

Klinefelter syndrome in clinical practice

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SUMMARY

Klinefelter syndrome is the most common sex-chromosome disorder; it affects approximately one in every 660 men. This syndrome is characterized by the presence of one or more extra X chromosomes, and the karyotype 47,XXY is the most prevalent type. The 'prototypic' man with Klinefelter syndrome has traditionally been described as tall, with narrow shoulders, broad hips, sparse body hair, gynecomastia, small testicles, androgen deficiency, azoospermia and decreased verbal intelligence. A less distinct phenotype has, however, been described. Klinefelter syndrome is an underdiagnosed condition; only 25% of the expected number of patients are diagnosed, and of these only a minority are diagnosed before puberty. Patients with Klinefelter syndrome should be treated with lifelong testosterone supplementation that begins at puberty, to secure proper masculine development of sexual characteristics, muscle bulk and bone structure, and to prevent the long-term deleterious consequences of hypogonadism; however, the optimal testosterone regimen for patients with Klinefelter syndrome remains to be established.

KEYWORDS Klinefelter syndrome, morbidity, mortality, testosterone treatment

REVIEW CRITERIA

The full PubMed database was searched (without time restrictions) on 23 October 2006 using the keywords "Klinefelter", "Klinefelter's" and "XXY" in titles and abstracts. Papers relevant to the topic were obtained and reviewed, as well as older articles selected by the authors. Publications cited in this Review were selected from those identified by the searches at the authors' discretion.

INTRODUCTION

In 1942, Harry F Klinefelter, Edward C Reifenstein and Fuller Albright described nine patients with a syndrome characterized by gynecomastia, azoospermia, hyalinized and small testes, elevated levels of follicle-stimulating hormone (FSH), and hypogonadism.¹ The cause of this syndrome was unknown until 1959, when Jacobs and Strong demonstrated the presence of an extra X chromosome in the karyotype of patients with Klinefelter syndrome.²

Early studies on inmates in prisons and institutions for mental health problems revealed disturbing findings of an increased risk of psychiatric disturbances, mental retardation and criminal behavior in patients with Klinefelter syndrome.³ These prejudicial beliefs are still wrongly held to be true by many people. Since the 1960s, a number of studies have added to our knowledge about this syndrome, especially the chromosome surveys that identified unselected newborn babies with sex-chromosome aberrations. These individuals were followed up throughout the 1970s and 1980s;⁴⁻⁶ the published studies, however, focused mainly on the development of affected individuals throughout infancy, childhood and adolescence, which left the natural history of adults with Klinefelter syndrome comparatively poorly described.

The 'prototypic' man with Klinefelter syndrome has traditionally been described as tall, with narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, androgen deficiency and reduced intelligence.⁷ An alternative phenotype has since been recognized, in which patients present with fewer clinical features than are observed in the classical phenotype.⁸ Although the syndrome has been known for more than 60 years and more than 3,000 articles on various topics related to Klinefelter syndrome have been published, our knowledge is still limited. This article focuses on aspects of epidemiology, endocrinology, cardiology, urology and fertility in Klinefelter syndrome,

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Table 1 Karyotype distribution among patients diagnosed with Klinefelter syndrome in Denmark.

Karyotype(s)	Number of cases diagnosed prenatally (%)	Number of cases diagnosed postnatally (%)	Total number of cases (%)
47,XXY	147 (90.2)	714 (89.7)	861 (89.8)
46,XY/47,XXY	15 (9.2)	48 (6.0)	63 (6.6)
48,XXX	0	11 (1.4)	11 (1.1)
49,XXXX	1 (0.6)	16 (2.0)	17 (1.8)
47,XXY/48,XXX	0	2 (0.3)	2 (0.2)
48,XXY + trisomy of chromosome 18	0	5 (0.6)	5 (0.5)
Total	163 (100)	796 (100)	959 (100)

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as well as on other causes of morbidity in these patients.

GENETIC BACKGROUND

Klinefelter syndrome is characterized by the presence of one Y chromosome and two or more X chromosomes in a phenotypic male. The most abundant karyotype is 47,XXY, but it is not uncommon for affected patients to have supernumerous X chromosomes, or to exhibit mosaicism with a mixture of normal and 47,XXY cells (or mixtures of 47,XXY and other karyotypes). In a Danish study of patients with Klinefelter syndrome, 90% had the 47,XXY karyotype, while the remainder had less common karyotypes (Table 1). Similar figures were found in a UK study.⁹

The genetic cause of Klinefelter syndrome is meiotic nondisjunction (i.e. abnormal partitioning of chromosomes or chromatids during meiosis, such that the resultant haploid gametes have too many or too few chromosomes). Trisomies and monosomies are both caused by meiotic nondisjunction, which can occur in either the father's or mother's germ cells (maternal and paternal meiotic nondisjunction each account for approximately 50% of cases of Klinefelter syndrome).¹⁰ Meiotic nondisjunction can result from a lack of, or reduction in, recombination between the pseudoautosomal regions on X and Y chromosomes.¹¹ Increased maternal age has repeatedly been shown to raise the risk of having a child with Klinefelter syndrome,^{12,13} but the influence of increased paternal age is more doubtful, since no effect of age on XY recombination has been found in men.¹⁴ The

phenotype of Klinefelter syndrome is relatively mild compared to that of other trisomies, however, because in cells that contain more than one X chromosome, all but one X chromosome undergoes inactivation (as happens in women). X-chromosome inactivation is, therefore, the means by which overexpression of X-linked genes is normally avoided.

The AR gene encodes the androgen receptor (via which testosterone exerts most of its effects), and is located on the X chromosome. The AR gene contains a highly polymorphic trinucleotide (CAG) repeat sequence in exon I, and the length of this CAG repeat is inversely correlated with the functional response of the androgen receptor to androgens. A short AR CAG repeat sequence, therefore, correlates with a particularly marked effect of androgens. In individuals with Klinefelter syndrome, the X chromosome with the shortest AR CAG repeat has been demonstrated to be preferentially inactivated, a process called skewed or nonrandom X-chromosome inactivation.¹⁵ In such patients, short AR CAG repeat lengths were associated with improved responses to androgen therapy, the ability to form more stable partnerships and with a higher level of education compared with long CAG repeats; conversely, long CAG repeat lengths were associated with increased body height and arm span, decreased bone density, decreased testicular volume and gynecomastia.¹⁵ The effect of this nonrandom X-chromosome inactivation—which preferentially leaves the allele with the longest CAG repeat active—might actually contribute to the hypogonadal phenotype seen in Klinefelter syndrome, and might also explain

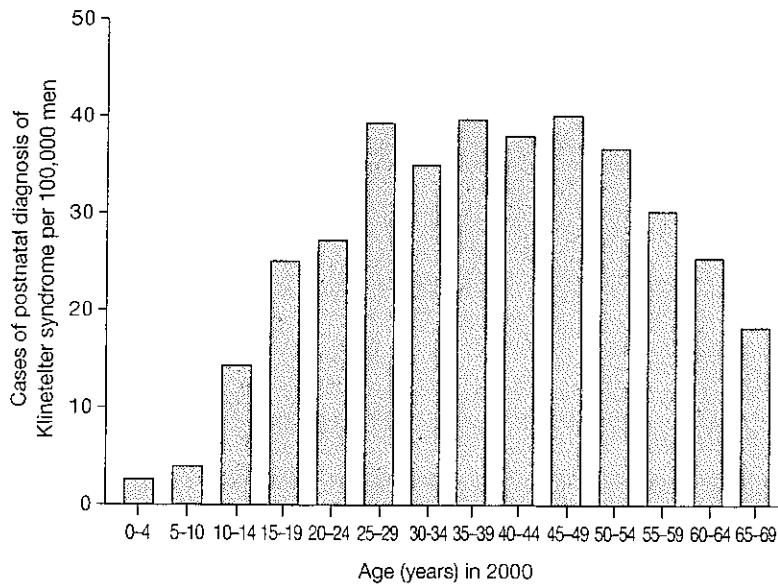


Figure 1 The prevalence of postnatal diagnosis of Klinefelter syndrome in Denmark in the year 2000. The maximum prevalence for any single age-group is around 40 cases per 100,000 males, which is approximately 25% of the expected prevalence (152 cases per 100,000 males). This discrepancy demonstrates the extent to which this condition is underdiagnosed. Only 10% of the expected number of patients are diagnosed before 14 years of age. Permission obtained from The Endocrine Society © 2003, Bojesen A *et al.* (2003) *J Clin Endocrinol Metab* 88: 622–626.

some of the diversity in physical appearance seen in affected patients.

DIAGNOSIS AND UNDERDIAGNOSIS

Diagnosis

Although there is no consensus on the correct clinical definition of Klinefelter syndrome, we believe that its diagnosis should always be based on clinical findings combined with a confirmatory cytogenetic evaluation. A phenotypically normal man with very low grade mosaicism should probably not, however, be given a diagnosis of Klinefelter syndrome.

Underdiagnosis and delayed diagnosis of Klinefelter syndrome is a major problem.¹² Early detection of the syndrome is important because it permits identification of speech problems and scholastic difficulties that require speech therapy and educational support. Moreover, early diagnosis facilitates prevention or remediation of the long-term consequences of gonadal insufficiency. In the future, it might be possible to prevent infertility in some individuals with Klinefelter syndrome, by preventing the testicular demise caused by prolonged luteinizing hormone (LH) hyperstimulation.

Prevalence

From the earliest published study, Klinefelter syndrome has been described as “not uncommon”,¹ but its prevalence was unknown until several large-scale sex-chromosome surveys were performed on newborn babies.^{16–18} Data summarized from these studies across countries and ethnicities yields a prevalence estimate of 152 cases per 100,000 males.¹²

In a study on both prenatal and postnatal prevalence of Klinefelter syndrome,¹² we found the exact same prevalence as the cumulative estimate from the above-mentioned surveys. This observation confirms that the true prevalence of Klinefelter syndrome is in fact around 150 per 100,000 males, or one in every 660 males. There was a large discrepancy between the prenatal and postnatal prevalence, however, which indicated severe underdiagnosis of the condition. Only 25% of the expected number of cases of Klinefelter syndrome cases were diagnosed postnatally, and less than 10% of these were diagnosed before puberty (Figure 1). This discrepancy could also be caused by a higher than normal incidence of intrauterine death, but although other aneuploidy syndromes (e.g. Turner syndrome, Down syndrome, and trisomies of chromosomes 13 and 18) are associated with prenatal mortality, it has not been described in Klinefelter syndrome. These data are consonant with those from the UK, where only 26% of the expected adults with Klinefelter syndrome have been diagnosed, and only 4% of 10-year-old children.¹⁹ The reason for this delay in diagnosis and the lower than expected rates of diagnosis is not known, but might be partly explained by the very variable phenotype of Klinefelter syndrome. The few boys who are diagnosed during childhood might have a particularly severe phenotype, with pronounced dyslexia, above-average height for their age and gynecomastia. By contrast, most patients who are diagnosed with Klinefelter syndrome as adults present with infertility and hypogonadism. Table 2 lists the most common clinical findings in patients with Klinefelter syndrome, with tentative frequencies. Our experience is that, when interviewed thoroughly, most of the patients who are diagnosed in adulthood report educational and other problems that are typical for patients with Klinefelter syndrome.

Screening

PCR-based screening methods that can detect sex-chromosome aneuploidy are available,

but have not yet been validated for use in newborn babies. If such screening for Klinefelter syndrome is offered, confirmatory karyotype tests will be needed. It is also important to have an infrastructure that allows for the follow-up and treatment of patients with sex-chromosome abnormalities, with support services to help parents and caregivers deal with the uncertainties inherent in this type of diagnosis.

If a fetus is prenatally diagnosed to have a 47,XXY karyotype professional genetic counseling should be offered, which should advise the parents that their baby has a relatively good prognosis. Despite this favorable prognosis, however, currently 75% of couples in Denmark who discover that they are expecting a child with Klinefelter syndrome choose termination.¹²

Ascertainment bias

Ascertainment bias is a major problem in the interpretation of data from studies on different populations of patients with Klinefelter syndrome, because only around 25% of the expected men with Klinefelter syndrome are actually diagnosed. As mentioned earlier, the phenotype of a patient diagnosed as having Klinefelter syndrome in childhood or at puberty might be different from that of a patient diagnosed as having Klinefelter syndrome in adulthood. Most published data so far are hampered by ascertainment bias. The least biased data currently available are those from prospective studies on boys diagnosed at birth, but the numbers of patients in these studies are small and there is, therefore, great variability in the estimates of certain clinical findings. As a consequence, it is important to interpret the prevalence data on clinical findings cautiously, and to avoid extrapolating prevalence rates found in one population to all patients with Klinefelter syndrome.

CONGENITAL MALFORMATIONS

Reaching a diagnosis of Klinefelter syndrome at birth on the basis of clinical findings is unlikely, as the syndrome has no specific clinical features that are apparent in newborn babies (unlike Turner syndrome or Down syndrome); however, an increased incidence of congenital malformations has been found in babies with Klinefelter syndrome. Minor congenital abnormalities were found in 26% of babies diagnosed with Klinefelter syndrome at birth in a sex-chromosome survey, with clinodactyly of the

Table 2 Abnormalities associated with Klinefelter syndrome and their approximate frequencies.

Feature	Frequency (%)
Adults	
Infertility ⁷	>99
Azoospermia ⁷	>95
Decreased facial hair ⁷	60–80
Decreased pubic hair ⁷	30–60
Abdominal adiposity ³¹	~50
The metabolic syndrome ³¹	46
Osteopenia ⁵²	~40
Type 2 diabetes ³¹	10–39
Osteoporosis ⁵²	10
Mitral valve prolapse ⁴⁶	≤55
Breast cancer ^{54,55}	Increased risk (~50-fold ^a)
Children	
Learning disabilities ⁶	>75
Gynecomastia ^{6,26}	38–75
Delayed speech development ⁶	≥40
Increased height ^{5,6}	≥30
Decreased penis size ⁶	10–25
Psychiatric disturbances ⁶	25
Mediastinal cancers ⁵³	Increased risk (~500-fold ^a)
All patients with Klinefelter syndrome	
Small testes (<4 ml) ⁷	>95
Increased gonadotropin levels ⁷	>95
Decreased testosterone levels ⁷	63–85
Cryptorchidism ^{6,21}	27–37
Congenital malformations (cleft palate and inguinal hernia) ⁵⁹	~18
Fractures ^{9,45}	Increased risk (2–40-fold ^a)

^aAbove normal. ^bPrepubertal.

fifth finger as the most frequent abnormality.²⁰ The same survey found major congenital abnormalities in 18% of boys with Klinefelter syndrome; cleft palate, inguinal hernia and testis retention were the most frequent findings.²⁰ Further evidence of a highly increased prevalence of testis retention in this syndrome comes from a large, cross-sectional study undertaken in an andrology clinic, where 27% of patients with Klinefelter syndrome had a history of undescended testes, compared to 8% of the total number of patients who attended the same clinic.²¹

TESTICULAR DEVELOPMENT

In the first report by Klinefelter *et al.*,¹ the typical testicular histology of patients with Klinefelter syndrome was described as hyalinization of the seminiferous tubules with loss of germ cells and Leydig-cell hyperplasia. In some patients with Klinefelter syndrome, however, focal spermatogenesis can be found, which offers the possibility of surgical extraction of sperm for *in vitro* fertilization.²² The exact cause of this hyalinization of the testes, which results in subsequent hypogonadism and infertility, is unknown. Only a few studies on testicular histology conducted in boys with Klinefelter syndrome have described a loss of spermatogonia from infancy,²³ while hyalinization of the seminiferous tubules probably does not occur until mid-puberty.²⁴

At the beginning of puberty, which usually occurs at the normal time in boys with Klinefelter syndrome,²⁵ the testes initially grow to approximately 4 ml in volume, and thereafter shrink to the pathological adult size of less than 4 ml.²⁶ The testes might also malfunction early on in development (i.e. before birth), as micropenis is seen in some newborn boys with Klinefelter syndrome. Micropenis is thought to result from decreased fetal testosterone production *in utero*.²⁷ The normal surge in testosterone seen in the first 1–6 months of life is attenuated in boys with Klinefelter syndrome, which probably reflects early Leydig cell dysfunction.^{27,28} Longitudinal studies conducted in boys with Klinefelter syndrome before and during puberty have shown that their testes are smaller than those of normal boys, even before puberty.²⁹ Boys with Klinefelter syndrome have normal levels of FSH, LH and testosterone during the prepubertal period, but experience a rise in FSH and LH and a decline in testosterone after the onset of puberty, compared to levels seen in normal boys.²⁶

In adults with Klinefelter syndrome, decreased levels of testosterone and insulin-like factor 3, a marker of Leydig cell function, have been described.³⁰ The function of the Sertoli cells seems to be normal in infancy, as normal values of both inhibin B and antimüllerian hormone have been reported in patients with Klinefelter syndrome.²⁸ At the end of puberty inhibin B levels diminish, which probably reflects a loss of Sertoli cells.²⁵ Hypogonadism, which is regarded as a hallmark of Klinefelter syndrome, is relative rather than absolute: most patients have testosterone levels just below the normal range.^{21,31}

Free testosterone levels are also reduced in patients with Klinefelter syndrome,^{21,31} and although testosterone levels of many patients are within the normal range, their gonadotropin levels are usually elevated.^{7,21,31} Raised gonadotropin levels indicate hypogonadism, and thus increased pituitary drive, and might be one of the causes of Leydig cell hyperplasia. Although levels of 17 β -estradiol and sex-hormone-binding globulin have previously been reported to be elevated in patients with Klinefelter syndrome,²¹ our latest study did not confirm this finding.³¹ We found, however, that levels of 17 β -estradiol were elevated relative to those of testosterone, in other words an elevated 17 β -estradiol:testosterone ratio.³¹

FERTILITY

Until 1996, men with Klinefelter syndrome were considered infertile, but with the development of testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) it is now possible to extract viable spermatozoa from the testes by surgical biopsy and to inject a spermatozoon directly into an ovum. Worldwide, more than 60 children have been born after successful ICSI in couples where the male partner has Klinefelter syndrome.^{22,32} A minority of men with Klinefelter syndrome have viable sperm in their ejaculate and might, therefore, be able to provide sperm for cryopreservation for future pregnancies.

There have been some concerns about an increased risk of chromosome aberrations in the offspring of patients with Klinefelter syndrome, because increased rates of both autosomal and sex-chromosome aneuploidy have been found in spermatozoa extracted or ejaculated from men with Klinefelter syndrome.³³ In one case of assisted conception for a couple in which the male partner had Klinefelter syndrome, one of the three embryos transferred was later shown to have an XXY karyotype, and the pregnancy was reduced in the 14th gestational week.³⁴ Whether the increased number of autosomal, aneuploid spermatozoa found in patients with Klinefelter syndrome reflects a genuinely increased risk of trisomies of chromosomes 13, 18 and 21 in their offspring awaits further studies.

As a consequence, professional genetic counseling and options of prenatal diagnosis or even preimplantation genetic diagnosis should always be offered to couples who seek infertility treatment because the male partner has Klinefelter syndrome.

GYNECOMASTIA

Gynecomastia is relatively frequent during puberty in normal boys, and can be very troublesome. In boys with Klinefelter syndrome the prevalence of gynecomastia is markedly increased, and has been reported to be up to 50%⁷ in some series, although the true prevalence is probably much lower than this value. A decreased testosterone level, in combination with a relatively elevated estradiol level, has been suggested as a possible cause of gynecomastia in boys with Klinefelter syndrome.²⁶ Testosterone treatment can lead to regression of gynecomastia, but some patients choose to have the breast tissue removed surgically.

LONG-TERM CONSEQUENCES OF HYPOGONADISM

The hypogonadism associated with Klinefelter syndrome can delay or reduce the development of normal male secondary sexual characteristics, such that affected individuals have reduced beard growth, muscle bulk, and secondary body hair compared to men with normal hormone levels.⁷ Sexual function has not been investigated in detail in patients with Klinefelter syndrome, but decreased libido has been reported in 70% of such men after the age of 25 years.²¹

The long-term consequences of hypogonadism in patients with Klinefelter syndrome are difficult to separate from the gene-dose effects of having an extra X chromosome, because there have been few studies on comparable hypogonadal diseases (e.g. Kallmann syndrome), due to the rarity of these conditions.

DIABETES AND THE METABOLIC SYNDROME

A number of case reports have described an association between diabetes and Klinefelter syndrome, but reasons for this association remain unclear. Epidemiological studies on both morbidity³⁵ and mortality in patients with Klinefelter syndrome⁹ have confirmed this increased risk of diabetes. We described³¹ a strikingly high incidence of metabolic syndrome and insulin resistance in 70 patients with Klinefelter syndrome who were compared to an age-matched control group. Almost half of the patients with Klinefelter syndrome fulfilled the US National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria

for the metabolic syndrome, whereas only 10% of the control group fulfilled these criteria. Plasma lipids including LDL cholesterol were increased, and HDL cholesterol was decreased, in patients with Klinefelter syndrome compared with those of the control group. Significantly more men with Klinefelter syndrome than controls had elevated fasting plasma insulin levels and insulin resistance. Despite similar BMIs in the two groups, individuals with Klinefelter syndrome had increased amounts of body fat and especially of truncal fat, and their maximal oxygen uptake (a marker of physical fitness) was severely diminished.

Prospective studies in other populations have shown that low levels of testosterone (and of sex-hormone-binding globulin) can predict abdominal adiposity,³⁶ the metabolic syndrome³⁷ and type 2 diabetes.³⁸ Apart from the associations between low testosterone and altered body composition, the metabolic syndrome and insulin insensitivity, low testosterone levels have also been associated with an adverse cardiovascular risk profile characterized by increased C-reactive protein and triglycerides but decreased HDL cholesterol.³⁹ By contrast, testosterone levels are inversely correlated with those of the cardioprotective and antidiabetic adipocytokine adiponectin,⁴⁰ and testosterone treatment has been shown to suppress the (relatively) elevated adiponectin levels in hypogonadal men.⁴¹ Adiponectin level is closely and inversely correlated to obesity.⁴² In our 2006 study of patients with Klinefelter syndrome,³¹ we found increased levels of C-reactive protein (a marker of chronic inflammation) and, surprisingly, normal levels of adiponectin (contrary to what might be expected from these patients' increased amount of fat) that probably resulted from their concomitant hypogonadism. This observation is interesting because although half of our group of patients with Klinefelter syndrome fulfilled the criteria for the metabolic syndrome, their blood pressure was no different to that of the control group. Although this theory is highly speculative, it seems possible that hypogonadism contributes to development of the metabolic syndrome (and exacerbates cardiac risk factors), but also protects against ischemic heart disease by increasing levels of adiponectin (Figure 2). This theory is in part supported by epidemiological data on mortality in patients with Klinefelter syndrome, where significantly increased mortality from diabetes

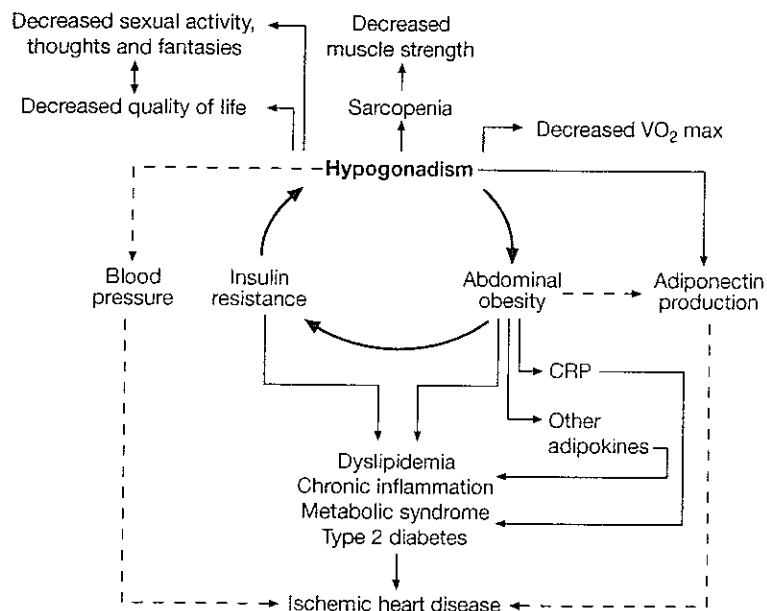


Figure 2 The vicious circle of hypogonadism, abdominal adiposity and insulin resistance has direct and indirect consequences. Solid arrows indicate promotion, dotted arrows indicate inhibition. Abbreviation: VO₂ max, the maximum capacity to transport and utilize oxygen during incremental exercise.

was found, but the mortality from ischemic heart disease was significantly decreased.⁹ Data from a study on castrated men also corroborate this theory; these men had a decreased risk of dying from acute myocardial infarction, in spite of a generally increased mortality risk.⁴³ It seems plausible that a vicious circle could exist, in which hypogonadism leads to abdominal obesity, which in turn leads to insulin resistance that might further aggravate the hypogonadism (Figure 2).⁴⁴

CARDIOVASCULAR DISEASE

Mortality from cardiovascular diseases is increased in patients with Klinefelter syndrome,^{9,45} even though their mortality from ischemic heart disease is reduced.⁹ One reason for this increased cardiovascular mortality could be mitral valve prolapse, which has been described to affect a large proportion of patients with Klinefelter syndrome in one study;⁴⁶ mitral valve prolapse is related to an increased risk of sudden death. Patients' risk of hypostatic leg ulcers can be significantly increased,⁴⁷ which might cause serious morbidity and mortality from pulmonary embolism.⁹ Dysfunction of the fibrinolytic system has been proposed as a reason for this association, and one study has

reported increased activity of plasminogen activator inhibitor 1 in patients with Klinefelter syndrome,⁴⁸ but further studies are needed to clarify this relationship.

OSTEOPOROSIS

Hypogonadism is a known cause of secondary osteoporosis in both women and men.⁴⁹ A number of studies on osteoporosis in patients with Klinefelter syndrome have been performed,⁵⁰⁻⁵² but these studies used a variety of methods and obtained inconsistent results. The majority of studies show a significant reduction in bone mineral density (BMD) in men with Klinefelter syndrome compared to normal men, although frank osteoporosis is uncommon. Epidemiological studies on morbidity and mortality showed that men with Klinefelter syndrome had an increased risk of admission to hospital with an osteoporotic fracture of the forearm, hip or spine,³⁵ and had an increased risk of dying from hip fractures,⁹ which indicated that the reported reduction in BMD might mirror an important clinical problem.

CANCER

Whether gynecomastia leads to an increased risk of developing breast cancer remains a matter of debate. A Danish study of cancer registry data on men with Klinefelter syndrome did not show that these patients had an increased risk of breast cancer;⁵³ however, a Swedish karyotype study⁵⁴ that evaluated nonmetastatic lymph nodes from men with breast cancer showed a 47,XXY karyotype in 7.5% of the examined patients, which was equivalent to a 50-fold increase in risk of breast cancer. An increased risk of breast cancer has been confirmed in a study on mortality and incidence of cancer in a large cohort of patients with Klinefelter syndrome (*n* = 3,518), which showed that these patients' risk of breast cancer was significantly elevated.⁵⁵

The Danish register study on cancer incidence in men with Klinefelter syndrome did not show an overall increased risk of cancer, but those patients did have a significantly increased risk of mediastinal germ-cell tumors.⁵³ By contrast, patients with Klinefelter syndrome in the most recent UK study (published in 2005) had an increased mortality risk from lung cancer (albeit with only marginal statistical significance), breast cancer and non-Hodgkin's lymphoma, and a significantly decreased risk of death from prostate cancer.⁵⁵ The UK study

could not, however, confirm the increased risk of mediastinal tumors found in the Danish study. The finding of a decreased risk of death from prostate cancer probably reflects the frequent hypogonadism in Klinefelter syndrome, because most prostate cancers are known to be testosterone-dependent, and anti-androgens have proven to be effective tools in the treatment of this common cancer. Although testis retention (a well-known risk factor for testicular cancer) is very common in Klinefelter syndrome, no increase in testicular cancer has been described.

In summary, the available data from several sources indicate that men with Klinefelter syndrome have a grossly elevated risk of cancer of the breast, mediastinal germ-cell tumors and non-Hodgkin's lymphomas. Additional studies will be needed to elucidate whether they also have an increased risk of other cancers.

COGNITIVE DISTURBANCES

In the early 1960s several investigators reported an increased prevalence of Klinefelter syndrome among inmates of prisons and institutions for the mentally retarded.^{3,56,57} This finding led to the conclusion that Klinefelter syndrome was associated with criminal behavior and low intelligence. This belief was challenged by prospective studies in newborn babies screened for sex-chromosome disorders during the 1970s. In later studies with long-term follow up,^{5,6,58} the overall intelligence of patients with Klinefelter syndrome was found to be near-normal, but they had decreased verbal abilities, delayed development of speech and a high proportion of educational problems.^{59,60} A study of patients with Klinefelter syndrome who were prenatally diagnosed showed remarkably good outcomes in relation to intellectual performance,⁶¹ but this finding might reflect elevated socioeconomic status and increased motivation among parents who chose to continue with the pregnancy despite the Klinefelter syndrome diagnosis.

One study on adults who had sex-chromosome abnormalities that were detected at birth showed that the decreased verbal intelligence and reading impairment of patients with Klinefelter syndrome persisted in adulthood,⁶² but there was a large variation in educational and vocational achievement. The reason for the delay in speech development and decreased verbal intelligence is unclear, but an MRI study of the whole brain found diminished grey matter volumes

in the left temporal lobes of five untreated patients with Klinefelter syndrome, compared to five patients with Klinefelter syndrome who were treated with testosterone, and to normal controls.⁶³ Another study on brain perfusion in patients with Klinefelter syndrome, which used single-photon-emission computed tomography (SPECT), described a diminished left lateralization of perfusion (compared with the pattern seen in normal controls) and a negative correlation between reduced perfusion in regions involved in language processing and scores in verbal tests.⁶⁴ These observations might, in part, explain the decreased verbal performance seen in patients with Klinefelter syndrome. Although these results were based on a small sample of patients, they also point towards a possible positive effect of testosterone-replacement therapy on verbal performance in men with Klinefelter syndrome. This potential positive effect is in accordance with the findings of a study on verbal intelligence, pubertal development and testosterone levels, which showed a positive association between testosterone levels and verbal intelligence.⁶⁵ Interestingly, a study published in 2006 showed impaired learning and memory function as well as testicular failure in an XXY mouse model.⁶⁶

PSYCHIATRIC ILLNESS

Studies from the late 1960s that were primarily based on screening for sex-chromosome abnormalities among inmates of penal institutions, psychiatric hospitals and institutions for the mentally retarded reported an increased incidence of psychiatric illness in individuals with Klinefelter syndrome.⁵⁷ Ratcliffe's long-term follow-up study of patients with Klinefelter syndrome who were identified by a chromosomal survey of newborn babies also revealed an increased frequency of referrals for psychiatric treatment.⁶ A survey of sex-chromosome aberrations among patients with schizophrenia found a 4–5-fold increased incidence of Klinefelter syndrome, compared with the expected incidence in the normal population.⁶⁷ Our epidemiological study on hospital admissions in patients with Klinefelter syndrome showed that these individuals had a significantly increased risk of discharge from hospital with a psychiatric diagnosis.³⁵ Moreover, patients with Klinefelter syndrome might show an increased incidence of pathological symptoms and traits associated with schizophrenia, compared to a

control group.⁶⁸ Overexpression of X-linked genes that escape X-chromosome inactivation has been suggested as a cause of some of the psychiatric disturbances seen in patients with Klinefelter syndrome.⁶⁹

CRIMINALITY

A follow-up study found no increased frequency of criminal behavior in patients with Klinefelter syndrome who self-reported whether they had ever received criminal sentences.⁷⁰ Another study that followed 34 patients with Klinefelter syndrome for 10 years and 20 years showed increased criminal behavior after 10 years of follow-up, compared with both hypogonadal men (from causes other than Klinefelter syndrome) and with a control group.⁵⁸ After 20 years of follow-up, however, there was no significant difference in criminality among the three groups.⁷¹ Data on 32 patients with Klinefelter syndrome who were diagnosed either prepubertally or during puberty showed that a large proportion of patients had severe psychosocial problems: 69% had problems with control of aggression, 28% had broken the law and 18% had been convicted.⁷²

TREATMENT

Treatment and care of patients with Klinefelter syndrome is a multidisciplinary task that should ideally involve speech therapists, psychologists, general practitioners, pediatricians, endocrinologists, urologists and infertility specialists. Patients with Klinefelter syndrome are rarely diagnosed in infancy because they lack clinical features that are specific for Klinefelter syndrome; however, some boys with Klinefelter syndrome have micropenis, which in some patients has been treated successfully with topical testosterone cream or single injections with intramuscular testosterone. The most serious problem associated with Klinefelter syndrome in early childhood is delayed speech, which affects perhaps half of all boys with this syndrome.⁶ Careful observation is needed in order to ensure that such boys are referred to speech therapists if there is a delay in their speech development. Referrals for specialist care should also be available for patients with learning disabilities, which have been observed in 77% of boys with Klinefelter syndrome who were followed from birth to adulthood.⁶

At puberty, when gonadotropin levels rise, testosterone treatment should probably be

initiated in order to aid proper masculine development of secondary sexual characteristics, but also to ensure a sufficient increase in muscle bulk and BMD. Testosterone treatment in pubertal boys with Klinefelter syndrome has also been reported to increase their energy and endurance, improve their mood and concentration, and to help these patients build improved relationships with other people.⁷³ Data from a group of patients who were diagnosed as having Klinefelter syndrome before and during puberty showed that these individuals had increased psychosocial problems in periods without testosterone treatment.⁷²

Testosterone-replacement therapy for these patients should probably be lifelong, in order to prevent osteoporosis, obesity, the metabolic syndrome and diabetes. Although most clinicians who care for patients with Klinefelter syndrome believe that testosterone treatment has a positive effect, both physically and psychologically, there are no evidence-based data that support this belief. Treatment with testosterone in young, hypogonadal men has been shown to have positive effects on fat mass, muscle mass, and muscle strength, as well as sexual activity, and it improves positive aspects of mood.⁷⁴ In elderly hypogonadal men the data suggest that testosterone treatment has positive effects on visuospatial cognition and verbal recall.⁷⁵

Although some patients with Klinefelter syndrome have normal testosterone levels, virtually all have increased gonadotropin levels. We believe that all patients with Klinefelter syndrome should probably receive testosterone treatment if their gonadotropin levels are elevated, even if their testosterone levels are in the low end of the normal range. Certainly, these patients should be treated if they have symptoms of hypogonadism (lack of energy and decreased libido), or increased abdominal adiposity.

The aim of testosterone treatment should be normalization of LH and testosterone levels to the middle of the normal range, rather than to achieve low-normal nadir values of testosterone. In our experience, LH can be normalized in virtually all patients with Klinefelter syndrome if the testosterone dose is carefully titrated. It follows that many patients with Klinefelter syndrome are undertreated, because their LH levels often remain high. Clinicians should also focus on the subjective symptoms reported by

Table 3 Testosterone preparations available and their suggested doses for adult patients with Klinefelter syndrome.

Substance	Brand name (manufacturer)	Format	Route of administration	Suggested dose
Testosterone undecanoate	Andriol® (Organon, Oss, the Netherlands)	Capsule	Oral	120–160 mg per day
Testosterone undecanoate	Nebido® (Schering, Berlin, Germany)	Injection	Intramuscular	1 g every 10–14 weeks
Testosterone enantate	Testoviron® (Schering, Berlin, Germany)	Injection	Intramuscular	250 mg every 2–3 weeks
Testosterone	Striant® (Columbia Laboratories, Livingston, NJ, USA)	Buccal adhesive	Buccal	60 mg per day
Testosterone	Testim® (Ipsen, Paris, France)	Gel	Skin	50 mg per day
Testosterone	Testogel® (Laboratoires Besins, Paris, France)	Gel	Skin	50 mg per day
Testosterone	Androderm® (Watson Pharma Inc., Corona, CA, USA)	Transdermal patch	Skin	2.5–7.5 mg per day
Testosterone	Testoderm® (Alza Corp., Mountain View, CA, USA)	Transdermal/ scrotal patch	skin/scrotal skin	4–6 mg per day

the patient, especially in order to avoid the transient, high levels of testosterone that can occur with injected formulations of testosterone, and which can cause discomfort.

Some testosterone preparations currently available are shown in Table 3. A possible negative effect of exogenous testosterone on fertility (or on the outcome of TESE and ICSI) has been reported, and that study also described the use of aromatase inhibitors and human choriogonadotropin to increase intratesticular testosterone in order to increase the chance of sperm recovery by TESE.³² These interesting data are based on the observation that sperm recovery by TESE failed in five patients with Klinefelter syndrome who were taking long-term testosterone treatment; these findings should, however, be confirmed in a randomized setting, before testosterone treatment is withheld from young men with Klinefelter syndrome.

A clinical outpatient program for the management of patients with Klinefelter syndrome is suggested in Box 1. Patients who are given testosterone treatment should initially be followed up with clinic visits every 3 months, until their testosterone dose has been titrated to achieve serum levels of testosterone and LH in the middle of the normal ranges and according to the patients' symptoms, and annually thereafter.

CONCLUSION

Not a single randomized, placebo-controlled study on the effects of testosterone-replacement therapy in patients with Klinefelter syndrome

Box 1 Proposed assessment and follow-up program for patients with Klinefelter syndrome.

At first assessment visit

- Confirm karyotype, if necessary
- Test sex hormone levels: testosterone, estrogen, sex-hormone-binding globulin, follicle-stimulating hormone and luteinizing hormone
- Measure fasting glucose and lipids
- Assess thyroid status, hemoglobin, hematocrit and serum PSA
- Physical examination, including assessment of blood pressure, height, weight, waist size, testes size, gynecomastia and varicose veins
- Bone densitometry (dual-energy X-ray absorptiometry), vitamin D status, and serum calcium phosphate levels
- Echocardiography
- Provide information to the patient (and family) about the syndrome
- Initiation of testosterone treatment (injected, transdermal or oral administration)
- Answer patient's questions about wellbeing, physical activity, energy, sexual activity, libido

At routine follow-up assessment (initially every 3 months, then annually)

- Physical examination, including assessment of blood pressure, height, weight, waist, testes size, gynecomastia and varicose veins
- Test sex hormone levels: testosterone, estrogen, sex-hormone-binding globulin, follicle-stimulating hormone and luteinizing hormone (nadir values)
- Measure fasting glucose and lipids
- Assess thyroid status, hemoglobin, and serum PSA
- Answer patient's questions about wellbeing, physical activity, energy, sexual activity, libido

At 2, 5 and 10 years, and then probably every 5 years thereafter

- Bone densitometry (dual-energy X-ray absorptiometry), vitamin D status and serum calcium phosphate levels

has been published. This glaring omission creates a major ethical problem: how can we compare the effects of testosterone—which is considered to be a potent medication for patients with Klinefelter syndrome—with those of placebo, especially in pubertal boys for whom a lack of active treatment might lead to long-term negative consequences? On the other hand, randomized, placebo-controlled studies on adults with Klinefelter syndrome could (and should) be performed. Such studies should evaluate doses and formulations that restore testosterone levels to normal in a population of adults with Klinefelter syndrome that is large enough to detect small changes in BMD, body composition, insulin sensitivity and quality of life.

In the absence of such studies, we recommend that testosterone treatment should be given to all patients with Klinefelter syndrome who have elevated gonadotropin levels, in order to counteract the many harmful effects of hypogonadism on body composition, glucose and lipid metabolism, wellbeing, sexual and other functions (both mental and physical). Future studies will hopefully provide the evidence that is essential to allow optimization of treatment in patients with Klinefelter syndrome.

KEY POINTS

- Klinefelter syndrome is the most common sex-chromosome aberration (present in 1 in 660 men), but remains underdiagnosed
- Common clinical findings in patients with Klinefelter syndrome include small testes (<4 ml), azoospermia, hypergonadotrophic hypogonadism, learning disabilities, gynecomastia, and cryptorchidism
- Patients with Klinefelter syndrome have an increased risk of developing diabetes, metabolic syndrome, osteoporosis, breast cancer, mediastinal germ-cell tumors and non-Hodgkin's lymphoma
- Treatment for patients with Klinefelter syndrome can include referral to a speech therapist if necessary (in cases where speech development is delayed) and testosterone treatment from puberty (when gonadotropin levels rise)
- Infertility in some men with Klinefelter syndrome can be overcome by use of assisted reproduction techniques: testicular sperm extraction and subsequent intracytoplasmic sperm injection

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Competing interests

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