CPQ Medicine (2020) 10:2
Review Article

Klinefelter Syndrome in Metabolic Syndromes Cardiovascular and Autoimmune Disorders

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Received: 21 August 2020

Published: 01 September 2020

Keywords: *Klinefelter Syndrome; Metabolic Syndrome; Diabetes; Autoimmune Diseases; C-Reactive Protein*

Abstract

Klinefelter syndrome (KS) is found in infertile men. It was first described in 1942 when Klinefelter *et al* described 9 men with gynecomastia, small testes, azoospermia, and elevated gonadotropin levels [1]. In 1959, the discovery that a patient with KS had 47 chromosomes, including an extra X chromosome (the karyotype of 47,XXY), established that the Barr body seen in KS represents an additional X chromosome [2]. It is shown that the prevalence is from 3% up to 15% in azoospermic patients. The supernumerary X chromosome is derived from meiotic non-disjunction during

gametogenesis of the parents; or from post-zygotic mitotic cell divisions during early embryogenesis. The patient chromosomal aberration such as 48,XXXY; 48,XXYY; 49,XXXXY; 49,XXXYY; 49,XXYYY; 49,XYYYY (chromosomal polysomy) has to be seen quite separate from patients with a 47,XXY karyotype. Some sex differences in human diseases are directly related with sex chromosome, for example male are more afflicted with X- linked diseases such as color blindness, DMD (Duschnene muscular dystrophy); women are protected from these recessive diseases, because they possess two X chromosome. Here we will discuss how the sex chromosome may influence factors that MS (metabolic syndrome) diabetes, autoimmune diseases, C-reactive protein, leptin adiponectin, thrombosis and hemostasis and dyslipidemia.

Introduction

Nonsyndromic 46,XX Testicular Disorders of Sex Development (XX-Male Syndrome/DSD)

Most 46,XX testicular DSD males arise from translocations of parts of the short arm of the Y chromosome to one of the X chromosomes [3,4].

Translocation of a DNA segment that containing gene SRY take place during paternal meiosis [3].

Individuals with 46,XX testicular DSD have normal external genital development, but micropenis, hypospadias or chryporchidism may be seen. Males with 46,XX testicular DSD are infertile because azoospermia and sertoli cell only syndrome or complete degeneration of the seminiferous tubules upon histological examination [5,6].

Males with an 46,XX karyotype having no SRY gene are rare with about 10% of all 46,XX testicular DSD and the testicular development may be activated due to other genetic aberrations [6].

From the data is shown that KS syndrome mortality is increased rate when compared with mortality among the population. Metabolic, cardiovascular and hemostatic complication are among of diseases who play a pivotal role in the death of persons with KS [7]. The aim of this review is to show relationship between KS and cardiovascular diseases, and autoimmune system. We search at pubmed/medline for different manuscripts with keywords: "cardiovascular diseases and KS", "diabetes and KS", association of KS with autoimmune diseases, "KS and C-reactive protein", "association of KS with leptin and adiponectine", "KS and thrombosis", "association of KS with dyslipidemia" and "KS and hemostasis".

Metabolic Syndrome and Klinefelter Syndrome

In few manuscripts it is shown the prevalence of metabolic syndrome (MS) in patients with KS.

Many authors suggesting that metabolic syndrome (MS), diabetes and cardiovascular disease (CV) are often associated with KS [8-10].

Corona *et al* shown association between hypogonadism, MS and CV which has also been emerging both in subjects with and without sexual dysfunction [11].

Yoshida *et al* and Corona *et al* shows that KS patients demonstrated a higher prevalence of erectile dysfunction [12,13] and hypertriglyceridaemia [14] when compared with patients without KS.

Bojesen *et al* 2006 (11) has compared 70 patients with KS with healthy population and showed increase in MS prevalence in KS (42% in KS v 10% in controls). Ishikawa *et al* 2008 [15] shows that prevalence of 34% of MS in 60 KS patients; this date confirming previous observations. Pasquali *et al* 2013 [16] in the recently publication show a prevalence of 50% in 69 patients with KS, compared with 10% in the control group. Bardsley *et al* 2011 [17] shows an increased prevalence of MS (7%) compared with healthy control group.

In a large group of prepubertal boys as young as 4-12 years with KS, 24% among them had insulin resistance, 36% among them met two criteria for metabolic syndrome and 7% among them had the metabolic syndrome. The boys with KS also had decreased activity levels compared with control groups, which strongly correlated with risk factors for metabolic syndrome. There are very few data regarding the prevalence of metabolic syndrome; generally in the paediatric population. In one of observation in 1960 children older than 12 years, the US prevalence was 9% [18], and another study examining 1192 girls ages 9-10 when it is shown a prevalence of 0.2% [19].

Diabetes and Klinefelter Syndrome

Many researcher report for increase of association of DM with KS. Bojesen *et al.,* 2004 [20] and Swerdlow *et al.*, 2005 [21] both showed a relative risk of DM of 1.64 and 7.07, respectively. It is shown that DM and KS together increase the mortality. Kota *et al.*, 2002 [22] report that among 895 Japanese KS patients, 61 were diagnosed with diabetes mellitus; from 61 just 20 patients were treated with insulin.

Bojesen *et al.*, 2006 [11] show that in a Danish study, from 832 patients with KS, 15 had type 1 diabetes mellitus (T1DM). Kota *et al.*, 2012 [24] in contrast form this, report that among 260 patients diagnosed with T1DM, five patients (1.9%) had KS, which was higher than the incidence in the normal population.

Till today it is not shown link between KS and DM; the insulin resistance can promote beta cell destruction, it is suggest that clinical examination of KS patients should include testing for the presence of diabetes-related antibodies, and further follow-up may be needed for autoantibody-positive KS patients [23].

Dahl *et al.* 2018 [24] report the second case of TNDM in an infant with KS. Genetic testing show the pathogenic heterozygous variant in KCNJ11. This has been the first reported case of neonatal diabetes due to a mutation in the KCNJ11 in a patient with KS.

Autoimmune Diseases and Klinefelter Syndrome

Systemic lupus erythematosus (SLE), primary Sjögren's syndrome (SS) is more frequently in 47,XXX; this is shown by Liu *et al* 2016 [25]. This work and many previous work show that the risk of SLE and SS increases with each additional X chromosome.

Liu *et al* 2016 [25] shown the 2090 non-affected SLE family controls may contain subjects with SS, but the same author show that when comparing 47,XXX enrichment in SS only with the healthy non-auto-

inflammatory controls, the result is still significant. The control population from 2680 members and control of non-sarcoidosis groups from 620 members may contain subjects with SLE or SS. Liu *et al.*, 2016 [25] showed that even when removing these control groups, our 47,XXX enrichment in SLE and will still be significant if not more so.

If both diseases SLE and 47,XXX occur at 1 in ~1000 and were independent, then only 1 in a million women would have both rare diseases SLE and 47,XXX. Liu *et al* 2016 [25] suggest that both rare diseases are coincident at 1 in ~40,000 women.

Among 136 patients with SS; men there were 4 with 47,XXY. This is different significantly from healthy controls (1 of 1254 had 47,XXY, p=0.0012 by Fisher's exact test) as well as men with rheumatoid arthritis (0 of 363 with 47,XXY), but not different if it is compared with men with systemic lupus erythematosus (SLE) (4 of 136 versus 8 of 306, Fisher's exact test p= NS) [26].

Previously has been reported association between KS and autoimmune syndrome. A retrospective study from Seminog *et al* 2015 demonstrated that KS was associated with a significantly increased risk of addison's other disease (RR 11.7), T1DM (RR 6.1), Sjögren's syndrome (RR 19.3) and systemic lupus erythematosus (RR 18.1) in comparison to controls [27].

C-Reactive Protein and Klinefelter Syndrome

The most condition observed above are more frequently in females. The testosterone in some groups have shown to responsible for hypogonadism and also is associated with reduced levels of inflammatory markers C-reactive protein (CRP), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) [28].

C-reactive protein (CRP) also is another biomarker which is measured in KS patients, a well-known inflammatory protein that predicts cardiovascular outcome [29]. In KS, CRP are significantly decreased in the testosterone -treated group but level of CRP [9] are increased at baseline [11,30]. Anti-inflammatory drugs have the opportunity to suppress inflammatory and inflammatory response; and using of anti-inflammatory drugs for long time it is possible to have therapeutic approach. Using of this drugs have the possibilities to developed novel therapeutic strategy involving modulation of the inflammatory process.

Leptin Adiponectin and Klinefelter Syndrome

Leptin is good biomarker for Klinefelter symptom study. Many times ago it is thought that adipose tissue is passive storage vessel discharging nutrients. This thought is change with identification of leptin as an adipocyte hormone. It is known that leptin function as an afferent signal in a negative feedback to regulate metabolism and homeostatic control of adipose tissue [31-33].

A number of components of the metabolic syndrome are present Klinefelter's syndrome, but, significant truncal obesity was present. Hypogonadism is very frequent in Klinefelter's syndrome, and Bojesen *et al.*, 2006 recommend that all patients with Klinefelter's syndrome should be treated with testosterone [11].

In Klinefelter syndrome higher level of leptin is demonstrated with no difference in the Testosterone-treated group [11]. Patients with Klinefelter syndrome are protected by hypertension; because lower level of this hormone are associated with arterial hypertension, and coronary diseases [32,34].

Higher level of leptin in KS patients compared with controls were not lowered after treatment with testosterone for 3 months, [35] but last time it is shown overproduction of CCL2 (small chemokine), could explain insulin resistance in KS [36].

Thrombosis and Hemostasis in Klinefelter Syndrome

Plasminogen activator inhibitor-1 (PAI-1) is encoded by gene *SERPINE1;* Plasminogen activator inhibitor-1 also it is known as endothelial plasminogen activator inhibitor or serpin. Increase of PAI-1 level it is shown to be a risk factor for thrombosis and atherosclerosis. PAI-1 is a serine protease inhibitor (serpin) and the pivotal functions of PAI-1 is to inhibit tissue plasminogen activator (tPA) and urokinase (uPA) [37].

The gene SERPINE1 is responsible for decoding of PAI-1, and location of this gene is on chromosome 7 (7q21.3-q22). The common polymorphism of this gene are 4G/5G in the promoter region. It is shown that 5G allele is less transcriptionally active than the 4G. The main function of PAI-1's is to inhibit urokinase plasminogen activator (uPA), an enzyme responsible for the cleavage of plasminogen to form plasmin.

Erkal *et al* 2018 [38] has made comparison of PAI-1 gene polymorphisms 4G/4G, 4G/5G, 5G/5G and PAI-1 plasma level in KS and control group. In this study has participate forty-one KS patients (47, XXY) and 50 age-matched healthy. It is done DNA real-time PCR and ELISA, and it is shown no significant difference between PAI-1 gene polymorphisms of KS patients and controls ($p > .05$). But the significant difference it is shown in PAI-1 plasma levels between two groups (high PAI-1 plasma level in KS patients compared to controls).

Amjad *et al* 2017 [39] report that Klinefelter syndrome increases the risk of thromboembolism. Thrombophilia workup should be done prior to starting testosterone replacement therapy in these patients. They also concluded that further research is needed to study the role of duration and dose of TRT (testosterone replacement therapy) in development of thrombosis.

Zoller *et al* 2016 [40] also has observed Venous thromboembolism (VTE) among KS patients. The aim of the study from Zoller *et al* 2016 was to examine whether KS is associated with VTE. They [40] concluded that KS is associated with high risk of VTE and KS could be considered a genetic hypercoagulable state. This is very important for clinical prevention and diagnosis of VTE among patients with KS.

Dyslipidemia and Klinefelter Syndrome

Dyslipidemia is another key component of the Metabolit Syndrome and often is associate with obesity. Pre-menopausal women are found to have higher levels of HDL cholesterol than men, and men have higher LDL cholesterol levels [41-45].

Dyslipidemia also has been reported in KS, consisting in high levele of low density lipoprotein (LDL) cholesterol and try glycerides.

Lee *et al* 2017 [46] show association between KS and dyslipidemia. The KS group from 55 patients who has visited the infertility clinic for an infertility evaluation were confirmed as having a diagnosis of KS. 120 patients were control group who visited the clinic for health screening. Lee *et al* show that testosterone levels in patients belonging to the KS group were significantly lower compared to the control group (2.4 ±2.6 vs. 5.2±1.8 ng/mL, P<0.001).

Compared to the control group, TG (try glycerides) levels in patients belonging to the KS group were increased (134.9 ±127.8 vs. 187.9 ±192.1 mg/dL, P=0.004) and HDL cholesterol was significantly decreased (51.2 ±22.0 vs. 44.0±9.5 mg/dL, P=0.009). LDL cholesterol and total cholesterol were not significantly different between the two groups (P=0.076 and P=0.256, respectively).

Han *et al.*, 2016 [47] show that obesity is common in Korean men with KS; and Hypogonadism in patients with KS was associated with obesity and hyperglycemia also.

Endothelial Dysfunction, Atherosclerosis and Klinefelter Syndrome

The role of the vascular endothelium is known as active paracrine, endocrine, and autocrine organ; in this form endothelium play pivotal role in regulation of vascular tone and vascular homeostasis Endothelial dysfunction is a systemic disorder and a key variable in the pathogenesis of atherosclerosis and its complications [48].

Recent study indicate that endothelial dysfunction, represent a key step in the development of atherosclerosis and are involved in plaque progression and atherosclerotic complications [49-51].

The results from study of Di Mambro *et al.*, 2010 show that endothelial dysfunction together with insulin resistance are prevalent even in the very young patients with KS; this patients have no other disorders such as metabolic or cardiac problems. Also, hypogonadism seems to play an important role for increased cardiometabolic risk in patients with KS [51].

It is shown that artherosclerosis is associated with decrease of endothelial progenitor cells [52].

In study which is done by Di Mambo *et al.* 2010, they demonstrate a reduced number of endothelial cells in patients with KS compared with control groups [51].

Although many study till today has done to explain the relationship between KS and endothelial cell, it is not clear yet this relationship and it is need to do other studies to explain in detail this relationship [53,54].

Conclusion

Clinical and genetic phenotype of KS are still not completely understood and need to be fully elucidated to improve the clinical management of this disease. KS remains largely underdiagnosed (only 25% of the

patients are correctly diagnosed and only a minority before the puberty onset) and the majority of patients are often diagnosed during adulthood. A major effort should be done in order to increase our ability to perform early diagnosis of the KS.

It is shown the patients which are affected by KS display an impaired metabolic risk profile characterized by an increased prevalence of MS and DM.

Taken together, patients with KS display an impaired cardiovascular risk profile characterized by increased prevalence of metabolic abnormalities including DM, dyslipidemia, and alteration in biomarkers of cardiovascular disease. However, KS does not appear to be associated with arterial hypertension.

Conflicts of Interests

No conflict of interest was declared by the authors.

Financial Disclosure

No financial disclosure was declared by the authors

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