor cells (EPCs) may be a specific independent predictor of coronary artery disease (Vasa et al., 2001). Ru et al. did not find any correlation between testosterone concentrations and the number of EPCs in KS patients (Ru, Gao, Yue, & Hu, 2012). This was consistent with an earlier study which found a reduced number of EPCs in 68 KS subjects which was independent of testosterone levels and did not rise after 6 months of TRT (Di Mambro et al., 2010).

6.3 | Thromboembolic risk

There seems to be a higher incidence (13%) of thromboembolic disease in KS patients (Lapecorella et al., 2003; Murray, 1988), as well as a higher prevalence (20%) of venous ulcers, associated with vein

insufficiency (Becker, 1972; Campbell & Price, 1981). There are several hypotheses for the occurrence of such disorders. The most plausible are hyperactivity of Factor VIII coagulant and plasminogen activator inhibitor-1, which causes an abnormal fibrinolysis and an increased platelet aggregability, and MTHFR gene mutations (particularly the homozygous mutation for the A1298C factor) (Angel, Parker, Sells, & Atallah, 2010; Becker, 1972; Di Minno et al., 2015; Dissemond, Knab, Lehnen, & Goos, 2005; Iwaki, Urano, & Umemura, 2012; Zollner et al., 1997).

Zöller et al. carried out a 31-year-follow-up of 1,085 Swedish KS inpatients for a diagnosis of venous thromboembolic disease (VTE), finding a strongly increased risk. The VTE events observed in these patients comprised venous thrombosis of the lower extremities (43%), other venous embolism or thrombosis (31%), and pulmonary embolism (26%), with a highest standardized incidence ratio in patients aged <30 years, dropping with increasing age. Their main conclusion was that KS should be considered as a genetic hypercoagulable state in the same way as inherited thrombophilias such as double heterozygosis for G20210A prothrombin and Leiden Factor V mutations, although the authors themselves were unable to establish the mechanism for the association between VTE and KS. Their main hypothesis was X-linked gene dosage, considering that the Factor VIII gene maps to chromosome X, and the increased incidence of MetS and autoimmune disorders (such as LES), which are risk factors for the development of VTE (Zöller, Ji, Sundquist, & Sundquist, 2016).

Finally, even though the role of testosterone in the clotting system is well known (Caron et al., 1989; Winkler, 1996), it is not yet clear how TRT influences thromboembolic risk. While several papers actually report an improvement in leg ulcers, others found that TRT had a damaging effect, but only in the presence of a thrombophilic condition (Ozbek et al., 2008; Thukuntla & Kumar, 2011).

Two more recent papers confirmed the higher incidence of VTE in KS subjects, but also revealed a protective or a neutral effect of TRT. Specifically, in their 2019 study Chang et al. found a reduced thrombin production in testosterone-treated KS patients in comparison with untreated subjects (Chang et al., 2019), while in 2020, they demonstrated a nonsignificant decrease in venous thromboembolism and thrombotic deaths in patients receiving TRT (Chang et al., 2020).

Table 1 summarizes the main original studies mentioned in the text.

7 | CONCLUSIONS

KS is a particularly heterogeneous condition which may manifest with a paucisymptomatic form rather than the classic phenotype. It is widely underdiagnosed, probably for this reason. It is very likely that body composition alterations, and hence MetS, may be found even in paucisymptomatic cases, putting these subjects at even greater risk of developing pathological conditions involving an increased cardiovascular risk, given their unawareness of having KS.

The relationship between hypogonadism, visceral obesity, insulin resistance, and MetS is still not completely clear, and it is not possible

TABLE 1 Overview of the original studies, mentioned in the text, investigating the MetS and the cardiovascular features in KS

Bibliography	Involved subjects	Results
MetS, body composition, and androgen replacement therapy		
Aksglaede et al. (2008)	18 untreated KS boys and 6 receiving androgen substitution (4–18 years)	Higher total body fat mass with an unfavorable lean mass-fat mass ratio in untreated subjects
Davis et al. (2016)	93 prepubertal boys (4–12.9 years)	Low Inhibin B levels were associated with higher concentrations of fasting blood glucose, triglycerides, LDL cholesterol, and lower HDL cholesterol; AMH had a protective role on MetS onset
Davis et al. (2017)	93 KS prepubertal boys (4–12 years), receiving oral oxandrolone at a dose of 0.06 mg/kg/daily or placebo, with a 1:1 allocation ratio, for 2 years	Treated subjects showed a significant reduction in total cholesterol, HDL cholesterol and triglycerides, and a significant decrease in body fat
Davis et al. (2019)	20 KS infants (6–15 weeks): 10 received a total of three i.m. injections with testosterone cypionate 25 mg, and 10 placebo	Treated subjects displayed a reduction in fat mass and an increase in fat-free mass compared with the placebo group
Bojesen, Juul, et al. (2006) and Bojesen, Kristensen, et al. (2006)	71 KS patients (of whom 35 received TRT), and 71 age-matched control subjects	Treated patients showed a significant drop in LDL cholesterol and adiponectin without significant changes in body composition, compared to untreated patients
Lee et al. (2017)	55 KS patients and 120 age-matched control subjects	Higher weight and height and lower levels of triglycerides and HDL cholesterol in the KS subjects
Høst et al. (2019)	13 KS subjects received oral TRT (160 mg/daily) or placebo for 6 months; 13 age-matched healthy subjects	Treated patients showed a significant reduction in subcutaneous abdominal and total body fat and a not statistical significant increase in lean body mass, physical fitness, and maximal muscle strength
Ehrhart et al. (2018)	81 treated and 181 untreated KS patients	No statistically significant differences in lipid profile and glucose-homeostasis status; significant increase in BMI in the treated group
Cardiovascular features		
Jørgensen et al. (2015)	62 KS males and 62 healthy subjects	KS subjects showed a shorter QTc interval, which became even shorter in patients under TRT. untreated KS patients had QTc interval comparable to controls
Zitzmann et al. (2015)	132 KS men: 97 received TRT, 35 were treatment-naïve, compared with age-matched male ($n = 50$)/female controls ($n = 50$)	The authors found a clearly shorter QTc interval in their cohort of KS patients
Bojesen, Juul, et al. (2006) and Bojesen, Kristensen, et al. (2006)	832 KS subjects and 4,033 age-matched control subjects	Higher rate of pulmonary embolism, ischemic heart disease, peripheral vascular disease, and intestinal vascular insufficiency in KS subjects
Granato et al. (2019)	221 KS men, mean age of 34.2 years	Strong correlation between EFT and truncal body fat; the major determinants of both EFT and truncal body fat were BMI and KS itself, independently of testosterone levels
Ru et al. (2012)	36 KS subjects with one or more cardiovascular risk factors, who underwent TRT	After TRT, the content of EPCs showed no significant rise
Di Mambro et al. (2010)	68 KS subjects and 46 age-matched control subjects	There was a reduced number of EPCs in KS subjects, which was independent of testosterone levels and that did not rise after 6 months of TRT

(Continues)

TABLE 1 (Continued)

Bibliography	Involved subjects	Results
Chang et al. (2019)	18 untreated KS men and 27 testosterone treated subjects	A reduced thrombin production in testosterone-treated KS patients than untreated was found
Chang et al. (2020)	1,155 KS men were each matched by year and month of birth to 100 men from the background population	A nonsignificant decrease in venous thromboembolism and thrombotic deaths in patients receiving TRT was demonstrated

Abbreviations: AMH, anti-Müllerian hormone; EFT, epicardial fat thickness; EPCs, endothelial progenitor cells; KS, Klinefelter syndrome; MetS, metabolic syndrome; QTc, corrected QT interval; TRT, testosterone replacement therapy.

to affirm that low testosterone is the only trigger. The effect of the extra X chromosome, the length of its CAG repeats and the nonexpression/overexpression of the genes mapping on it all might influence this relationship.

Furthermore, it is not even clear how and to what extent androgen therapy, and TRT in particular, reshapes the body composition, although there is sufficient evidence of its beneficial effect on blood metabolites. Despite this uncertainty, early diagnosis of KS is crucial to enable prompt treatment and avoid the onset of androgen deficiency symptoms.

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CONFLICT OF INTEREST

None.

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