Expert Review of Endocrinology & Metabolism

ISSN: 1744-6651 (Print) 1744-8417 (Online) Journal homepage: https://www.tandfonline.com/loi/iere20

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To cite this article: Giacomo Accardo, Vanda Amoresano Paglionico, Rosa Di Fraia, Antonio Cittadini, Andrea Salzano, Daniela Esposito, Annamaria De Bellis & Daniela Pasquali (2019) Management of cardiovascular complications in Klinefelter syndrome patients, Expert Review of Endocrinology & Metabolism, 14:2, 145-152, DOI: 10.1080/17446651.2019.1584036

To link to this article: https://doi.org/10.1080/17446651.2019.1584036

Accepted author version posted online: 16 Feb 2019.
Published online: 22 Feb 2019.

EXPERT REVIEW OF ENDOCRINOLOGY & METABOLISM
2019, VOL. 14, NO. 02, 145–152
https://doi.org/10.1080/17446651.2019.1584036

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REVIEW

Management of cardiovascular complications in Klinefelter syndrome patients

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ABSTRACT

Introduction: Klinefelter syndrome (KS), also known as 47, XXY, shows increased mortality when compared with mortality rates among the general population. Cardiovascular, hemostatic, metabolic diseases are implicated. Moreover, cardiac congenital anomalies in KS can contribute to the increase in mortality.

Areas covered: In this study, we have systematically reviewed the relationships between KS and the cardiovascular system and the management of cardiovascular complication. In summary, patients with KS display increased cardiovascular risk profile, characterized by increased prevalence of metabolic alterations including dyslipidemia, diabetes mellitus (DM), and abnormalities in biomarkers of cardiovascular disease. KS subjects are characterized by subclinical abnormalities in endothelial function and in left ventricular (LV) systolic and diastolic function, which – when associated with chronotropic incompetence – may negatively influence cardiopulmonary performance. Moreover, KS patients appear to be at a higher risk for cardiovascular disease, due to thromboembolic events with high prevalence of recurrent venous ulcers, venous insufficiency, recurrent venous and arterial thromboembolism leading to deep venous thrombosis or pulmonary embolism.

Expert opinion: Considering the unequivocal finding of increased mortality of KS patients, we suggest a periodic cardiovascular follow up in specialized centers with multidisciplinary care teams that comprise endocrinologists and cardiologists dedicated to KS syndrome.

ARTICLE HISTORY
Received 7 November 2018
Accepted 14 February 2019

KEYWORDS
Klinefelter; intima-media thickness; cardiovascular disease; platelet reactivity; metabolic syndrome; testosterone

1. Introduction

Klinefelter syndrome (KS) is the most common genetic cause of human male infertility. It was described in 1942 by Klinefelter as a clinical syndrome characterized by gynecomastia, facial and body hair reduction, in men with small testicles and infertility [1]. Only in 1959, this condition was associated with the presence of an extra X chromosome in the karyotype. The incidence of KS has been estimated in 1:500 to 1:1000 men [2]. The most common classic form of karyotype in KS is 47, XXY, and it is present in about 90% of the cases. The remaining 10% of the cases consists of mosaicisms (karyotype 46, XY/47, XXY) and other uncommon forms of aneuploidies (48, XXXY 48, XXYY) [3]. 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 [4]. The above-mentioned comorbidities are considered the most important factors that negatively influence the life expectancy of KS patients. 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 [4]. Despite the higher standardized mortality rate in KS than the normal population, little data are available with regard to the morbidity and mortality of KS. Data from recent large registry-based studies [5–9] indicated an increase in mortality in KS patients when compared with the general population. Interestingly, mortality was specifically increased by concomitant cardiovascular diseases. Several reports suggest that KS is associated with a higher cardiovascular risk profile, subclinical cardiovascular abnormalities, and impaired exercise performance. Surprisingly, it appears that KS patients are at lower risk for ischemic heart disease, although other cardiovascular events are more common in patients with KS [8]. The increased cardiovascular mortality observed in KS is apparently not directly related to the genetic features of this syndrome but to a higher prevalence of cardiometabolic risk factors in these subjects [7]. Patients with KS are more frequently insulin resistant, obese and prone to develop type 2 diabetes mellitus (T2DM) [1,5], a condition considered a cardiovascular disease equivalent. The onset of T2DM in patients with KS is a turning point in worsening of the CVD risk profile. With this in mind, we have explored and reviewed the most important cardiovascular abnormalities in men with KS, the relationship between KS and metabolic abnormalities, and how to manage these complications in the follow-up of these patients. We have searched Medline for articles published in any language until 2017, with

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Article highlights

In this work we describe:

- KS and its comorbidities
- The most important metabolic alterations
- Cardiovascular risk profile, such as structural and functional cardiovascular abnormalities, congenital alteration, platelet reactivity, leg ulcers
- The increased risk of cerebrovascular abnormalities
- Indications about management of cardiovascular complication

the following keywords: 'Klinefelter syndrome', 'cardiovascular', 'heart disease', 'cardiac congenital abnormalities', 'diabetes', 'metabolic syndrome', 'hemostasis and thrombosis', 'platelet reactivity'. Accordingly, we identified 169 articles.

2. Metabolic risk profile in men with KS

KS patients may have an increasing risk to develop obesity and metabolic syndrome (MetS) and/or type 2 diabetes mellitus (T2DM). Many observational studies have highlighted a close association between KS, metabolic diseases and T2DM that contribute in association with other important disorders (such as lung and cerebrovascular diseases, thrombotic events, and osteoporosis), to the increased mortality of these patients [10]. Bardsley et al., in a study including 89 prepubertal boys with KS, showed that about 10% of them have MetS, and more than 24% have insulin resistance [11]. In addition, many patients with KS, even before puberty, have an increase of truncal body fat, with a reduction in lean body mass and muscle strength [12,13]. Bojesen et al. evidenced that the truncal fat distribution in KS is the most important factor leading to insulin resistance and MetS, independently of serum testosterone levels [14,15]. Ishikawa et al. [16] found a prevalence of 34% of MetS in 60 KS patients, confirming previous observations. On the other hand, Pasquali et al. [17] showed a prevalence of 50% in 69 KS subjects, compared with 10% in the control group, and a MetS prevalence of 28% in a population of non-KS, testosterone-treated, hypogonadotropic hypogonadal subjects. Bardsley et al. [11] showed an increased prevalence of MetS (about 7%) in prepubertal adolescents with KS, compared with healthy age-matched subjects. Andersen et al. [18] suggested that hypogonadism in KS might influence body composition, causing an increase in body fat (especially intra-abdominal fat), with subsequent deterioration of carbohydrate metabolism, causing insulin resistance which further aggravates the hypogonadism via a direct effect on Leydig cell production of residual testosterone.

In adult KS, several studies have shown an elevated prevalence of MetS (according to the National Cholesterol Education Program criteria), hyperlipidemia (especially hypertriglyceridemia) insulin resistance and hyperinsulinemia, and even overt T2DM [14–16]. In these patients, the increased cardiovascular risk can be explained not only with these metabolic conditions but also to an increased platelet activity [19]. 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. It is generally accepted that low serum testosterone levels predict the development of abdominal obesity and MetS in men independently of chromosomal disorders [20,21].

2.1. Role of testosterone replacement therapy (TRT) in the metabolic risk of KS

A meta-analysis including different cross-sectional studies, 850 subjects with T2DM and 2900 healthy men, have showed that serum testosterone levels were significantly lower in T2DM men even after standardization for BMI, waist to hip ratio and age [22]. On the other hand, weight loss consequent to hypocaloric diet and lifestyle changes, improved serum testosterone levels as well as the metabolic disorders in obese men [23]. 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 [24]. In these patients, it is still unclear whether the effects on insulin sensitivity were due to testosterone, estradiol (E2), or both. Several lines of evidence suggest that E2 may play a role in mediating the effects of testosterone effects on insulin action. Administration of dihydrotestosterone, a nonaromatizable androgen, has no effect on insulin sensitivity in men with central obesity in contrast to the beneficial effects of testosterone in the same population [25]. In addition, insulin resistance is part of the phenotype of congenital estrogen deficiency due to mutations in either the aromatase [26–30] or estrogen receptor-α (ERα) genes [31,32] in both human or mouse models. Moreover, estrogen therapy causes a significant improvement in insulin sensitivity in these models [27–29]. Therefore, additional studies employing selective suppression of T and E2 are needed to determine their relative importance in influencing insulin action. During a 1-week hyperinsulinemic-euglycemic clamp, the treatment of healthy, not obese men with an aromatase inhibitor (letrozole) resulted in an increase of serum testosterone slightly above the physiological levels and in an improvement of insulin sensitivity [33]. A recent meta-analysis of randomized controlled studies have showed that TRT in eugonadal or hypogonadal patients, especially in younger men and in those with metabolic diseases, is able to improve metabolic parameters, such as glycemia and insulin resistance, and to reverse body composition by both lowering the fat mass and increasing the lean one [34,35]. 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 [13]. On the other hand, a group of 10 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 liraglutide (a glucagon-like peptide-1 agonist) [36].

Since the body composition has already been unbalanced in favor of 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 androgen receptor (AR) (all of them mapping on the X chromosome) may be involved in this process [37,38]. 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 [39]. Men with KS had increased CCL2 circulating levels and the authors found a direct correlation between CCL2 and testosterone levels [39], but further studies are needed.

2.2. Endothelial progenitor cells (EPCs)

The decrease of reduced circulating endothelial progenitor cells (EPCs) is a predictor of atherosclerotic progression and morbidity/mortality due to cardiovascular disease [40]. Di Mambro and colleagues demonstrated a reduced number of EPCs in 68 KS subjects compared with age-matched controls and hypogonadal patients, independent of testosterone levels and of the presence/absence of other cardiovascular risk factors [41,42]. Interestingly, TRT exerted no effect on EPCs number, differently from what has been observed in normal, testosterone-treated subjects [43]. Furthermore, Ru et al. [44] showed that in KS subjects testosterone levels were not correlated with the number of EPCs, but many other studies are needed to explain the relationship between EPCs and KS. Condorelli et al., evaluating the effects of TRT on the sexual function, treated with testosterone 35 middle-aged TRT-naïve hypogonadal patients: of which, 20 patients had acquired prepubertal hypergonadotropic hypogonadism (HrHy), and 15 were age- and BMI-matched KS patients. After 6 months of TRT, in HrHy patients mean IIEF-5 score was significantly higher than patients with KS, such as cavernous artery peak systolic velocity; on the other hand, mean acceleration time was significantly lower. 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 [45].

3. Cardiovascular risk in men with KS

In the cohort of Bojesen, composed by 832 KS and 4033 controls, 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 et al. 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 [8]. In a cohort of 69 KS [48 of them had already started TRT while the remaining 21 were TRT-naïve] compared with 48 age-matched controls with comparable physical activity and Body Mass Index (BMI), Pasquali et al. found 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 [17]. All these abnormalities, including preclinical alterations that may forecast future cardiovascular events, were recognized as independent predictors of long-term poor outcome.

4. Structural and functional cardiovascular abnormalities in Klinefelter syndrome

4.1. Alterations of QTc interval in KS

Jørgensen et al. [46] have found a shorter QTc-interval (QTc) in KS treated with TRT compared with controls, while untreated and hypogonadal KS had intervals comparable to controls. No mutations of genes related to short QT syndrome have been found. These results suggest that genes on the X chromosome could be involved in the regulation of the QTc-interval and that testosterone treatment significantly modulates this mechanism. In the EXAKT trial, a cross-sectional prospective project involving 132 KS patients, authors have demonstrated that QTc time was significantly shorter in those patients showing higher levels of differentially expressed genes (DEGs). Pathologically short QTc times (<370 ms) were observed in 11 KS patients but in none of the controls. In particular, the effect has even been more pronounced in those men with a paternal origin of the supernumerary X chromosome. Moreover, serum testosterone levels were not associated with QTc times [47]. Karagoz et al. [48] reported a case of a sinus node dysfunction requiring permanent pacemaker implantation in a 22-year-old man with KS.

4.2. Left ventricular (LV) alterations in KS

A prevalence of 55% of mitral valve prolapse (MVP) was found by Fricke et al. in 22 patients with KS [49,50]. On the contrary, two more recent large studies [17,18], with 69 and 25 patients, respectively, have not confirmed this finding. Andersen et al. [18] found only subclinical alteration of the LV systolic function (reduction in LV strain and strain rate) with a normal LV fraction in 25 KS subjects. In other studies, the correlation between strain/Doppler indices of systolic function and fasting triglyceride and truncal body fat suggest that myocardial systolic function impairment was strictly related to METS rather

than to KS itself. To support this hypothesis, this pattern is commonly found in patients with obesity and MetS and appears linked to insulin resistance [51,52]. Pasquali et al. showed no significant difference in LV structure in 69 KS patients compared with controls, nor evidence of MVP. In the same study, no significant alterations of LV systolic function were reported, although strain analysis was not performed [17]. A prevalence of 20% of diastolic dysfunction was found by Andersen et al. in KS patients prevalence (5/25). In particular, they demonstrated that velocities ratio between the measurements of mitral inflow, peaks E (early diastolic filling) and A (late diastolic filling), (E/A) were significantly correlated with truncal body fat [18]. Accordingly, Pasquali et al. [17,53] have reported a significant prolongation of isovolumic relaxation time and mitral deceleration time, decreased E/A ratio, and pulmonary vein velocities consistent with mild diastolic dysfunction, with no differences observed between treated and untreated KS patients. Notably, patients with secondary hypogonadism on testosterone therapy did not display normal cardiovascular parameters.

4.3. Peak oxygen uptake, chronotropic incompetence and carotid intima-media thickness (cIMT)

With regard to cardiopulmonary exercise performance, Bojesen et al. [7] showed a reduced peak oxygen uptake (VO2 max) in 70 KS patients, with no difference between treated and untreated subjects. In a multivariate analysis, VO2 max was negatively correlated to body truncal fat, diagnosis of KS, 17beta-estradiol, and age, but positively to the intramuscular adipose tissue-free skeletal mass. KS per se was the strongest (negative) predictor of VO2 max, followed by skeletal muscular mass. Pasquali et al. [17] observed an impaired cardiopulmonary performance and exercise capacity in KS reporting a marked reduction in VO2 peak and workload both at peak exercise (–34% vs. controls) and anaerobic threshold (–24% vs. control) compared with controls. Interestingly, KS displayed a remarkably increased prevalence of chronotropic incompetence (CI) defined as a lower proportion of predicted maximum heart rate (HRa) (78 vs. 91%, $P < 0.05$) and a lower increase in HRa from baseline to exercise peak (74 vs. 91 bpm, $P < 0.01$). CI is a common finding in several cardiovascular diseases [45], produces exercise intolerance that greatly impact on quality of life, and it is an independent predictor of major adverse cardiovascular events and overall mortality in the asymptomatic population [54,55]. Several studies have reported the predictive role of carotid intima-media thickness (cIMT), a surrogate marker of atherosclerotic disease, on future cardiovascular event. Reduced flow mediated dilation (FMD), briefly described as endothelium-dependent vasodilation assessed by measuring the maximum increase in brachial artery diameter during reactive hyperemia created by the inflation of a cuff (250 mmHg for 5 min) placed on the right arm, has been considered as a predictor of cardiovascular disease, although its value for risk stratification is still debatable [56,57]. Foresta et al. [58], comparing 92 KS subjects with controls, showed reduced diameters of brachial, common carotid, common femoral arteries, and abdominal aorta arteries. No difference between KS patients and control with regard to cIMT and FMD were found. On the other hand, KS patients enrolled in the study by Pasquali et al. [17] exhibited a significant increase in cIMT. It should be highlighted that difference in cIMT is not clinically relevant, because, in both studies, it was lower than 0.9 mm [59]. Recent data have suggested that the vasculature of the testis might be altered in animal models of KS [60]. Interestingly, an alteration in vascular density and flow is observed early in KS boys during pubertal development [61] and it has been correlated with progressive luteinizing hormone (LH) rise. Little is known on the microvascular status of other tissues; however, the increased frequency of autoimmune disorders in KS [62] suggests that other than hormonal mechanisms could also be involved in altering tissue perfusion.

4.4. Congenital cardiovascular diseases in KS

In spite of the fact that KS is the second most frequently occurring chromosome disease and that almost 15–20% of all congenital cardiovascular diseases (CCDs) are related to chromosomal disease [63–65], few and quite old data are available addressing the prevalence of congenital heart diseases in this population. Three patients with KS (XXY karyotype) and associated congenital heart disease were described. Review of the literature coupled with this data seems to suggest an association between KS and congenital cardiac malformations. Compared with the general population, Bojesen et al. [7] showed a significant increase in CCD risk (HR 4.71) in KS. Among 3550 KS subjects, Swerdlow et al. [8] reported that CCD was the specific cause of mortality in five patients (SMR = 7.3). In summary, KS patients are characterized by subclinical abnormalities in LV subclinical systolic and diastolic function and endothelial function, which, together with chronotropic incompetence, may lead to impaired cardiopulmonary performance. Moreover, KS patients appear to be at a higher risk of CCD [66–69].

4.5. Increased platelet reactivity

KS subjects exhibit increased platelet reactivity compared with healthy-matched controls [19]. In particular, the significantly lower AC-50% in KS than in controls shows that lower doses of pro-aggregating agonists are needed to induce platelet aggregation and this is clearly suggestive of a pro-thrombotic state [70–72]. Further confirming the presence of platelet hyper-reactivity, the stimulation with low doses of AA (0.2 mM) induced an irreversible platelet aggregation in 70% of KS patients and in only 15% of controls. Moreover, KS patients have exhibited a maximal platelet aggregation 15–20% higher than controls after stimulation with different doses of AA. The results were also confirmed by the finding that levels of 8iso-PGF2a and 11-dehydro-TXB2, recognized markers of oxidative stress and of platelet activation [73,74], were higher in KS than in controls and correlated with the degree of platelet reactivity. Overall, our results have consistently suggested increased oxidative stress and platelet hyper-reactivity in patients with KS. This is another piece in the complex puzzle of the increased cardiovascular risk and mortality in KS men. Platelet hyper-reactivity plays a key role in the genesis and

in the progression of atherothrombosis and is often associated with metabolic syndrome, insulin resistance, inflammation, oxidative stress, and hormonal levels [75]. These data suggest an adequate cardiovascular prevention strategy in KS patients.

4.6. Leg ulcers in KS

Ulcerative lesions of the lower extremities are a complication of KS. To date, the pathogenesis of ulcers in KS has not been clarified, but several factors, such as abnormalities of fibrinolysis and prothrombotic states, might be involved. Moreover, this risk can be worsened by the co-existence of one or more thrombophilic conditions, such as diabetes, and obesity that are more frequent in KS, although these conditions are not the only causes. 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 [76].

4.7. Cerebrovascular risk in KS

Swerdlow et al. have shown that mortality for cerebrovascular disease was significantly increased (SMR 2.2; 95% CI, 1.6–3.0), in particular, subarachnoid hemorrhage. Price et al. reported that the deaths due to cerebrovascular diseases were increased in any age in KS (25–84 years) [52], but the rupture of a berry aneurysm was identified as the third cause of death in KS patients aged 25–44 years [77]. It is still unclear if the cause of the death for cerebrovascular disease is thrombosis or hemorrhage: Swerdlow described six cases of subarachnoid hemorrhage, four cases of other intracerebral hemorrhages, and nine patients with cerebrovascular occlusion or thrombosis. In addition, the study has confirmed a higher standardized mortality ratio (SMR) for subarachnoid hemorrhage. On the other hand, another study [7] has showed no association between cerebral hemorrhage and KS. Generalized atheromasia does not explain the raised cerebrovascular risk, considering the significantly reduced SMR reported for ischemic heart disease [8]. In literature, 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 is reported; he also had polydactyl and patent ductus arteriosus [78].

5. Management of cardiovascular complications in KS

Counseling from an early age regarding a healthy diet and regular exercise is imperative for KS patients. Screening for dyslipidemia with a fasting lipid panel at age 9–11 years and after puberty is completed (or sooner if additional risk factors are present) could be a good strategy to recognize MetS or its features as soon as possible. This assessment needs to be repeated after puberty, and it is necessary to consider KS patients at high risk of developing MetS and T2D throughout their life. In KS patients with MetS or prediabetes, a Diabetes Prevention Program (DPP) should be considered. DPP, consistent in lifestyle changes such as nutritional suggestions (e.g. reducing caloric intake and increasing consumption of food high in monounsaturated fats), and physical activity (exercise prescriptions designed to prevent diabetes are based on aerobic activity and may include resistance training) have provided the strongest evidence for diabetes prevention in the general population. In the medical management of KS [79–85], a complete cardiovascular work-up in KS patients must be considered, aiming a diagnosis of preclinical and clinical abnormalities and the decrease of the cardiovascular risk. In childhood, all KS patients may take an echocardiographic study for the identification of possible cardiac abnormalities. In adulthood, echocardiography should identify preclinical systolic and diastolic dysfunction. If no alterations are found, patients need follow-up based on available risk-assessment [86,87]. A possible flowchart [5] suggests that KS must be suspected in children with cardiac congenital abnormalities (transposition of great arteries, patent ductus arteries, tetralogy of Fallot and/or other multiple cardiac defects), while in the adulthood, KS must be suspected in the evidence of subclinical abnormalities in LV in systolic, diastolic function, endothelial function; chronotropic incompetence or reduced cardiopulmonary performance, a history of recurrent venous ulcer, vein insufficiency, recurrent venous and artery thromboembolism, thrombosis or pulmonary thromboembolism. In both cases these cardiac alterations must coexist with clinical alterations suggestive for KS Considering the unequivocal finding of an increased mortality of KS patients mostly related to cardiovascular disease, more research is needed to characterize these alterations and explain the underlying pathophysiological background.

6. Conclusions

Patients affected by KS have an increased prevalence of MetS and T2DM. This may lead to subclinical systolic and diastolic dysfunction and vascular abnormalities, which in turn might sustain the impaired cardiopulmonary performance and the increased morbidity and mortality rates in these patients. In most studies, there is no definitive evidence that TRT reverts cardiovascular abnormalities. More information is also needed about the effect of TRT on metabolic diseases, body composition, and carotid IMT. It is also demonstrated that metabolic control and obesity treatment reduce cardiovascular risk in men with KS, but more research is needed to identify these alterations and their pathophysiological background.

7. Expert opinion

Klinefelter syndrome is the most frequent chromosomal abnormality in males and is associated with an increased risk of metabolic cardiovascular diseases (CVD). The mechanisms involved in increased risk of cardiovascular morbidity and mortality are not completely understood. The attention of the researchers has been focused about the increased incidence of metabolic abnormalities in KS as a possible mechanism involved in cardiovascular disease, but another possible explanation could be found in the genetic disorders of these patients. In KS, TRT does change the prevalence of MetS, suggesting that more complex and unclear mechanisms sustain the link between KS and MetS. More research is warranted to clarify

the relationship between testosterone administration and heart, in the look of recent evidence that suggests a role of testosterone in some cardiovascular disease. Early diagnosis and tailored intervention strategy seem mandatory in patients with KS and should be aimed at targeting excessive visceral fat deposition. Although KS patients are more insulin resistant and have an increased risk of developing MetS and T2D, they are not listed among groups requiring a more frequent screening for metabolic impairment. Since T2D severely impacts mortality in KS and current standards of TRT failed to prove effective in this respect, an open issue remains about how to prevent or treat diabetes in KS patients. Specifically, no information is available within current guidelines regarding a particular strategy to be used in the prevention of diabetes or its complication in this particular group of patients. Another opening question is how to treat T2DM in these patients. Although few data are available on the effect of hypoglycemic agents in KS, some drugs appear to be preferential, such as metformin and GLP-1 receptor agonists, but. Future research should directly address the issue to provide evidence regarding the best approach for patients with KS and diabetes. A complete cardiovascular work-up in KS patients is needed, for diagnosis and treatment of preclinical and clinical abnormalities, with the aim of an overall reduction of the cardiovascular, morbidity and mortality risk. The main issue concerns how to improve a precocious diagnosis in order to reduce the number of patients who remain undiagnosed, at risk of delayed treatment and earlier development of complications, such as cardiovascular diseases. Despite the insights provided by numerous studies concerning the clinical consequences of KS performed so far, our knowledge of the molecular and cellular mechanism underlying the KS pathogenesis is still limited. Furthermore, considering the associated neuropsychological and behavior disorders described in KS, the multidisciplinary management of this aspect is an important factor that needs to be considered in the management of metabolic and cardiovascular complications in KS. As in literature, there is disparate evidence about cardiovascular risk and KS, our findings suggest that there is a generalized increase of cardiovascular risk factors that are known to predispose to future cardiovascular accidents and are independent predictor of poor outcomes, such as CI and impaired exercise capacity. In addition to the known genetically aspects of KS, several genetic mechanisms may play as other possible modulators of the variability of the phenotype observed in KS patients. This is the most important field in which further investigations must be addressed.

Growing attention to the cardiovascular abnormalities will be necessary for the correct management of cardiovascular complications in men with KS, for a better prognosis and a better quality of life.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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