Klinefelter Syndrome—A Clinical Update

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Context: Recently, new clinically important information regarding Klinefelter syndrome (KS) has been published. We review aspects of epidemiology, endocrinology, metabolism, body composition, and neuropsychology with reference to recent genetic discoveries.

Evidence Acquisition: PubMed was searched for “Klinefelter,” “Klinefelter’s,” and “XXY” in titles and abstracts. Relevant papers were obtained and reviewed, as well as other articles selected by the authors.

Evidence Synthesis: KS is the most common sex chromosome disorder in males, affecting one in 660 men. The genetic background is the extra X-chromosome, which may be inherited from either parent. Most genes from the extra X undergo inactivation, but some escape and serve as the putative genetic cause of the syndrome. KS is severely underdiagnosed or is diagnosed late in life, roughly 25% are diagnosed, and the mean age of diagnosis is in the mid-30s. KS is associated with an increased morbidity resulting in loss of approximately 2 yr in life span with an increased mortality from many different diseases. The key findings in KS are small testes, hypergonadotropic hypogonadism, and cognitive impairment. The hypogonadism may lead to changes in body composition and a risk of developing metabolic syndrome and type 2 diabetes. The cognitive impairment is mainly in the area of language processing. Boys with KS are often in need of speech therapy, and many suffer from learning disability and may benefit from special education. Medical treatment is mainly testosterone replacement therapy to alleviate acute and long-term consequences of hypogonadism as well as treating or preventing the frequent comorbidity.

Conclusions: More emphasis should be placed on increasing the rate of diagnosis and generating evidence for timing and dose of testosterone replacement. Treatment of KS should be a multidisciplinary task including pediatricians, speech therapists, general practitioners, psychologists, infertility specialists, urologists, and endocrinologists. (J Clin Endocrinol Metab 98: 0000–0000, 2013)
most agree that the cardinal stigmata include small testes in virtually all KS, hypergonadotropic hypogonadism, gynecomasia, learning difficulties, and infertility. However, the clinical presentation of XXY males may appear in many cases to be similar to that of XY males, and thus it is difficult to make a diagnosis of KS without karyotyping. A number of congenital malformations and conditions are often seen in KS (Table 1).

The genetic background for the KS phenotype is based on the presence of the extra X-chromosome. The genetic disorder is also seen in domestic and wild animals (2). As in women, one of the extra X-chromosomes undergoes inactivation, and the phenotype is presumed to be the consequence of the presence of the non-inactivated extra genes from the X-chromosome, although other genetic mechanisms are possible. Of these genes, the only one that has been clearly shown to influence the phenotype in KS is the short-stature homeobox-containing gene on chromosome X (SHOX) situated in the pseudoautosomal region 1 on Xp. SHOX haploinsufficiency has been implicated in growth retardation and bone changes in Turner syndrome and Leri-Weill dyschondrosteosis (3, 4) and is also implicated in the slightly accelerated growth in Klinefelter, 47,XXX and 47,XYY syndrome (5). Brain natriuretic peptide and fibroblast growth factor receptor 3 are transcriptional targets of SHOX (6, 7), and this knowledge may enhance our understanding of the phenotypic consequences of the syndrome. The CAG repeat number in the androgen receptor seems to be related to some phenotypic traits in KS, like height and hematocrit and possibly others (8–10), whereas it is more doubtful whether parental origin of the extra X-chromosome influences phenotype. More than 10% of the genes located on the X-chromosome are expressed in the testis and therefore likely to play a role in KS (11).

In the first publication, the syndrome was described as “not uncommon” (1), but it was not until large-scale chromosome analyses in newborns were performed that the “true” prevalence was established, however with great variation. By pooling the data from eight different studies, we estimated the prevalence to be 152 per 100,000 live-born males, confirmed by the prevalence in prenatally diagnosed KS in Denmark (12) and a large screening study from Georgia where DNA from dried blood spots from 36,124 newborn boys showed a prevalence of 158 per 100,000 (13). An increase in the prevalence has been proposed (14), and the prevalence of KS may differ between populations, exemplified by a recent Australian study finding a prevalence of 223 per 100,000 (15).

Establishing the prevalence has enabled us to study the incidence of diagnosis. In Denmark, only 25% of the expected numbers are diagnosed, and barely 10% of these are diagnosed before puberty, indicating a severe delay in diagnosis, underdiagnosis, and nondiagnosis (12). Similar frequency of diagnosis was estimated from a British study finding approximately 100 of estimated 525 each year (16), but in Australia the diagnostic activity seems greater because they find approximately 50% of the expected numbers (15). The reason so many KS men will go through their lives without a diagnosis is unknown, but the relatively mild phenotype is a tempting explanation. The hidden proportion of nondiagnosed patients should be kept in mind when looking at data concerning KS because ascertainment bias is always present, apart from screening studies in the newborn.

Epidemiological studies in KS have been conducted in two major cohorts, the British and the Danish. Data concerning mortality and cancer incidence have been pub-

### TABLE 1. Abnormalities associated with KS and their tentative frequencies

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility (adults) (8, 57)</td>
<td>91–99&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Small testes (bi-testicular size &lt;6 ml) (8)</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Increased gonadotropins levels (57)</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Azoospermia (adults) (57)</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Learning disabilities (children) (74)</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Decreased testosterone levels (57)</td>
<td>63–85</td>
</tr>
<tr>
<td>Decreased facial hair (adults) (57)</td>
<td>60–80</td>
</tr>
<tr>
<td>Decreased pubic hair (adults) (57)</td>
<td>30–60</td>
</tr>
<tr>
<td>Gynecomasia (adolescents, adults) (8, 33, 74)</td>
<td>38–75</td>
</tr>
<tr>
<td>Delay of speech development (children) (74)</td>
<td>40</td>
</tr>
<tr>
<td>Increased height (prepubertal, adults) (74, 123)</td>
<td>30</td>
</tr>
<tr>
<td>Abdominal adiposity (adults) (36)</td>
<td>~50</td>
</tr>
<tr>
<td>Metabolic syndrome (adults) (36)</td>
<td>46</td>
</tr>
<tr>
<td>Osteopenia (adults) (51, 124)</td>
<td>5–40</td>
</tr>
<tr>
<td>Type 2 diabetes (adults) (19, 36)</td>
<td>10–39</td>
</tr>
<tr>
<td>Cryptorchidism (8, 74)</td>
<td>27–37</td>
</tr>
<tr>
<td>Decreased penile size (children) (74)</td>
<td>10–25</td>
</tr>
<tr>
<td>Psychiatric disturbances (children) (74)</td>
<td>25</td>
</tr>
<tr>
<td>Congenital malformations, cleft palate, inguinal hernia (125)</td>
<td>~18</td>
</tr>
<tr>
<td>Osteoporosis (adults) (124)</td>
<td>10</td>
</tr>
<tr>
<td>Mitral valve prolapse (adults) (126, 127)</td>
<td>0–55</td>
</tr>
<tr>
<td>Breast cancer (adults) (16, 128)</td>
<td>Increased risk (~50 fold)</td>
</tr>
<tr>
<td>Mediastinal cancers (children) (22)</td>
<td>Increased risk (~500 fold)</td>
</tr>
<tr>
<td>Fractures (17, 18)</td>
<td>Increased risk (2–40 fold)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The hidden proportion of nondiagnosed patients should be kept in mind when studying the estimates given in this table. Ascertainment bias is present in all studies presented so far, and no separate study has presented more than 25% of a given population of KS individuals.

<sup>b</sup> Lanfranco et al. (8) found 8.4% of males with sperm in the ejaculate. Whether this translates into 8.4% of KS males being able to achieve a normal pregnancy is doubtful.
lished from the British cohort (16, 17). In the Danish cohort, mortality, morbidity, socioeconomic data, and criminality have been studied (18–21). Together, these studies show clearly that the average KS individual who comes to clinical diagnosis fares less well than his peers. The expected life span was found to be reduced by 1.5 to 2 yr, with increased mortality from a range of different disorders including diabetes, lung diseases, epilepsy, cerebrovascular disease, and vascular insufficiency of the intestine (17, 18). Mortality from breast cancer was greatly increased in the British cohort, as well as mortality from non-Hodgkin lymphoma and lung cancer (16). In a former study in the Danish cohort, the risk of breast cancer was not increased, but the risk of mediastinal tumor was greatly increased (22). The risk of being admitted to hospital was increased by 70% overall, and the highest risks of being admitted were due to congenital malformations and psychiatric, endocrine, and metabolic disorders (19).

In seeking to understand the basis for the increased morbidity and mortality, we studied the socioeconomic profile of the KS population compared with a large background population and found that KS men are characterized by shorter education, lower income, earlier retirement, more unemployment, and entering marriage less frequently and with fewer offspring. Mortality among KS men was significantly increased (hazard ratio, 1.9) and remained so after adjustment for cohabitation and educational status (hazard ratio, 1.5), indicating that socioeconomic parameters may explain some but not all the excess mortality in KS (20).

During the 1960s and 1970s, increased prevalence of KS and 47,XYY was found in prisons and institutions for mentally handicapped individuals, and a general increased rate of criminal behavior and an increased crime rate were reported among both cohorts, especially due to sexual crimes (23, 24). These studies were criticized because of ascertainment bias because they investigated institutionalized individuals and were hence disregarded as prejudicial. We wanted to investigate crime rates in our cohort of nearly 1000 KS men compared with a control group of nearly 100,000 age-matched men, simply to describe whether the prejudice of increased criminality was true or false. To our surprise, it was true; even after adjustment for some socioeconomic parameters, the crime rate for sexual abuse and arson was still significantly increased, whereas traffic offenses and drug-related crime were significantly decreased (21).

The Pituitary Testicular Axis

Males with KS are considered infertile; however, recent studies have shown that modern technology such as testicular sperm extraction followed by intracytoplasmic sperm injection can allow fatherhood in KS (25), and many couples also opt for adoption or the use of donor semen as a means of becoming parents (20). The most recent results with advanced technology show a sperm recovery rate of 66% (which is euploid in the vast majority), and 45% of these achieved a live birth of a child (26). If an increase in circulating testosterone, and thus also testicular testosterone, was achieved by treatment with either human chorionic gonadotropin or aromatase inhibitors, better results were observed (26). There are also indications that sperm may decline or disappear with age (27), which could be an argument for early retrieval of sperm by modern techniques. However, the pathophysiological background for the development of infertility and hypogonadism is still poorly understood. The “mini-puberty” seen in infants during the first 3 months of life, with a surge in testosterone, was at one point described as blunted in KS infants (28, 29); however, a more recent study did not confirm this finding (30). Typical testicular histology in KS is with hyalinization of semiferous tubules with loss of germ cells and Leydig cell hyperplasia; although focal spermatogenesis may be found with the possibility of surgical extraction of viable sperm (25). The hyalinization of the semiferous tubules probably occurs at midpuberty (31), which is usually timed correctly (32) with bi-testicular growth to approximately 6 ml and shrinkage thereafter to a pathological adult size of less than 6 ml as examined by ultrasonography (8). At the beginning of puberty, the levels of FSH, LH, and testosterone are normal, but FSH and LH start to increase and testosterone to decline compared with normal boys (33). In adult KS patients, levels of testosterone, insulin-like factor 3 (34), inhibin B (32), and anti-Müllerian hormone (35) are decreased, whereas FSH and LH are elevated and 17β-estradiol and SHBG are comparable to controls. The ensuing hypogonadism is relative rather than absolute, with the typical level of testosterone in the low normal range or subnormal (8, 36). Sexual dysfunction in KS is probably high, but it seems to be linked to low testosterone (37).

Glucose Homeostasis and Physical Fitness

An association between KS and diabetes has long been recognized. In 1969, Nielsen et al. (38) described an increased prevalence (39%) of a diabetic oral glucose tolerance test, whereas others found decreased insulin sensitivity and elevated fasting insulin levels in seven patients with KS (39). We recently described a strikingly high incidence of the metabolic syndrome and insulin resistance...
in 70 patients with KS compared with an age-matched control group. Almost half of the KS patients fulfilled criteria for the metabolic syndrome, whereas it was true for only 10% of the control group (36), findings corroborated by Ishikawa et al. (40). Most recently, a study on 89 pre-pubertal KS boys found 37% to have elevated low-density lipoprotein cholesterol, 24% with insulin resistance, and 7% meeting the criteria of the metabolic syndrome (41).

Cross-sectional studies have consistently reported an inverse relationship between plasma testosterone and insulin resistance in normal males (42). Type 2 diabetes is frequent in hypogonadal patients (19), and vice versa, hypogonadism is also more prevalent among type 2 diabetics with presumed normal karyotype than in age-matched controls (42). These findings are minimized (43), or even absent, in some studies (36, 44) when correcting for body mass index (BMI) or waist to hip ratio, and question whether this association is largely mediated by adiposity rather than testosterone itself. Indeed, testosterone treatment of hypogonadal patients with type 2 diabetes primarily improves insulin sensitivity in obese patients (45), but not in lean patients (46). This indicates that improvements in insulin sensitivity after therapy largely depend on the amount of “modifiable fat,” especially visceral fat. Conversely, in a recent meta-analysis encompassing several cross-sectional studies and some 2900 men, of whom 850 had type 2 diabetes, testosterone levels were significantly lower in type 2 diabetics even after controlling for age, BMI, and waist to hip ratio, whereas high testosterone levels were associated with a decreased risk of type 2 diabetes mellitus (47).

Indeed, there are indications that testosterone itself has direct effects on insulin sensitivity. In patients with hypogonadotropic hypogonadism, cessation of testosterone replacement therapy resulted in deteriorated insulin sensitivity within only 14 d (48). Other studies using a hyperinsulinemic euglycemic clamp found no effect on insulin sensitivity during short-term hypogonadism in healthy controls (49), whereas 1-wk treatment of healthy lean men with aromatase inhibitors resulted in slight supraphysiological testosterone levels and improved insulin sensitivity (50).

KS patients have altered body composition with increased total body and truncal fat (36) and decreased lean body mass accompanied by lower aerobic capacity and muscle strength in both biceps and quadriceps muscles (51). At present, no studies have examined the effects of testosterone treatment on muscle strength or other measures of physical fitness in KS patients. In a recent cross-sectional study of elderly men, low testosterone by multivariate analysis was associated with lower grip strength and hemoglobin, but not with 4-m walking speed or muscle mass (52). In hypogonadal elderly men, testosterone has been shown to increase hand-grip strength and physical performance during 36-month treatment (53) and to improve lower and upper body muscle strength (54). In addition, results from a recent randomized, placebo-controlled study suggest that testosterone treatment may prevent the age-related loss of muscle mass, strength, and physical function, and that it may improve quality of life in frail elderly men with low to borderline-low testosterone (55).

Combined, both epidemiological and clinical studies show clear evidence of a dramatically increased risk of diabetes and metabolic syndrome in KS. Available evidence does not support testosterone replacement therapy of KS patients with the aim of improving insulin sensitivity, but such effects may occur indirectly through favorable effects on body composition and physical fitness, although formal studies are not at hand in these patients.

Anthropometry and Body Composition

The KS phenotype varies greatly, and there is no exclusive symptom to define the syndrome. This might be one of the reasons why the syndrome is highly underdiagnosed, with less than 25% of adult male patients diagnosed (12). Many different phenotypic abnormalities have been associated with KS (Table 1). KS patients have an accelerated growth from early childhood and tend to become taller than controls. Final height tends to be greater in patients who initiated testosterone therapy after the age of 18 compared with patients treated from the time of puberty (56). The increased height is mainly attributed to abnormally long legs (8, 57). Although KS patients are abdominally obese, BMI may often be in the normal range due to an unfavorable muscle/fat ratio with decreased muscle mass and increased body fat, along with greatly elevated leptin levels (36). Greater body fat mass, however, is already present before puberty, pointing toward genetic influences on body fat in KS (58). In addition, we know that androgens can prevent the differentiation of pluripotent cells into an adipogenic lineage (59), whereas hypogonadism independently predicts development of abdominal adiposity in men with normal chromosomes (60). Conversely, testosterone treatment causes dose-dependent changes in fat-free mass (which inversely relates to increased testosterone levels), and treatment of middle-aged abdominally obese men reduces the amount of intraabdominal fat (61). Recently, a study in KS patients showed that testosterone treatment only partially corrected the unfavorable muscle/fat ratio, but these findings may be a result of the insufficient testosterone doses used (58). Lower levels of testosterone, free testosterone, and SHBG are found in obese
men compared with nonobese men (62), but the mechanism for lower testosterone in obese men remains unclear. In fact, it is still unclear how hypogonadism leads to abdominal adiposity and how the abdominal adiposity leads to decreased testosterone production, but both scenarios may be part of a self-perpetuating vicious circle—the so-called hypogonadal-obesity circle (63).

Despite the close relationship between testosterone and body composition, it is uncertain whether hypogonadal males and KS patients are comparable or whether genetic factors related to KS add another layer of complexity. Prospective studies in KS are needed to address these issues and perhaps clarify whether early androgen deficiency predisposes to the hypogonadal-obese insulin-resistant phenotype of KS, or whether other factors related to the sex chromosome trisomy are responsible. Such information will help clinicians decide the optimal timing and mode of hormone therapy to these patients.

### Bone mineralization

Decreased bone mass (51, 64–66) and outright fractures and osteoporosis affecting morbidity but also mortality (17–19) have long been linked to KS. This propensity toward low bone mass is readily explained by hypogonadism, fueling low physical exercise capacity and muscle strength (Fig. 1), and treatment with testosterone improves bone mineral density (BMD) (65), but future studies are needed to provide evidence for a positive effect on fractures and the development of osteoporosis as well. Speculatively, changes in thyroid functioning may exacerbate low BMD (67, 68).

### Neurocognitive function

The neuropsychological phenotype in boys and adults with KS is highly variable. The most radically impaired area is the verbal, which includes delay in early language development (69–75), learning disabilities in reading and spelling (74, 76–78), difficulties in production of syntax (78), word retrieval (78, 79), and nonsemantic cues in spoken language (80), resulting in a high degree of these boys getting speech and language therapy and special help in school (74, 79, 81–83). These disabilities in verbal cognitive function are probably part of the explanation for adults with KS being found to have a lower educational level (20, 84). The general cognitive ability seems to be close to normal levels, with a mean IQ of 87.9–110 (78, 85–94). Other cognitive problems include impairments in both verbal (86, 87) and nonverbal memory (78, 95) and in executive functions (90, 91, 95–98). Visual and spatial cognitive abilities are normal in boys and adults with KS (79, 87–89, 91), and arithmetic abilities are normal (89) or mildly impaired (83, 87, 97, 99).

A positive effect of testosterone therapy has been seen on behavior (100, 101), energy level (100), well-being (100), learning capacity (100, 101), and verbal fluency in patients with KS (102), whereas two other studies did not report any effects of testosterone treatment (89, 103). Data concerning the effect of testosterone therapy on brain volumes are sparse. A significant reduction in left temporal lobe gray matter volumes in untreated KS patients has been reported in one study (102), but this was not supported by another study (89). Thus, more studies are needed to investigate the effect of testosterone therapy on cognition and brain morphology. Several genetic mechanisms have been proposed to contribute to the neuropsychological phenotype, which include skewed X-chromosome inactivation, parental origin of the supernumerary X-chromosome, polymorphism of the androgen receptor gene CAG repeat, and a gene dosage effect of testosterone gene CAG repeat, and a gene dosage effect based on the presence of the extra X-chromosome. Skewed X-chromosome inactivation occurs in 9–21% of KS patients; however, due to the small number of KS subjects with skewed X-chromosome, no information on this is available (103). Regarding parental origin of the supernumerary X-chromosome, one study reported significantly higher speech and language problems in the group with paternal origin (104); however, other studies do not support these findings (70, 103). Short androgen receptor CAG repeat length was associated with stable partnership and professions that require higher educational levels (9); however, an association between the androgen receptor gene polymorphism and neuropsychological outcome is not supported by other studies (103, 104). A recent study found differentially expressed genes in KS patients showing significant correlations with verbal cognitive test scores (105). These interesting results need further confirmation by other studies.
Psychiatric morbidity

A review of studies of male psychiatric inpatients from the 1960s to the 1990s found a frequency of KS ranging from 0 to 4.8% (mean, 0.8%) among schizophrenic patients (106), a 4- to 5-fold increase compared with the prevalence of KS in the general population. Prospective studies of KS also reported higher rates of psychiatric referral among boys with KS (74), and in adolescence, 54% of KS males had mild to moderate psychiatric disorders (77). A register study reported that individuals with KS have an increased hazard ratio of 3.65 (95% confidence interval, 2.92–4.55) of being hospitalized with a psychotic disorder (19). Studies on unselected KS boys and adults for psychiatric disorders support this by finding a significantly increased prevalence of schizotypal traits, schizophrenia symptoms, psychotic disorders (93, 95, 107, 108), depressive disorders (107, 108), anxiety disorder (108), autism spectrum diseases (94, 108, 109), and attention deficit/hyperactivity disorders (91, 92, 108). Recently, two studies have investigated the relationship between parent-of-origin of the extra X-chromosome and the psychopathology seen in KS patients (107, 108) and found conflicting results.

Clinical care

We believe that treatment and care of patients with KS is a multidisciplinary task that ideally should involve speech therapists, psychologists, general practitioners, pediatricians, endocrinologists, urologists, and infertility specialists. Infants with KS are rarely diagnosed because they lack KS-specific stigmata. Rarely, however, KS boys have micropenis, which can be treated successfully with topical testosterone cream or single injections with im testosterone (110). The most serious problem in early childhood is the delay of speech development and learning problems affecting perhaps half of the boys with KS (74). Careful observation is needed to refer these boys to speech therapists if delay of speech is observed. The same holds true for learning disabilities that were observed in 77% of boys with KS followed from birth to adulthood (74), and it is necessary to develop schemes to enhance learning in schools.

### TABLE 2. Testosterone preparations available and suggested dosages for adults

<table>
<thead>
<tr>
<th>Substance</th>
<th>Brand name (manufacturer)</th>
<th>Format</th>
<th>Route of administration</th>
<th>Suggested dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone undecanoate</td>
<td>Andriol (Organon, Oss, The Netherlands)</td>
<td>40-mg capsule</td>
<td>Oral</td>
<td>120–160 mg/d</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Nebido (Schering, Berlin, Germany)</td>
<td>1000-mg injection</td>
<td>Intramuscular</td>
<td>1000 mg every 9–16 wk</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>Testoviron (Schering, Berlin, Germany)</td>
<td>250-mg injection</td>
<td>Intramuscular</td>
<td>250 mg every 2–4 wk</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testim (Ipsen, Paris, France)</td>
<td>Gel</td>
<td>Skin</td>
<td>50 mg/d</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testogel (Laboratoires Besins, Paris, France)</td>
<td>Gel</td>
<td>Skin</td>
<td>50 mg/d</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Tostran (ProStrakan, Galashiels, UK)</td>
<td>Gel</td>
<td>Skin</td>
<td>40–60 mg/d</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Implants (Organon, Oss, The Netherlands)</td>
<td>Pellets</td>
<td>Subcutaneous</td>
<td>400–800 mg every 4–6 months</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Striant (Columbia Laboratories, Livingston, NJ)</td>
<td>Buccal adhesive</td>
<td>Buccal</td>
<td>60 mg/d</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Androderm (Watson Pharma Inc., Corona, CA)</td>
<td>Transdermal patch</td>
<td>Skin</td>
<td>5–15 mg/d</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testoderm (Alza Corp., Mountain View, CA)</td>
<td>Transdermal patch</td>
<td>Scrotal skin</td>
<td>2.5–10.0 mg/d</td>
</tr>
</tbody>
</table>

For children and adolescents, lower doses should be given (118). Some preparations are not available in all countries.

### TABLE 3. Outpatient program for patients with KS

**At baseline**
- Confirmation of karyotype, if necessary
- Sex hormones: testosterone, estrogen, SHBG, FSH, and LH
- Fasting glucose, lipids, and HbA1c
- Thyroid status, hemoglobin, hematocrit
- Physical examination including BP, height, weight, waist, testes, gynecomastia, and varicose veins
- Bone densitometry (DEXA scan) and vitamin D status, p-calcium
- Information about the syndrome
- Initiation of androgen treatment (injections, transdermal, or oral)
- Questions about well-being, physical activity, energy, sexual activity, libido, socioeconomic situation
- Echocardiography if deemed necessary
- Discussion of fertility issues often resulting in referral to a fertility clinic
- Consider referral to plastic surgeon for correction of gynecomastia
- Consider referral to psychologist

**Annual (every 3 months initially)**
- Physical examination including BP, height, weight, waist, and gynecomastia
- Sex hormones: testosterone, estrogen, SHBG, FSH, and LH (nadir values)
- Fasting glucose, lipids, and HbA1c
- Thyroid status, hemoglobin, hematocrit
- Questions about well-being, physical activity, energy, sexual activity, libido
- Every second year or up to every tenth year
  - Bone densitometry (DEXA scan) and vitamin D status, p-calcium

HbA1c, Glycosylated hemoglobin; BP, blood pressure; DEXA, dual-energy x-ray absorptiometry.
We suggest initiation of testosterone treatment at the beginning of puberty, as FSH and LH start to rise, to secure a proper masculine development of sexual characteristics but also to secure a sufficient increase in BMD and muscle bulk to prevent subsequent osteoporosis. It is very important to discuss fertility, and postponement of treatment may be an option if one wants to retrieve viable sperm at this stage. Testosterone treatment in pubertal KS boys has also been reported to increase energy and endurance and to improve mood, concentration, and relations to others (111), and it seems that there are increased psychosocial problems in periods without testosterone treatment in pubertal KS (112).

We advise lifelong treatment in order to prevent osteoporosis, obesity, metabolic syndrome, and diabetes. However, this practice is not evidence-based. Treatment in young hypogonadal men has been shown to have a positive impact also on fat mass, muscle mass, and muscle strength, as well as sexual activity and related areas, and it improves positive aspects of mood (113). In older hypogonadal males, there are also limited data to suggest positive effects of treatment on visuospatial cognition and verbal memory (114). Although some KS patients have normal testosterone values, virtually all have increased gonadotropin levels. Some with KS may not realize that they have symptoms, and only after a trial period of treatment do they see the benefits of treatment. We believe that all KS patients should receive testosterone treatment if their gonadotropins are elevated, although their testosterone levels may be within the lower end of the normal range (115), using bivariate charts of testosterone vs. LH for proper dosage (116). Certainly, patients should be treated if they are suffering from hypogonadal symptoms (lack of energy, decreased libido, and also including abdominal adiposity, etc.).

### TABLE 4. Major issues in KS

<table>
<thead>
<tr>
<th>Problem</th>
<th>Possible solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will early diagnosis lead to better outcome?</td>
<td>Prospective screening studies with health technology assessment with reference to medical ethics</td>
</tr>
<tr>
<td>Late diagnosis and nondiagnosis Poor learning in school</td>
<td>Examination of dried blood spots with new molecular genetic techniques Early diagnosis leading to better learning schemes and perhaps early treatment with T</td>
</tr>
<tr>
<td>Effect of T</td>
<td>Randomized clinical trials with T and placebo with study of numerous variables</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Randomized clinical trials with T and placebo</td>
</tr>
<tr>
<td>Poor socioeconomic outcome</td>
<td>Improvements in schooling and possibly early treatment</td>
</tr>
<tr>
<td>Increased morbidity</td>
<td>Improvements in adult care with multidisciplinary approach</td>
</tr>
<tr>
<td>Infertility</td>
<td>Improved understanding of pathophysiology of germ cell loss through animal models; better testicular sperm extraction techniques</td>
</tr>
</tbody>
</table>

T, Testosterone.
Our clinical outpatient program for patients with KS is presented in Table 3. Initially, testosterone treatment should be followed with visits every 3 months until testosterone dose is adjusted, and thereafter annually.

**Perspectives**

Our perception of KS is changing, and the way we see KS today is multifaceted with much new knowledge being added in recent years (Fig. 2). A number of issues need to be resolved in KS (Table 4), and large, possibly international, collaborations are suggested in this regard. Not a single randomized, placebo-controlled study addressing the effects of testosterone in KS patients has been published. We propose randomized, placebo-controlled studies on adults with KS, with testosterone preparations that will restore testosterone to normal values, in a population large enough to detect small changes in BMD, body composition, insulin sensitivity, and also modalities of quality of life. The recently established animal models are exciting and could shed new light on fertility (119), bone morphology (120), and brain functioning and learning difficulties (121), as well as other issues. The delay in diagnosis and outright nondiagnosis is also problematic—we need to devise programs to improve the advent of early diagnosis, and we think that new approaches, such as pervasive testing of all neonatal dried blood spot samples with new molecular genetic techniques, should reduce the costs substantially in comparison with karyotyping (122). However, before such an approach is implemented, it is important to discuss whether or not early diagnosis will in fact lead to a better outcome, and to that end we dearly need more scientific data. We need large, prospective, nationwide screening studies with health technology assessment. Hopeful scientific data. We need large, prospective, nationwide screening studies with health technology assessment. Hopefully, future studies will provide the evidence that is essential for optimizing the treatment of KS patients.

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