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SHORT REVIEW

Klinefelter syndrome: cardiovascular abnormalities and metabolic disorders

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Abstract Klinefelter syndrome (KS) is one of the most common genetic causes of male infertility. This condition is associated with much comorbidity and with a lower life expectancy. The aim of this review is to explore more in depth cardiovascular and metabolic disorders associated to KS. KS patients have an increased risk of cerebrovascular disease (standardized mortality ratio, SMR, 2.2; 95% confidence interval, CI, 1.6–3.0), but it is not clear whether the cause of the death is of thrombotic or hemorrhagic nature. Cardiovascular congenital anomalies (SMR, 7.3; 95% CI, 2.4–17.1) and the development of thrombosis or leg ulcers (SMR, 7.9; 95% CI, 2.9–17.2) are also more frequent in these subjects. Moreover, cardiovascular abnormalities may be at least partially reversed by testosterone replacement therapy (TRT). KS patients have also an increased probability of endocrine and/or metabolic disease, especially obesity, metabolic syndrome and type 2 diabetes mellitus. The effects of TRT on these abnormalities are not entirely clear.

Keywords Klinefelter syndrome · Testosterone · Hypergonadotropic hypogonadism · Chromosome abnormalities · Cardiovascular disease · Metabolism

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Introduction

The Klinefelter syndrome (KS) was, for the first time, described in 1942 by Klinefelter as a male clinical syndrome characterized by gynecomastia, facial and body hair rarefaction, small testicles and infertility [1]. In 1959, this condition was associated with the presence of an extra X chromosome in the karyotype. The classic form of KS is indeed characterized by a 47, XXY karyotype and it represents about 90% of the cases. The remaining 10% of the cases consists of mosaicisms (karyotype 46,XY/47,XXY) and other uncommon form of aneuploidies, as 48, XXXY e 48, XXYY [2].

As regards to the prevalence of KS in the newborn, it is about 0.1–0.2%, but it increases to 3–4% if we consider the infertile population, and up to 10–12% in azoospermic patients [2]. The incidence of this condition has been estimated to be present in 1:500 to 1:1000 men [3].

KS is actually the most common genetic cause of human male infertility, but many cases remain undiagnosed because these patients often do not present clinical or phenotypic abnormalities. However, it is associated with much comorbidity that may cause serious consequences. The aim of this review is to investigate cardiovascular and metabolic disorders present in patients with KS.

Klinefelter syndrome: comorbidities and mortality rate

It is well known that patients with KS have an increased risk of being hospitalized (>70%), and they are more susceptible to congenital malformations, cardiovascular diseases, psychiatric syndromes, and endocrine/metabolic disorders, compared to subjects of the same age (Table 1) [4]. The above-mentioned comorbidities are considered the most important factors that negatively influence the life expectancy of KS patients, whereas socioeconomic factors seem to play a less significant role [5]. As a result, the expected lifespan seems to be lower in patients with KS [4, 6–8].

Swerdlow and colleagues reported a significant increase of the mortality rate in 646 KS patients because of diabetes and cardiovascular diseases [9]. In a subsequent study, these authors consistently reported that the mortality rate was increased by 50% in 3518 patients who had been diagnosed with KS from 1959 until mid-2003 [7]. A lower life expectancy was even found in a cohort of 532 subjects with KS recorded in a register of patients with chromosome abnormalities, instituted in Edinburgh in 1959. These cases, notified from all parts of UK (mainly from Scotland and Northern England), were followed-up from their inclusion in the registry. The analysis of this cohort showed that the median survival was lower by about 5 years [10]. More recent registry-based studies reported a median survival lower than 2.1 years in KS patients [4, 6–8]. The lower life expectancy does not seem to relate to the karyotype, given that no significant differences were found between patients with classical KS (47, XXY) and those with mosaicism (46,XY/47, XXY) or those with karyotypes with more than one extra X chromosome [6].

Klinefelter syndrome and cardiovascular risk

Bojesen and colleagues, analyzing a cohort of 4865 subjects, composed by 832 KS and 4033 controls, reported that KS patients more frequently had ischemic heart disease (standardized mortality ratio, SMR, 0.7; 95% confidence interval, CI, 0.5–0.9), peripheral vascular disease (SMR, 7.9; 95% CI, 2.9–17.2), pulmonary embolism (SMR, 5.7; 95% CI, 2.5–11.3) and even intestinal thrombosis causing intestinal vascular insufficiency (SMR, 12.3; 95% CI, 4.0–28.8) [4]. On the other hand, Swerdlow and colleagues reported that the SMR was significantly higher for each of the above-mentioned diseases with the exception of the ischemic heart disease, whose SMR was significantly lower in mosaic and non-mosaic KS, but not in men with more than three sex chromosomes [7].

After excluding previous or current cardiovascular, respiratory and renal chronic diseases, Pasquali and colleagues analyzed 69 KS [48 of them had already started testosterone replacement therapy (TRT) while the remaining 21 were TRT-naïve] and 48 age-matched controls with comparable physical activity and Body Mass Index (BMI). The results of this study showed that KS patients had a wide array of cardiovascular abnormalities, including left ventricular diastolic dysfunction, reduced maximal oxygen consumption, increased intima-media thickness (IMT) and a high prevalence of chronotropic incompetence. All these abnormalities, including preclinical alterations that may forecast future cardiovascular events, were recognized as independent predictors of long-term poor outcome [11].

Table 1 Main comorbidities present in men with Klinefelter syndrome

Pathology	SMR (95% CI)	Main manifestations
Cardiovascular diseases	1.3 (1.1–1.5)	Left ventricular diastolic dysfunction Decreased maximal oxygen consumption Increased intima-media thickness Chronotropic incompetence Congenital anomalies Thrombosis/leg ulcers
Cerebrovascular diseases	2.2 (1.6–3.0)	Subarachnoid hemorrhage Intracerebral hemorrhage Cerebrovascular thrombosis Arteriovenous malformation
Metabolic disorders	4.8 (2.9–7.4)	Obesity Insulin resistance and hyperinsulinemia Hyperlipidaemia Metabolic syndrome Diabetes

SMR standardized mortality rate, *CI* confidence interval

Klinefelter syndrome and cerebrovascular risk

As for morbidity and mortality risk arising from cerebrovascular diseases or congenital malformations, KS patients have a significant increase of cerebrovascular diseases, and in particular, subarachnoid hemorrhage. Indeed, Price and colleagues reported that the deaths due to cerebrovascular diseases were strikingly increased in patients with KS of any age (25–84 years), whereas the rupture of a berry aneurysm was identified as the third cause of death in KS patients with an age range of 25–44 years [10]. On the other hand, Swerdlow and colleagues concluded that mortality for cerebrovascular disease was significantly increased (SMR 2.2; 95% CI, 1.6–3.0). However, it is not clear whether the cause of the death certificates for cerebrovascular disease is of thrombotic or hemorrhagic nature; in the cohort of Swerdlow and colleagues, six deaths were due to subarachnoid hemorrhage, four to other intracerebral hemorrhage, and nine to cerebrovascular occlusion or thrombosis. In addition, the study confirmed a higher SMR for subarachnoid hemorrhage, but generalized atheromasia is unlikely to be the explanation for the raised risk, considering the significantly reduced SMR reported for ischemic heart disease [7]. This evidence disagrees with another study [6], which showed no association between cerebral hemorrhage and KS. Finally, a case of a 12-year-old boy with KS who had acute cerebellar hemorrhage due to an arteriovenous malformation in the right cerebellar hemisphere was reported; he had bilateral thumb polydactyly and patent ductus arteriosus [12].

Klinefelter syndrome and cardiovascular congenital anomalies

Cardiovascular congenital anomalies are more frequent in patients with KS than in the general population (SRM 7.3; 95% CI, 2.4–17.1) [7]. Fricke and colleagues reported a higher prevalence of mitral valve prolapse, a condition associated with an increased risk of sudden death [13]. Many case reports have strengthened the relevance of detecting cardiac abnormalities by echocardiography and peripheral districts echography in KS patients. Acute mitral regurgitation by idiopathic chordal rupture [14], hypoplasia of the bilateral internal carotid arteries and dilatation of the bilateral vertebral arteries with weakness of the limbs [15], hypertrophic cardiomyopathy [16], atrial septal defects, ventricular septal defects, partial anomalous pulmonary venous connection with pulmonary arterial hypertension [17] have been reported in patients with KS. Moreover, patients with KS, as well as men with Down syndrome, have a higher prevalence of atrial septal and ventricular septal defects with patent ductus arteriosus, pulmonary hypertension and mild tricuspid regurgitation [18], infective endocarditis associated with valve prolapse and severe mitral regurgitation [19], hypertrophic cardiomyopathy and mesenteric venous thrombosis [20]. Finally, Karagoz and colleagues described a 22-year-old KS patient who had bradycardia and syncope because of a sinus node dysfunction requiring a permanent pacemaker implantation [21].

Little information is available about the nature of the underlying cardiovascular abnormalities. Foresta and colleagues analyzed the structure and the function of arteries in different districts to search for possible abnormalities. Ninety-two patients with non-mosaic KS and 50 age-matched healthy male controls were studied. KS patients and controls evaluation included complete anamnesis, physical examination, measurement of reproductive hormone concentrations, lipid and glycemic metabolism, androgen receptor function and sensitivity, ultrasound examinations of several vascular districts (brachial, common carotid and common femoral artery, abdominal aorta). The results of this study showed that patients with KS had significantly reduced artery diameters in different districts (brachial, common carotid and common femoral artery). No statistically significant correlation was found between artery diameter and reproductive hormones, metabolic parameters, anthropometric measures and CAG repeats of the androgen receptor gene [22]. However, it cannot be excluded that the increased mortality for different cardiovascular factors may originate from thromboembolic events, related to an abnormality in fibrinolysis in these patients (see "Klinefelter syndrome and thrombosis/leg ulcers" section).

Klinefelter syndrome and thrombosis/leg ulcers

Patients with KS have an increased risk of developing thrombosis or leg ulcers, even in the absence of any triggering event. Moreover, as many case reports have shown, this risk can be worsened by the co-existence of one or more thrombophilic conditions, such as obesity, hypertension, diabetes, that are more frequent in KS, although these conditions there are not the only causes. The association between KS and thrombophilic conditions is characterized by a worse outcome. Lapecorella and colleagues reported the case of a 39-year old patient with KS who underwent a severe deep venous thrombosis with pulmonary embolism in the absence of any triggering event. This condition was associated with double heterozygosis for G20210A prothrombin and Leiden factor V mutations [23]. Indeed, different examples of thrombosis and leg ulcer due to various mechanisms are reported in the literature. Some cases of recurrent leg ulcers, associated with immunological disorders (positive antinuclear factor, antiphospholipid antibodies and cryoglobulins) without

venous insufficiency, have recovered after TRT [24]. According to this evidence, Goto and colleagues described two cases of patients with KS and systemic lupus erythematotus (SLE) (positive lupus anticoagulant) affected by leg ulcers in whom TRT improved wound healing [25].

Finally, the case of a KS patient with mixed connective tissue disease (Sharp's syndrome) is present in the literature [26]. It should be taken into account that some patients with KS may suffer from different coagulation abnormalities that underpin the risk of ulceration. These include hyperactivity of factor VIII coagulant [27] and the presence of homozygous mutation for the A1298C factor of the methylenetetrahydrofolate reductase (MTHFR) gene [28]. Finally, refractory chronic venous leg ulcers have been reported by Gattringer and colleagues in two men with sex chromosome aberrations (47,XXY/48,XXXY) and in a patient with Jacob syndrome (47,XYY). Among them, patients with karyotype 47,XXY/48,XXXY, although had hypogonadism, showed normal PAI-1 activity [29].

Elevated activity of plasminogen activator inhibitor-1 (PAI-1), causing alterations in platelet aggregability and fibrinolysis, has been documented in patients with KS and leg ulceration without underlying venous insufficiency [30]. To ascertain whether increased PAI-1 activity is a general feature of KS, or more specifically associated with leg ulceration, Zollner and colleagues investigated the parameters influencing PAI-1 activity in KS patients with ($n=7$) or without ($n=6$) leg ulcerations. By analyzing those parameters, such as age, body mass index, triglycerides, C-reactive protein, testosterone, cigarette smoking habit, presence of diabetes mellitus, and arterial hypertension, no statistically significant differences were found between the two groups, although PAI-1 activity turned to be elevated in KS patients with leg ulcers. Since PAI-1 activity elevation might play a crucial role in the pathogenesis of leg ulceration in KS subjects, the treatment should include a strategy aimed to reduce PAI-1 activity until PAI-1 normal serum levels are achieved [31]. In a recent study, twenty-three consecutive KS patients under testosterone replacement therapy were included in a case control study to evaluate platelet reactivity and the expression of platelet activation markers (8-iso-prostaglandin F2a[8-iso-PGF2a] and 11-dehydro-thromboxane-B2[11-dehydro-TXB2]). The authors found increased platelet reactivity in KS and no correlation between the percentage of maximal aggregability, testosterone and estradiol levels [32].

Testosterone treatment and cardiovascular risk in patients with Klinefelter syndrome

Given the growing interest for the relationship between serum T deficit and cardiovascular abnormalities, several authors have recently conducted a large number of studies to evaluate whether this relationship may exist in patients with KS. Since the effects of testosterone on its target tissues depends on both its metabolites (5α reduction into dihydrotestosterone or aromatization into 17β-estradiol) and its receptor, these studies have been carried out to verify whether the cardiovascular abnormalities found in KS depend on serum T levels, its effect on target tissues or both.

Di Mambro and colleagues found that the lower artery diameters in different districts (brachial, common carotid, common femoral artery and abdominal aorta) of KS patients did not relate with low (<10.4 nmol/L) or normal (>10.4 nmol/L) serum testosterone levels [33]. In addition, flow-mediated dilation (FMD), carotid IMT, AR sensitivity and blood pressure did not show any statistically significant difference between KS patients with normal or low serum T [22]. Finally, no statistically significant difference was found in cardiovascular abnormalities between treated and untreated KS patients. Consequently, the cardiovascular abnormalities are not reversed by TRT, being dependent upon KS itself rather than on the patient hormonal condition. Therefore, cardiovascular abnormalities may represent the pathophysiological underpinnings, perhaps induced by chromosomal abnormality, of the increased risk of death for heart disease [11]. Thus, early diagnosis of KS is important to start TRT as soon as possible [34] to avoid the onset of androgen deficiency symptoms [35], but not the other features related to the genetic abnormality [36]. Some studies suggest that men with KS should start TRT during puberty with a target testosterone level in the higher part of the normal range, but there are no randomized placebo-controlled studies to support this approach [37]. Therefore, the efficacy of precocious versus delayed TRT to prevent cardiovascular risk is not known.

Testosterone replacement therapy and circulating endothelial progenitor cells or endothelial microparticles in patients with Klinefelter syndrome

A reduced number of circulating endothelial progenitor cells (EPCs) is an independent predictor of morbidity and mortality for cardiovascular diseases. Di Mambro and colleagues [33] evaluated EPCs in 68 KS patients and 46 healthy men, subdivided in two groups according to the absence or presence of cardiovascular risk factors (CRFs). Controls without CRFs had significantly higher levels of EPCs than controls with CRFs; on the contrary, KS patients without CRFs had similar levels of EPCs compared to KS patients with risk factors and significantly lower levels than controls without CRFs. Moreover, the number of EPCs in

hypogonadal and eugonadal patients was not significantly different. Twenty-two hypogonadal patients were re-evaluated after 6 months of TRT, but the results did not show modifications in the number of EPCs. These findings suggest that factors involved in KS (CRFs or other genetically determined factors related to the supernumerary X chromosome) may contribute to a reduction in EPCs number that could lead to a further increase in mortality rates of these patients [33].

Condorelli and colleagues, aiming at evaluating the effects of TRT on the sexual function, prescribed testosterone to a group of 35 middle-aged TRT-naïve hypogonadal patients, consisting of 20 patients with acquired prepubertal hypergonadotropic hypogonadism (HrHy), and of 15 age- and BMI-matched KS patients. After 6 months of TRT, patients with HrHy had significantly higher mean IIEF-5 score and cavernousal artery peak systolic velocity and a significantly lower mean acceleration time than patients with KS. In addition, patients with HrHy showed significantly lower mean apoptotic endothelial microparticles (EMPa) values and vitronectin receptor (VR) serum concentrations than patients with KS. These latter subjects showed, after TRT, a significant improvement of IIEF-5 scores and Doppler parameters, but not of EMPa or VR serum concentrations. These results, in agreement with other studies, suggest that TRT does not improve the severity of endothelial cell apoptosis in KS patients [38].

Body composition, metabolic syndrome and diabetes mellitus type 2 in Klinefelter patients

There is a growing clinical and scientific interest for the metabolic disorders in patients with KS. Both in adolescence and, especially, in adulthood, these patients may have different metabolic diseases ranging from obesity and metabolic syndrome (MetS) to overt type 2 diabetes mellitus (T2DM). Several observational studies, published in the last 40 years, have highlighted a close association between KS, metabolic diseases and T2DM. Moreover, these metabolic diseases, in association with other important disorders (such as lung and cerebrovascular diseases, thrombotic events, and osteoporosis), contribute in increasing mortality of patients with KS [5, 32].

Recently, a study including 89 prepubertal boys with KS showed that about 10% of them have MetS, and more than 24% have insulin resistance [39]. In addition, many patients with KS, even before puberty, have an altered body composition characterized by an increased body fat, especially in the truncal region, with a reduction in lean body mass. Therefore, these patients have lower muscle strength [40, 41]. The multivariate analysis showed that the truncal fat distribution is the most important factor leading to insulin resistance and MetS, independently of serum testosterone levels [42].

In adult KS patients, several studies have shown an elevated prevalence of MetS (diagnosed by the National Cholesterol Education Program criteria), hyperlipidaemia (especially hypertriglyceridaemia) insulin resistance and hyperinsulinemia, and even overt T2DM [42–44]. These patients have an increased cardiovascular risk that cannot be only referred to these metabolic conditions, but also, at least in part, to an increased platelet activity [32]. Conversely, blood hypertension is not a frequent finding in patients with KS as recently reported [11].

It is not entirely clear the predisposition in patients with KS to metabolic diseases, insulin resistance and unbalanced body composition is a consequence of a specific gene expression pattern, the hormonal status or both in patients with KS. It is generally accepted that low serum testosterone levels predict the development of abdominal obesity and MetS in men independently from chromosomal disorders [45, 46]. A meta-analysis including different cross-sectional studies, 850 subjects with T2DM and 2900 healthy men, showed that serum testosterone levels were significantly lower in T2DM men even after standardization for BMI, waist to hip ratio and age [47]. On the other hand, weight loss consequent to hypocaloric diet regimen and lifestyle changes, improved serum testosterone levels as well as the metabolic disorders in obese men [48].There is some evidence that testosterone itself may have a direct effect on insulin sensitivity. Indeed, TRT discontinuation in patients with central hypogonadism led to insulin resistance within a couple of weeks [49]; while during a 1-week hyperinsulinemic-euglycemic clamp, the treatment of healthy not obese men with aromatase inhibitor (letrozole) resulted in an increase of serum testosterone slightly above the physiological levels and in an improvement of insulin sensitivity [50]. Furthermore, a recent meta-analysis of randomized controlled studies showed that TRT in eugonadal or hypogonadal (testosterone <350 mg/dl) patients, especially in younger men and in those with metabolic diseases, is able to improve metabolic parameters, such as glycaemia and insulin resistance, and to reverse body composition by both lowering the fat mass and increasing the lean one [51, 52]. Nevertheless, although several findings show a close relationship between serum testosterone levels and metabolic disease, in patients with KS, despite TRT, no conclusive data can be drawn on body composition and metabolic control. In fact, Aksglaede and colleagues showed that TRT alone only partially corrects the unfavorable muscle/fat ratio, suggesting that the unfavorable metabolic profile found in adult patient with KS may already be present in childhood [41]. On the other hand, a group of ten obese KS patients with T2DM and erectile dysfunction was able to lose weight, to reach the metabolic control, and to improve

erectile dysfunction only by a combination therapy made up of testosterone, metformin and liraglutade (a glucagon-like peptide-1 agonist) [53].

Since the body composition is already unbalanced in favor to the adipose component in pubertal and adolescent KS boys, other causes beyond the testosterone deficiency should be taken into account. Different genetic anomalies have been hypothesized as possible causes of the altered body composition in these patients by several authors. In particular, the over-expression of X-linked genes, skewed X chromosome inactivation, transcriptional dysregulation of apoptosis cascade, glucose metabolism and inflammation genes or CAG repeat polymorphism of the AR (all of them mapping on the X chromosome) may be involved in this process [54, 55]. Finally, Rotondi and colleagues showed that MetS is associated with a low-grade chronic inflammatory status characterized by abnormal cytokine production. CCL2, produced by monocytes, dendritic cells and macrophages, induces chronic low-grade inflammation by accelerating macrophage infiltration in adipose tissue and its overproduction is associated with insulin resistance [56]. Men with KS had increased CCL2 circulating levels and the authors found a direct correlation between CCL2 and testosterone levels [56]. Hence, further studies are needed.

Conclusions

Patients with KS have an increased morbidity and mortality that can be due to ischemic heart disease, cerebrovascular diseases (e.g., subarachnoid hemorrhage), thrombosis of the deep veins (e.g., pulmonary embolism and intestinal thrombosis) and leg ulcer. In addition, KS patients have an increased prevalence of metabolic disease (obesity, metabolic syndrome and T2DM) diseases that contribute to the increased morbidity and mortality rates in these patients.

Several studies have shown a relationship between the deficit of testosterone, metabolic diseases and cardiovascular risk in patients with KS. The role of the additional X chromosome and the dysregulation of different genes mapping on this chromosome may be involved in this association. Unfortunately, there is no definitive evidence on the effect of TRT on metabolic diseases, body composition and markers of cardiovascular risk, such as serum PAI-1, EPCs number and carotid IMT, in these patients. Indeed, in case of important metabolic disorders, such as T2DM with insufficient metabolic control and obesity, the combination of two drugs effective in lowering blood glucose and body weight, should be prescribed to reach a good metabolic control and the weight loss.

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Compliance with ethical standards

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