INTRODUCTION

In 1942, Klinefelter and Albright reported that nine men had a “Syndrome characterized by gynecomastia, aspermatogenesis without Leydigism and increased excretion of follicle-stimulating hormone”. Karyotype analysis elucidated that this syndrome was caused by an extra X chromosome (XXY). The classic form (nonmosaic type) of Klinefelter syndrome (KS) is observed in one per 660 births, with up to 3%-4% occurring in infertile men and 10%-12% occurring in nonobstructive azoospermia (NOA). A study on the KS prevalence in Japan found a lower prevalence at 60 per 100 000, indicating the presence of racial differences. KS is the most common sex chromosome abnormality associated with male infertility, and men with KS have been shown to be potentially fertile by using a testicular sperm and intracytoplasmic sperm injection (ICSI) protocol. Approximately 85% of KS cases are due to a single aberrant X chromosome (47,XXY), whereas the remaining 15% display multiple aneuploidies (48,XXXXY; 48,XXYY; 49,XXXXXY), causing the development of more severe phenotypes, which are usually diagnosed during prenatal and infantile periods as abnormalities of the external
genitalia. A structurally abnormal X chromosome (eg, 47,iXq,Y) or mosaicsms (eg, 47,XXY/46,XY) are also included in KS. The origin of the aberrant X chromosome in KS, of either paternal or maternal origin, and how the presence of a supernumerary X chromosome causes the phenotype and morbidity in KS are not fully understood.

The multiple aneuploidies causing the abnormalities of external genitalia and children with KS with severe intellectual and behavioral problems are relatively rare compared with other cases of male infertility, usually NOA. These are symptoms often present among men with KS, and in most of the cases, lead to its diagnosis during the workup for infertility. Less than 10% of these patients are diagnosed before puberty. On the other hand, we should not forget that KS is also responsible for general comorbidities related to metabolic and psychological disorders and risks of specific malignancies, which, in part, are caused by low testosterone in KS patients. As microdissection testicular sperm extraction (micro-TESE) has been shown to be an ideal sperm retrieval method by many urologists and, in Japan, gynecologists, the chances of low-testosterone-related symptoms and comorbidities are increasing. The testicular size is significantly smaller and serum testosterone levels are lower in KS patients compared to those in other NOA cases; thus, a post-micro-TESE decline in testosterone is enhanced in KS patients. Unfortunately, we often see many KS patients who claim to have impaired sexual function, general fatigue, and comorbidities after micro-TESE, and they are not properly followed up after micro-TESE irrespective of the results of sperm retrieval. Diagnosing KS should be the beginning of a strict follow-up of general health; however, reproductive medicine has caused new and severely low levels of testosterone in men with KS in the era of assisted reproductive technologies (ART).

Data related to infertility treatment are apt to be focused on the sperm retrieval of KS. The purposes of this review are to understand the background pathophysiology of KS patients, including how they grew up, which symptoms occurred before they were treated for infertility, what information is available after their infertility treatment, and finally how they should be managed for lifelong basis.

2 | KS AND INFERTILITY TREATMENT

For a long time, KS was considered to be an absolute infertility condition once diagnosed. In 1996, Tournaye et al reported a successful testicular sperm retrieval by conventional TESE in men with KS. One year later, Palermo et al reported the first pregnancy and live birth resulting from a KS father after TESE/ICSI. A recent review reported by Majzoub et al indicated that publications from many different centers documented sperm retrieval rates (SRRs) in KS adults of approximately 50%-70%, which are higher than those of general NOA cases, and reported excellent pregnancy rates and healthy 46,XY or 46,XX offspring. A recent meta-analysis has shown an overall SRR of approximately 40%, ranging from 1% to 50%, in both conventional TESE and micro-TESE. These results indicate that micro-TESE, but not conventional TESE, is an ideal method to retrieve sperm from men with KS. A survey conducted on Dutch patients reported that the majority of KS patients and their partners would like to have a positive attitude toward TESE/ICSI to conceive a child.

The age at micro-TESE is the only parameter to predict successful sperm retrieval. Okada et al reported that the SRR was 81% in patients 25-29 years of age, 73% in patients 30-34 years of age, 25% in patients 35-39 years of age, and 22% in men 40-44 years of age, and proposed that micro-TESE should be performed before 35 years of age in men with KS. Data from the Cornell group showed that the SRR in men with KS was 71% in the 22- to 30-year age-group, 86% in the 31- to 35-year age-group, and 50% in the 36- to 50-year age-group. In fact, age affects the SRR, but the data are not bleak.

The hormonal pattern and testicular volume have been advocated as possible prognostic factors for successful SRR in KS patients. Rohayem et al reported that the combination of total serum testosterone above 7.5 nmol/L and LH levels below 17.5 U/L resulted in higher retrieval rates of spermatozoa by micro-TESE in both adolescents and adults with KS. Similar results were more recently reported by Cissen et al. Interestingly, Rohayem et al did not document any clinical difference in nonmosaic KS patients with or without spermatozoa in their seminal fluid. The lack of prognostic value of the FSH levels might be related to the low inhibin B levels (which is almost undetectable during early puberty) in all patients with KS, which does not allow for the negative feedback of FSH secretion.

It should be recognized that postoperative testicular damage leading to a decrease in testicular function has been described as a complication of micro-TESE. The transient but statistically significant decrease in testosterone levels indicates that men are at risk of developing hypogonadism after micro-TESE, but there is insufficient evidence for whether patients actually experience clinical symptoms in the case of decreased serum testosterone levels. One apparent parameter to predict post-micro-TESE hypogonadism is KS, and a recent meta-analysis has shown that men with KS and men with NOA had the strongest decreases in total testosterone levels at 6 months after TESE. The largest disaster regarding this issue is that a majority of men with KS are not properly followed up after micro-TESE, which will be addressed in another section in this review.

3 | PRENATAL, INFANTILE, AND PEDIATRIC PERIODS

The opportunity for physicians to diagnose and manage KS may occur even during the prenatal period, as the diagnosis is sometimes established by prenatal genetic information. The recent development of noninvasive prenatal screening is anticipated to increase the number of couples seeking counseling; however, a discussion on whether to abort has never occurred in KS cases.

Studies in KS infants have found that the postnatal temporary surge in gonadotropins (“mini-puberty”) may be accompanied by low testosterone levels or normal testosterone levels. Simultaneously, FSH levels increase at 2-3 months after birth,
followed by a subsequent rapid decline. This early exposure of androgens is severely disturbed with an increase in the number of X chromosomes. Genital anomalies (microphallus, undescended testis, bifid scrotum, and hypospadias) might present at birth, but whether they are due to the effects of supernumerary X chromosome(s) or androgen deficiency during the fetal period remains undetermined. Figure 1 shows a case of a KS baby with 49,XXXXY that was referred to us for the evaluation of sex development disorders. He underwent bilateral orchiopexy and two-stage hypospadias repair, and he can now void at standing position. On the other hand, individuals with mosaic KS tend to present with milder symptoms.

Basically, testosterone-related symptoms do not occur during infancy or early pediatric periods. Signs and symptoms appearing during this period, such as longer legs, disturbance of speech and cognition, adaptation problems, attention deficits, and social skill impairments, have been attributed to the genetic abnormality rather than to hypogonadism. As a result, men with KS are prone to learning difficulties, and their academic and professional status achievements are reported to be inferior to those without KS; however, this finding has not been fully investigated, and men with KS who visit our infertility clinic, of course they are only limited cases of KS, are always highly educated and talented. The management of children with KS warrants the collaboration of a multidisciplinary team consisting of pediatricians as well as behavioral specialists to ameliorate the developmental defects in early life. In addition, an echocardiographic study should be performed to reveal congenital cardiovascular abnormalities.

Although multidisciplinary treatment for each child with KS should be administered and testosterone may not play a major role in the treatment of KS during this period, there are some anticipated benefits of testosterone replacement therapy (TRT) on the improvement of the energy level, attention span, mood, and cardiac health of young KS patients. Recently, two reports have indicated that early TRT may be beneficial for developmental and behavioral issues in boys with KS without serious adverse effects. However, there is concern that TRT might cause obstructive sleep apnea and venous thromboembolism. In addition, there is evidence that TRT in boys with KS is not as effective as that observed in males with a normal karyotype, at least regarding body proportions and bone mineral density (BMD). Studies that apply population-based genetic screening should be performed to investigate a proper evaluation of the costs and benefits of such an approach in KS patients. Randomized controlled trials are also needed to evaluate the efficacy of TRT on different aspects of the symptoms, to determine optimal dose regimens and, most importantly, to prevent the impairment of spermatogenesis or to stimulate future spermatogenesis in boys with KS. In this situation, psychological aspects regarding their future reproductive function should be taken into consideration to avoid negative impacts on reproductive health, and follow-up should be performed by a specialized team consisting of pediatricians, adult endocrinologists/andrologists, and psychologists during the transition from pediatric and adolescent periods to adulthood.

4 | ADOLESCENT PERIOD

Although the onset of puberty in KS patients occurs at the same time as that in normal boys, hypogonadism remains silent until pubertal onset because testosterone levels are usually sufficient for satisfactory development of the body and genitalia. Additionally, the severity of low-testosterone-related symptoms is mild in KS patients during the adolescent period, unlike in male hypogonadotropic hypogonadism. Furthermore, the negative feedback elevation of LH activates aromatase, resulting in an increase in estradiol, which may contribute to the development of gynecomastia. At puberty, only a few patients notice overt hypogonadism signs, such as poor muscle development, a short penis, and a lack of or sparse pubic, axillary, and facial hair. Low-to-normal testosterone levels contribute to the development of tall stature and distort the ratio between the upper and lower skeletal segments. On the other hand, Bojesen et al reported that 65%-85% of KS patients present overt hypogonadism after the age of 25, and this number might differ among countries and according to the circumstances surrounding KS patients.

Along with LH, FSH is increased via the negative feedback mechanism of testosterone, estradiol, and inhibin B, which ultimately cause the hypergonadotropic levels observed in adult KS patients. Additionally, we suspect that some disturbances in testicular development occur during this period. The testes of KS adolescents can develop to a volume of 6 mL due to the proliferation and maturation of Sertoli and Leydig cells, which is considered to be normal initial testicular development. Rising intratesticular testosterone levels are subsequently followed by an accelerating decline in germ cells,
hyalinization of the tubules, degeneration of Sertoli cells, and hyperplasia of Leydig cells,\(^{47}\) resulting in the loss of testicular volume and a decrease in serum testosterone levels. It is still unclear why the rise in serum or intratesticular testosterone during puberty is associated with accelerated destruction of the seminiferous tubules during this period.\(^{48}\) Lue et al\(^{49}\) suggested that germ cell defects occurred secondary to a defect in spermatogonial migration during the postnatal period and not the prenatal period in XXY mice. On the other hand, normal spermatogenesis in KS can potentially be explained by the following three mechanisms: (a) Occult intratesticular mosaicism in which 46,XY spermatogonia are able to differentiate normally into mature sperm\(^{50};\) (b) Spermatogenesis arising from 47,XXY spermatogonia. It has previously been demonstrated that 47,XXY spermatogonia and spermatocytes are able to enter the spermatogenic process, leading to the formation of mature sperm\(^{51};\) and (c) Active repair of testicular stem cell renewal via the silencing or loss of the extra X chromosomes.\(^{52}\) This phenomenon causes the presence of ejaculate sperm during the adolescent period in some KS patients, which leads to the hypothesis that SRR by TESE might be superior during the adolescent period rather than in the adult period to preserve future fertility potential.

## 5 IS TESE DURING ADOLESCENCE EFFECTIVE IN KS PATIENTS?

Limited data suggest that sperm production in men with KS, as determined by the results of TESE, is rapidly impaired after a certain age (approximately 35 years of age), and it might be better to retrieve sperm as soon as the diagnosis is made. This suggestion was generated from data reported by Okada et al.\(^{14}\) In their study, the SRR in 25 patients >35 years of age was only 23%. On the other hand, data from Cornell University showed that the SRR in men with KS was 71% in the 22- to 30-year age-group, 86% in the 31- to 35-year age-group, and 50% in the 36- to 50-year age-group. In our experience, the SRR in 84 men with KS was 61% (11/18) in the 21- to 30-year age-group, 55% (21/38) in the 31- to 35-year age-group, 52% (14/27) in the 36- to 50-year age-group, and 100% (1/1) in 52-year-old men. Based on these results, spermatogenesis in men with KS declines gradually and not rapidly. Taking these results together with the biological information that progressive hyalinization of seminiferous tubules is observed after puberty in men with KS,\(^{47,48}\) it has been suggested that performing earlier TESE procedures might result in better SRR results.\(^{17}\) A meta-analysis has shown that successful SRR in KS patients is independent of age.\(^{12}\)

Several studies have reported the presence of sperm by ejaculation in adolescents and young adults with KS.\(^ {15,53,54}\) and these sperm should be cryopreserved for future treatment. However, problems arise in KS adolescents who have never performed masturbation or whose semen analysis results in azoospermia. In this situation, TESE is an option for evaluating spermatogenesis and sperm retrieval. In 2001, Damani et al\(^{55}\) first reported the results of TESE in a 15-year-old adolescent to preserve fertility before TRT for the symptoms of hypogonadism. In 2004, Wikstrom et al\(^{47}\) performed a single-site testis biopsy for histologic analysis in 14 adolescents with KS, which is the same procedure used for conventional TESE, and reported that no mature sperm were observed in any tissue sections. In this study, a few types of Ap and Ad spermatogonia were found in seven boys aged 10-12.5 years, whereas no spermatogonia of any type were detected in the other seven boys aged 11.7-14 years, and they concluded that diploid germ cells vanished in early puberty in boys with KS.\(^{47}\) In 2012, Gies et al\(^ {54}\) reported data from testicular biopsy in seven boys aged 10.2-15.6 years, and they could not find any mature sperm; however, they could identify spermatogonia upon histologic analysis in four of the boys. In 2013, Rives et al\(^{55}\) published their results in five adolescents with KS who underwent bilateral conventional TESE and noted that sperm were found in a 16-year-old boy, elongated spermatids and spermatocytes were found in a 15.5-year-old boy, and no germ cells were found in the remaining three boys aged 15-16.5 years. In the same year, Van Saen et al reported that no mature sperm were found in adolescents boys with KS, but 72% (5/7) of the patients, boys with KS from 13 to 16 years of age, presented with spermatogonia. The overall number of spermatogonia in the boys with KS was significantly reduced compared with that in normal adolescent boys.\(^{58,59}\)

The micro-TESE procedure performed in adolescent boys with KS was first performed by a Cornell group and reported by Mehta et al in 2013. Ten KS patients aged 14-22 years underwent micro-TESE, and mature sperm were found in seven patients (SRR: 70%).\(^ {60}\) A subsequent publication from the same institution showed a 65% retrieval rate in 127 KS adult men, which was the same rate of success for adolescents and adults.\(^ {51}\) Plotten et al\(^ {62}\) investigated the largest series to date comparing SRRs at the same institution for young KS patients aged 15-23 years and adult KS patients more than 23 years of age and found SRRs of 52% and 62%, respectively, which were not significantly different. In the same year, Rohayem et al\(^ {18}\) reported the results of micro-TESE in 50 adolescents from 13 to 19 years of age, and the SRR was 38% (19/50). Their result was interesting because the SRR was 10% (1/10) in the subgroup of adolescents between 11 and 14 years of age, whereas in the adolescents between 15 and 19 years of age, the SRR was much higher at 45% (18/40). Most recently, Nahata et al\(^ {55}\) reported a 50% SRR in 10 adolescent boys with KS between 15 and 23 years of age and indicated no distinct pattern or prediction based on the clinical data. The accumulated data from these publications showed that total SRRs by conventional TESE were 30% (15/50) and 42.6% (29/68) by micro-TESE, which is summarized in Figure 2. It is clear that micro-TESE has a substantial advantage for retrieving sperm, but the risks and benefits of the procedure must be considered. Information related to reproductive outcomes is still lacking; for example, the ICSI results related to using frozen sperm, how many KS patients have successful sperm retrieval, how many KS patients are married, and how many KS patients could have a child born live have not been determined. Experimentally, there are several options for cryopreservation of spermatogenic stem cells from either a testicular cell suspension or testicular tissue. However, there are no reports of inducing haploid
cells in vitro using 47,XXY spermatogonia. In summary, fertility preservation techniques for adolescent boys with KS are still experimental, and use of the cryopreserved material when the boys reach adulthood cannot be guaranteed.

One dilemma in the management of adolescent KS patients is the negative effect of TRT on spermatogenesis. TRT has previously been reported to have a negative impact on the future fertility of KS patients, as an SRR of 20% was observed in five adults with KS.63 In contrast, Plotton et al.62 found no negative influence of TRT on sperm retrieval in 41 KS patients and reported an SRR by micro-TESE in 9/17 (52.9%) men with previous TRT and a positive TESE in 14/24 (59.1%) men with KS who never had TRT. TRT was stopped 9 months prior to micro-TESE. Another study included 10 KS adolescents who received continuous topical testosterone replacement and/or an aromatase inhibitor and found mature sperm by micro-TESE in seven of 10 participants (70%).60 Considering these results together, TRT is unlikely to have a permanent negative impact on spermatogenesis, but larger studies and other medical treatment (e.g., gonadotropins, clomiphene, other aromatase inhibitors) are warranted to confirm these findings.

Most importantly, we must consider how patients and their families feel about fertility preservation, especially in cases in which micro-TESE needs to be performed. A psychosocial investigation clearly demonstrates a high incidence of negative feelings toward infertility and its effect on overall life satisfaction and well-being.64 Two other studies have shown that reproductive function is not an issue of awareness in adolescent boys with KS, whereas their parents and physicians appreciate fertility preservation at a young age.57,65

6 | POSTINFERTILITY MANAGEMENT: DIAGNOSIS OF KS IS A PROXY OF GENERAL HEALTH

A 26-year-old man with KS was referred to our clinic and complained of decreased libido and general fatigue. His testicular size was 0.5 mL bilaterally, and his total testosterone concentration was 15 ng/dL. He underwent micro-TESE at an IVF clinic 6 months prior to visit at our clinic, and his preoperative total testosterone level was 276 ng/dL. Unfortunately, no sperm were found in his testes, and his management was stopped at the clinic. At our hospital, he started TRT every 3 weeks, and his symptoms were dramatically improved. This type of case is not rare but rather very common in our urology department. What are the problems in this case?

In addition to reproductive medicine, many urologists in Japan are engaged in general urology as well as nephrology, hemodialysis, and renal transplant, which enables a quick start to the management of comorbidities, such as hypertension, diabetes, dyslipidemia, and hyperuricemia, in most men with KS after infertility treatment.
(Figure 3). If micro-TESE is performed at an IVF clinic by either a urologist or gynecologist, patients are recommended to visit the urology/andrology or endocrinology department as soon as possible for follow-up for an extended period. In other words, micro-TESE induces new and severely low testosterone levels in recipients. Furthermore, we must make every effort to improve our ability to diagnose KS. The high frequency of mild KS phenotypes explains, at least in part, why a majority of the patients remain undiagnosed. A distinct racial difference in the prevalence of KS and the patterns of symptoms during the pediatric and adolescent periods are still unclear; in our experience, the BMIs of men with KS who visited an infertility clinic are obviously low (approximately 23) compared with

| TABLE 1 Comorbidity of Klinefelter syndrome (KS) |
|-----------------------------------------------|
| **Findings** | **References** |
| Cancer |  |
| Extranodal germ cell tumors | Nonseminomatous subtype Younger than non-KS | Nichols (1987)\(^{103}\) |
| Breast cancer | 4- to 60-fold compared with non-KS Younger than non-KS | Swerdlow et al (2005)\(^{94}\) Brinton (2011)\(^{73}\) Sasco et al (1993)\(^{74}\) Gomez-Raposo et al (2010)\(^{75}\) |
| Metabolism |  |
| Obesity, metabolic syndrome | Abdominal fat is increased 4- to 5-fold compared with non-KS Odds ratio of 2.3 with low testosterone Effect of TRT on BMI is controversial | Bojesen et al (2006)\(^{70}\) Akslaeide (2008)\(^{104}\) Laaksonen (2014)\(^{105}\) Pasquali et al (2013)\(^{38}\) |
| Diabetes | 8%-50% in Western countries 3.9%-4.1% in Japan HR of 2.21 for T1D and 3.71 for T2D Prediabetes is more frequent No effect of TRT | Takeuchi (1999)\(^{106}\) Lichiardopol (2004)\(^{107}\) Swerdlow et al (2005)\(^{94}\) Bojesen et al (2006)\(^{70}\) Pasquali et al (2013)\(^{38}\) |
| Cardiovascular disease |  |
| Congenital abnormalities | Mitral valve prolapse Diastolic dysfunction | Fricke (1981, 1984)\(^{108,109}\) Pasquali et al (2013)\(^{38}\) |
| Conduction defects | Short QTc interval Atrial fibrillation | Jorgensen (2015)\(^{93}\) Liu (2010)\(^{110}\) Lai (2009)\(^{111}\) |
| Thrombosis | Hazard ratio of 3.6 to 5.7 for pulmonary thrombosis Hazard ratio of 6.6 to 7.9 for deep vein thrombosis | Bojesen et al (2006)\(^{70}\) Swerdlow et al (2005)\(^{94}\) Campbell et al (1981)\(^{35}\) |
| Bone disease |  |
| Osteoporosis/fracture | Decreased bone mineral density Femur fracture 8-fold increase compared with non-KS Low levels of 25-OH vitamin D | Bojesen et al (2006)\(^{70}\) Swerdlow et al (2005)\(^{94}\) Bojesen and Gravholt (2011)\(^{58}\) Ferlin et al (2015)\(^{98}\) |
| Immunological diseases |  |
| Autoimmune diseases | 13-fold increase in systemic lupus erythematosus compared with non-KS Rheumatic diseases Addison's disease Diabetes mellitus type 1 Multiple sclerosis Acquired hypothyroidism Sjogren's syndrome | Scofield (2008)\(^{112}\) El-Mansoury (2005)\(^{113}\) Sawalha et al (2009)\(^{100}\) Rovensky et al (2010)\(^{101}\) Seminog et al (2015)\(^{102}\) |

TRT, testosterone replacement therapy.
those described in data from the United States and Europe (approximately 24-30). Investigations regarding the patterns of comorbidity and the TRT treatment regimen for KS patients from Japan and Asian countries are warranted.

Based on data from epidemiological studies, KS is associated with increased morbidity and mortality although all the information collected regarding KS is derived from diagnosed cases comprising only approximately 25% of the expected affected number of patients. In other words, the diagnosis of KS at the time of infertility treatment is a special opportunity to evaluate their general health, and patients and medical providers should begin follow-up and the management of comorbidities. Multidisciplinary management is needed for lifelong follow-up (Figure 3).

Comorbidities associated with KS, such as metabolic syndrome, diabetes, osteoporosis, and cardiovascular diseases, often appear in adulthood, with many of the patients being of reproductive age; these comorbidities increase with age. It is ultimately related to a significant increase in mortality risk. Actually, men with KS require more frequent hospitalization, and the life span of KS patients appears to be shorter by approximately 2.1 years compared to that of the general population. 68 The main comorbidity associated with increased mortality risk is the increased prevalence of type 2 diabetes and thrombosis/embolism disorders, both of which are risk factors of cardiovascular events. 69 Other conditions increasing the morbidity of men with KS are osteoporosis and bone fractures as well as the higher prevalence of specific types of cancer and immunological diseases (Table 1). The reason for this impaired mortality is not well understood, and further investigations are needed to clarify whether it is due to the syndrome per se or is mainly a consequence of low testosterone levels. A number of reports show that low testosterone is a biomarker for increased mortality in normal healthy men. 70

In addition to the comorbidities mentioned above, the loss of muscle and a depressed mood due to low testosterone are not directly related to mortality but are associated with a markedly decreased quality of life. 71 Of note, from observational studies, some positive effects of TRT in KS have been reported, including decreased fatigue, less irritability, and improved libido, muscle strength, and sleep. 72,73 The general consensus indicates that most men with KS should be offered TRT around the time of puberty with a target testosterone level in the high normal range. 45 However, no randomized placebo-controlled trials have been performed to date to verify this recommendation, and data on future spermatogenesis remain unknown. As a result, the timing of the initiation and the dose of TRT in KS patients remain topics for further investigation. Specifically, a study on treatment during the pediatric period showed promising results for improving behavior and neurodevelopment, 33 and this treatment could have an overall positive effect on social integration during the pediatric and adolescent periods and, presumably, also in adult life.

### 6.1 KS and cancer

Breast cancer and germ cell tumors, especially extragonadal tumors, occur more frequently in KS patients than in the general population (Table 1). Several meta-analyses concerning the prevalence of male breast cancer have shown the incidence of breast cancer in KS to be increased 4- to 30-fold compared with that in normal men, which supports that KS is the strongest independent risk factor for breast cancer in males. The mean age of breast cancer onset in KS patients is 58 years, which is earlier than the mean age of healthy men (67 years of age). The early diagnosis of breast cancer requires monthly breast self-examination and a periodic physical examination by a specialized physician. 75 A markedly increased prevalence of germ cell tumors in KS patients has been confirmed in pathology-based studies, and nonseminomatous tumors are the major pathological type. Additionally, the diagnosis occurs at a younger age in KS patients than in normal healthy men. A recent Italian consensus suggests a biannual chest X-ray to address the risk of extragonadal germ cell tumors.

On the other hand, the prevalence of prostate cancer and the associated mortality have been reported to be lower in KS patients than in normal healthy men. The reason for these lower rates may be because the presence of hypogonadism does not stimulate the growth of prostate cancer cells, whereas recent studies cast doubt on the correlation between intraprostatic testosterone levels and the carcinogenesis and progression of prostate cancer. Interestingly, the level of prostate-specific antigen, a marker of prostate cancer, stays below the normal range regardless of the presence of TRT. 83

### 6.2 KS and diabetes

In the general population, a clear relationship between the serum testosterone concentration and insulin sensitivity has been reported. Low testosterone levels are associated with increased insulin resistance, and the onset of insulin resistance may be influenced by testosterone levels. Serum testosterone levels are independently associated with insulin resistance, suggesting that low testosterone might be responsible for diabetes (in this review, type 2 diabetes), and a 5-fold increase in metabolic syndrome has been observed in men with KS. After a diabetes diagnosis, atherosclerosis progressively follows, requiring the evaluation of endothelial function.

We expect and hope for a high efficacy of TRT on glucose metabolism. Some studies have reported that the actual treatment for low testosterone improves metabolic risk factors and insulin resistance in some individuals, but not all studies have shown positive results. Unfortunately, KS is a condition in which TRT does not have positive effects on glucose metabolism. In a study reported by Pasquali et al that included 48 men with KS and 21 men with hypogonadotropic hypogonadism who were all treated with TRT for 3 years, KS patients were more insulin resistant, had increased body fat and lower levels of HDL, and showed an increased prevalence of metabolic syndrome than those with hypogonadotropic hypogonadism treated with TRT. Compared to other types of hypogonadism, TRT has not been shown to improve metabolic syndrome or diabetes in KS patients, indicating either a potential hormonal resistance,
consistent with the accompanying elevated gonadotropins, an increased aromatization, or more simply, that testosterone is not involved in the glucose metabolism of KS, and more complex and unrevealed mechanisms exist that are associated with KS and glucose metabolism. However, information regarding the effect of TRT on glucose metabolism in Japanese men with KS is lacking, and investigations are needed to determine optimal therapeutic regimens and follow-up schedules for Japanese patients.

6.3 | KS and cardiovascular disease

A number of reports indicate that KS is closely associated with CVD and abnormalities in electrocardiography and cardiopulmonary exercise tests (reviewed in Salzano et al). There are no standardized guidelines for the follow-up of men with KS. In addition to the current guidelines of TRT for hypogonadism, including T, PSA, and hematocrit evaluation, KS patients should be followed up for related comorbidities, especially for CVD. Because CVD is the most life-threatening comorbidity, the initial evaluation has been proposed to include risk assessment for metabolic syndrome and thromboembolic disease as well as echocardiography. AS structural and functional cardiovascular abnormalities, a shorter QTc interval in KS patients compared with that in controls, and a 55% prevalence of mitral valve prolapse was found in 22 patients with KS. Data from large registry-based studies indicate that men with KS are at an increased risk of thromboembolic events. One reason for this increased risk is that the viscosity of blood in KS patients is high, causing the formation of venous thromboembolism. In addition, Campbell et al found that the risks of pulmonary embolism and deep venous thrombosis were 5-20 times higher in KS patients than in normal healthy men. The updated AUA guideline for the evaluation and management of testosterone deficiency indicates that whether TRT increases or decreases the risk of cardiovascular events cannot be definitively stated. This guideline also indicates that there is no definitive evidence linking TRT to a higher incidence of venous thromboembolic events. Obviously, this guideline is for general hypogonadal men, and data on men with KS are needed for future investigations.

6.4 | KS and bone disease

Klinefelter syndrome patients also face an increased prevalence of bone disorders, particularly reduced BMD. A study found that 42.5% of KS patients had a combination of osteoporosis and osteopenia, which was 8-fold higher than the incidence in men with a normal karyotype. Reduced BMD is caused by increased bone turnover and is accompanied by an increased risk of bone fractures, especially in the femoral area. Unlike fractures that occur in aging males, men with KS are more active, and the influence of fractures on their body and socioeconomic aspects are more serious. Furthermore, decreased BMD and fractures affecting morbidity and mortality have long been associated with KS. The mechanism of decreased BMD changes upon normal aging because the hypogonadism that occurs during the critical pubertal stages of bone development accompanying low physical exercise capacity and muscle strength is present in KS patients. TRT has been shown to improve BMD, but vitamin D repletion has been demonstrated to be superior to TRT for improving BMD; KS patients are more prone to 25-OH vitamin D fluctuations than normal men. Practically, biannual assessments of BMD and 25-OH vitamin D levels to evaluate the risk of osteoporosis are recommended.

6.5 | KS and immune diseases

The association between KS and immune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic juvenile arthritis, psoriatic arthritis, polymyositis/dermatomyositis, systemic sclerosis, and mixed connective tissue disease, has long been described; however, there has been no systematic evidence or rationale to account for the link. A retrospective study has demonstrated that compared to that of normal healthy men, men with KS have a significantly increased risk of developing Sjogren’s syndrome (risk ratio: 19.3), SLE (risk ratio: 18.1), Addison’s disease (risk ratio: 11.7), type 1 diabetes mellitus (risk ratio: 6.1), multiple sclerosis (risk ratio: 4.3), RA (risk ratio: 3.3), and acquired hypothyroidism (risk ratio: 2.7).

7 | CONCLUSION

The incidence of KS syndrome is 1:600, and the majority of patients in Japan are diagnosed upon a male infertility evaluation by medical providers, especially gynecologists and urologists. Finding sperm via micro-TESE is only one consideration for men with KS among a number of comorbidities that are found during adulthood, especially after infertility treatment. In other words, patients need lifelong care and often need a multidisciplinary team that includes general practitioners, psychologists, speech therapists, and endocrinologists in addition to urologists and gynecologists. Additionally, infertility specialists should understand the pathophysiology and previous histories of KS patients before they visit the IVF clinic, and discussions with general practitioners and pediatricians are sometimes needed to properly treat these patients. Again, KS should be managed from the infantile and pediatric periods to the geriatric period.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. Human rights statement and informed consent: This article does not contain any study with human participants that have been performed by any of the authors. Animal studies: This article does not contain any study with animal participants that have been performed by any of the authors.

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