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Mini-Review

Klinefelter's syndrome and cardiovascular disease

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ABSTRACT

Klinefelter's syndrome (KS) is the most common sex-chromosome male disorder, characterized by one or more extra X chromosomes. It is associated with a significant increase of cardiovascular mortality and morbidity. This review examines cardiovascular (CV) abnormalities known in KS until now. KS is associated with both functional and structural CV alterations, particularly KS patients show a wide range of CV abnormalities, specifically LV diastolic dysfunction, impaired exercise performance, Chronotropic Incompetence (CI), and increased carotid intima-media thickness (IMT). Regarding diastolic function, they display an increased Isovolumetric Relaxation Time (IVRT) but no prolongation of Mitral deceleration Time (MdT). This condition indicates the presence of a mild diastolic dysfunction. KS patients also have an exercise intolerance, that depends on reduced stroke volume during exercise, caused by the limited increase in the LV end-diastolic volume despite normal ejection fraction and the increased LV filling pressure and left atrial pressure during exercise. Patients with KS also display a significant increase of carotid IMT, a surrogate marker of atherosclerotic disease. This alteration represents a subclinical marker of early atherosclerosis and is the most important risk factor of new or recurrent stroke and myocardial infarction. Testosterone replacement therapy does not normalize the impaired cardiovascular parameters. This wide range of CV abnormalities represents the pathophysiological underpinnings for the raised mortality observed in KS.

KEYWORDS: Klinefelter's syndrome, cardiovascular disease, chronotropic incompetence

1. INTRODUCTION

Klinefelter's syndrome (KS) is the most common genetic cause of human male infertility with a prevalence of 1 in 660 men [1, 2]. It was described for the first time in 1942 by the young clinician Harry F. Klinefelter as a syndrome characterized by hyalinised and small testes, azoospermia, gynecomastia, elevated levels of FSH and hypogonadism, and consequently infertility [3]. The cause of this syndrome was discovered in 1959 by Jacobs and Strong, who demonstrated the presence of an extra X chromosome in the karyotype of KS patients. The most common karyotype is 47, XXY, but is not uncommon for affected patients to have supra-numerous X chromosomes, or to exhibit mosaicism with a mixture of normal and 47, XXY cells (or mixtures of 47, XXY and other karyotypes). Patients with mosaicism often present only fewer clinical features than that observed in the classical phenotype [4]. This syndrome has been known for more than 70 years, but in many cases KS is an underdiagnosed condition; only 25% of the expected number of

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patients are diagnosed, and of these only a minority is diagnosed before puberty. The reason of this underdiagnosed condition is attributed to the clinical presentation that may be subtle with few symptoms. In other cases unexpected phenotype can also be found [5]. Diagnosis is often made during evaluation for hypogonadism and/or infertility in adulthood. Signs of hormonal testicular failure, such as sexual dysfunction, and the presence of co-morbidities such as diabetes, metabolic syndrome, osteoporosis and cardiovascular diseases may also lead to diagnosis [5, 6, 7]. This review reports the most recent knowledge on cardiovascular abnormalities known in KS, that are important causes of morbidity and mortality.

2. Cardiovascular disease in KS

Cardiovascular involvements are an important clinical feature in KS. Indeed several epidemiological studies have demonstrated an increased mortality and morbidity from CV causes in KS [7]. The cause of such elevated morbidity and mortality from CV diseases is still unclear, although several abnormalities described in KS, such as hypogonadism and high frequency of metabolic syndrome may increase overall cardiovascular risk [8]. The aim of the current article is to perform a systematic assessment of cardiovascular structure and function in KS subjects and to evaluate relationship with metabolic and hormonal status.

2.1. Metabolic and hormonal status

KS subjects show increased levels of fasting glucose, insulin, total cholesterol, LDL cholesterol and triglycerides, and reduced levels of HDL cholesterol and insulin sensitivity [8, 9, 10]. Despite similar BMI, compared to healthy subjects, KS patients have increased amounts of body fat and especially of truncal fat, with a reduction of lean mass. Indeed, most of available literature, of which Bojesen's studies, shows higher prevalence of Metabolic Syndrome (MeS) (50% in KS subjects vs. 10% healthy subjects) [10]. The pathogenesis of this association is not completely clear although there is increasing evidence that low level of testosterone has important effects on body composition, MetS and insulin resistance (IR) [11]. In fact, low T levels induce a reduction in muscle mass and an increase in visceral fat, causing an increase in free fatty acid production, the central pathogenetic mechanism for IR and thus MetS. In addition, the adipose tissue produces adipokines, which are implicated in the pathogenesis of dyslipidaemia, IR and MetS [11].

2.2. Cardiovascular abnormalities

Cardiovascular diseases have become the top factor causing human death in both western and eastern world. Simple, reproducible, non-invasive procedures, such as blood pressure, ECG, and heart rate, for determinants of prognosis are therefore very useful to observe the current heart status. KS patients show no differences in baseline blood pressure, heart rate, and ECG findings compared to healthy subjects; also left ventricular (LV) architecture and systolic function are similar [8]. However, many studies show a reduced life expectancy and an increased mortality from cardiovascular disease in KS [12]. Already Fricke *et al.*, for the first time in 1984 showed higher incidence of mitral valve prolapse in KS. Particularly in Fricke's echocardiographical studies 12 of 22 patients with Klinefelter's syndrome, (55%) had mitral valve prolapsed, which was not correlated with the degree of the chromosomal aberration. The incidence of mitral valve prolapse in an otherwise healthy male population is reported to be approximately 6%. Thus Fricke concluded that in Klinefelter's syndrome, the frequency of mitral valve prolapse was markedly increased [13, 14]. Also according to Bojesen there is an increased risk of dying from heart disease among patients with KS for several reasons: primarily for the high prevalence of hypogonadism and metabolic syndrome, and in addiction because patients with KS may have subclinical changes in the left ventricular function. Particularly Bojesen, in his studies, showed that KS patients had a decreased systolic long axis function, due to metabolic syndrome, truncal body fat and hypogonadism, but was not correlated to insulin sensitivity [15].

Left ventricular (LV) systolic function is generally analysed to diagnose the heart status. LV diastolic function is also an important indicator of the heart condition. Both of them are

important determinants of prognosis. A clinical assessment demonstrated that the utilization of both LV systolic and diastolic function is better than only one of them. More recent studies show that KS patients exhibit a wide range of cardiovascular abnormalities, specifically LV diastolic dysfunction, impaired exercise performance, chronotropic incompetence (CI), and increased intima-Media Thickness (IMT) [16]. Chronotropic incompetence (CI), broadly defined as the inability of the heart to increase its rate compared with increased activity or demand, is common in patients with cardiovascular disease, produces exercise intolerance that impairs quality of life, and is an independent predictor of major adverse cardiovascular events and overall mortality [17]. The IMT is an accepted surrogate marker of atherosclerosis and its measurement directly correlates with pathology; it is indicative of the thickness of the arterial wall, and is precisely imaged using ultrasound technology. In clinical studies, the c-IMT measurement corresponds to the significance of traditional cardiovascular risk factors [18, 19, 20].

With regard to diastolic status, KS patients display a diastolic dysfunction. During diastolic phase, ventricular pressure is balancing at the atrial rate and the mitral valve opens and the filling of the left ventricle begins. This phase of cardiac cycle corresponds to Isovolumic Relaxation Time (IRT). Indeed, diastole is divided in early stage (E), in which atrium empties passively, and a late phase (A) of the atrial systole, in which there is atrium contraction. Phase E is responsible for 75% of ventricular filling. KS patients show a diastolic filling pattern characterized by reduction of the E/A ratio, with a prolongation of IRT. This pattern is consistent with a mild diastolic dysfunction, more specifically with an abnormal relaxation pattern without elevated resting diastolic filling pressures [21, 22, 23]. An impairment of diastolic function is a common finding in many cardiac diseases, and it often precedes and causes systolic dysfunction. It has been documented that 30-40% of heart failure syndromes are secondary to impaired diastolic function. Therefore, the diastolic dysfunction observed in KS could be the prelude to more serious limitations of cardiac function and physical performance. Abnormal relaxation, indeed, results in persistent pressure generation at the end of diastole and may thus lead to reduced LV distensibility, which in turn is known to contribute to exercise intolerance [23].

Exercise capacity and cardiopulmonary performance are significantly impaired in patients with KS compared with normal subjects, as documented by the markedly reduced VO_2 uptake and workload both at peak exercise (-34% vs. normal subjects) and at anaerobic threshold (-24%). KS displays a remarkably increased prevalence of Chronotropic Incompetence (CI): 52% in KS *vs*. no subjects in normal subjects. Exercise intolerance is largely dependent on reduced stroke volume during exercise caused by the limited increase in the LV end-diastolic volume despite normal ejection fraction and the increased LV filling pressure and left atrial pressure during exercise [24, 25, 26]. Generally, CI is a common finding in patients with cardiovascular disease and produces exercise intolerance that potentially impairs quality of life, and more importantly, is an independent predictor of major adverse cardiovascular events and overall mortality in asymptomatic populations [26]. With regard to the underlying mechanisms of CI, they are not completely understood but seem to result from a disruption of the delicate balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. Interestingly, heart recovery in KS patients, which describes another relevant feature of CI, is similar or even slightly improved compared with normal subjects. Heart Recovery Rate (HRR), the physiological drop of HR after physical exercise, appears directly related to the parasympathetic tone. Thus, the perturbation of the autonomic nervous system observed in KS patients appears dependent upon increased sympathetic drive commonly associated with reduced β-receptor density and sensitivity rather than upon impaired parasympathetic withdrawal [27].

The vascular studies display a significant increase of IMT in KS patients compared with normal subjects (+45%). This alteration is present for each side on carotid axis in KS patients and causes a diffuse and homogeneous increase of the arterial wall thickness in both the common and internal carotid arteries [16]. It is widely accepted

that ultrasonographic findings of increased carotid artery IMT represent subclinical markers of early atherosclerosis and are associated with unchanged and modifiable risk factors, with the occurrence of new carotid plaques and with the subsequent risk of new or recurrent stroke and myocardial infarction [28, 29]. Evaluation of atherosclerosis is relevant in a population like KS since low levels of testosterone have been associated with coronary artery disease in men. The clinical relevance of increased IMT has been recently outlined by Polak and colleagues, who demonstrated in the Framingham cohort that the maximum IMT of the internal carotid artery improves the classification of risk of cardiovascular disease.

Taken together, the abnormalities found in KS, such as increased IMT and metabolic syndrome, and reduced exercise capacity, partly due to chronotropic incompetence and diastolic dysfunction, include preclinical alterations that may prelude to future cardiovascular events. As mentioned above, some of these alterations are recognized as independent predictors of a poor outcome.

3. Testosterone replacement therapy

During pubertal development, it is considered rational to start testosterone replacement therapy (TRT) [2] when a pathological increase in gonadotropin levels is found, in order to allow the regular development of secondary sexual characteristics and muscle mass and achieve a normal peak bone mass. Literature data show that androgen therapy during puberty enhances muscle strength, improves mood and concentration, relational skills and is useful in improvement of asthenia, low sexual desire, and to reduce abdominal adiposity. Indeed, TRT should be considered lifelong, in order to prevent hypogonadism complications such as osteoporosis, obesity, diabetes and metabolic syndrome [30, 31]. Therefore all KS patients should be treated with testosterone therapy if their gonadotropins levels are elevated, even if their testosterone levels are in the low end of the normal range [2]. Indeed, in according with Bojesen, TRT seems to improve CV status in KS, as he shows that CV abnormalities are mainly correlated with hypogonadism [7]. In more recent studies, instead, TRT does not appear to normalize the impaired cardiovascular parameters known in KS. So, according to these studies, the observed cardiovascular findings seem specific features of KS and are not related to hormonal status. This hypothesis is further supported by the presence of CI that is neither correlated with testosterone levels, nor is known to be associated with hypogonadism in the general population [16]. More importantly, the observation that KS patients treated with replacement therapy still present with cardiovascular abnormalities similar to naïve patients support the concept of KS specific cardiovascular disease. So CV abnormalities seem to be related directly to chromosomal abnormalities or androgen receptor signaling defects in KS rather than testosterone circulating levels [32, 33].

CONCLUSION

Most of the available data comes from Bojesen's group in Denmark, who performed landmark studies showing higher prevalence of metabolic syndrome in KS, that is a known CV risk, as well as reduction of maximal exercise performance and subclinical changes of LV function [10]. In these studies, the authors generally found significant correlations between hormonal parameters, in particular between testosterone levels and cardiac alterations, leading to the speculation that the hypogonadism secondary to KS may significantly reverberate on body composition by increasing truncal fat and decreasing muscle mass, in turn reducing exercise performance [15]. Fricke and colleagues in two consecutive papers found a markedly increased prevalence of mitral valve prolapse in patients with KS, confirming a known relation between such valve disease and sexual karyotype alterations, e.g. Turner's syndrome [13, 14]. In more recent studies [16], by an accurate echocardiographic examination of the mitral valve, the increased prevalence of mitral valve prolapse in KS is not confirmed. On the other hand, most of Bojesen's findings are confirmed by recent acquisitions, as the high prevalence of metabolic syndrome, the subtle alterations of LV diastolic function, the significant reduction of peak oxygen consumption, and the lack of mitral

valve alterations. These findings are further expanded by the demonstration of CI and augmented IMT. However, according to these recent studies there are no significant correlations between altered cardiovascular indexes and hormonal parameters at variance with Bojesen's data. A possible reason might be related to the complexity of the androgen receptor pathway and in particular to the notion that different clinical outcomes and the response to testosterone therapy (bone mass density, gynecomastia, testes and prostate volume, hemoglobin concentration) have been associated with chromosomal abnormalities and androgen receptor signaling defects in KS rather than testosterone circulating levels [31, 33].

To provide further insights into the relative roles of hypogonadism in KS in determining the cardiovascular phenotype, Pasquali *et al.* studied another group of patients affected with secondary hypogonadism under adequate testosterone replacement therapy. This group of normal karyotype hypogonadal patients displayed cardiovascular parameters similar to those observed in the control group and, consequently, it is also significantly different from KS under adequate testosterone replacement therapy. Therefore, in this study they concluded that testosterone therapy does not normalize cardiovascular abnormalities in KS patients despite normal testosterone levels at variance with patients with secondary hypogonadism, suggesting that the chromosomal abnormality plays a major role in the induction of the cardiovascular phenotype of KS patients.

In conclusion, in KS there is a generalized increase of cardiovascular risk. Primarily, in KS there is an high prevalence of metabolic syndrome, which is itself an important CV risk factor, in addition is known a wide range of CV abnormalities, that predispose to future cardiovascular accidents and are independent predictors of poor outcome such as LV dysfunction, CI, impaired exercise capacity, and increased IMT. This broad range of cardiovascular abnormalities represents the pathophysiological underpinnings for the raised mortality consistently observed in KS syndrome [10, 15, 16].

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