

Klinefelter Syndrome. The Effects of Early Androgen Therapy on Competence and Behavioural Phenotype

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Potential Negative Effects of Androgen Supplementation in KS

The available evidence addressing early androgen supplementation in boys with KS is predominately limited to retrospective series and is subject to biases inherent to these types of studies. As such, clinicians must consider the evidence for potential benefit and the potential negative effects and harm in using this therapeutic strategy. Furthermore, the results are not easily quantifiable, and thus it is difficult to determine the number needed to treat to improve physiologic or psychological outcomes. Negative effects from androgen supplementation include penile pain from prolonged erections, development of pubic hair without progression of puberty, which could be embarrassing to the child and the parents, and excessive masturbation and penile length. During puberty, adverse events can include premature closure of epiphyses, possible downregulation of androgen receptors, and exacerbation of acne. In our experience, the use of topical T applications with aromatase inhibitors seems to have minimal impact on lowering follicle stimulating hormone and luteinizing hormone levels in adolescents with KS(64); however, topical use must be prescribed in an appropriately selected population of reliable patients because of the potential risk of transference to others. Deep vein thrombosis and pulmonary embolism were reported at significantly higher rates in men with KS and should be considered and discussed when initiating therapy.(65)

Furthermore, oxandrolone (oral), T enanthate (injection), and topical T have been predominately reported in the literature for patients with KS. Oxandrolone is an anabolic steroid related to T. It is consumed orally, and relevant contraindications for men with KS as issued by the Food and Drug Administration (FDA) include nephrosis, hypercalcemia, and carcinoma of the breast or prostate. Other side effects can include insomnia, depression, or libido changes, bleeding in patients with concomitant anticoagulation therapy, gynecomastia, body hair growth, acne, premature closure of epiphyses, edema through retention of sodium chloride, potassium, phosphate, and calcium, decreased glucose tolerance, increased renal creatinine excretion, inhibition of gonadotropin secretion, impaired spermatogenesis, and liver toxicity.(66)

As discussed earlier, the use of topical T therapy in children and adolescents must be appropriately selected because of the risk of transference and potential harm to other children. T enanthate is one of the most common forms of T replacement. It is injected intramuscularly, and relevant contraindications for men with KS as issued by the FDA include men with prostate cancer and those with a history of insensitivity to any of the drug components. Warnings of use have been issued for individuals with breast cancer, immobilization, and hypercalcemia from increased resorption of calcium among other electrolytes such as sodium, chloride, phosphate, and potassium; prolonged use has been reported in cases of cholestatic and peliosis hepatitis and hepatic neoplasms; edema; gynecomastia; accelerated bone maturation and premature closure of epiphyses; impaired spermatogenesis from decreased gonadotropin release; and venous thromboembolic events and potential cardiovascular events in general in older men.

In cases of excessively increased oestradiol levels, some clinicians will consider off-label use of aromatase inhibitors such as anastrozole to bring the levels within normal limits. Anastrozole is taken orally. Relevant warnings and precautions as issued by the FDA include decreased bone mineral density, increased cholesterol, and hypersensitivity reactions. Serious adverse reactions are rare, occurring in less than 1 in 10,000 patients, and include skin reactions, allergic reactions, and changes in serum liver function tests.(68)

Disclosure and Initiation of Treatment

In our practice, managing androgen supplementation in individuals with KS requires an individualized and tailored approach to each boy according to his natural curve of pubertal development. Typically, we wait with initiation of androgens until 13 to 14 years of age, which corresponds to the time of pubertal onset among most boys in the United States. Other centres also prescribe androgen therapy in the infantile period (3 - 6 months). Adolescent interventions before puberty would be justified in cases of severe muscle loss and hypotonia and in boys with significant developmental concerns. The androgen doses are adjusted to mimic normal pubertal progression over 3 to 5 years. The best indicators of the appropriate titration of androgen supplementation are biological determinants such as development of armpit hair, pubic hair, increase in penile length and thickness, upper body muscle development, and increase in semen volume. In addition to using total T, we rely on signs and physical development during adolescence and titrate to appropriate progression of Tanner stages over 3 to 5 years during puberty. An objective measurement for age-specific strength parameters that can be used includes a digital hand dynamometer grip strength measuring device; age- and sex-stratified normative data in a population-based study have been published and can be used as a practical guide. Clinicians also can follow normative height and weight growth curves and penile growth curves during puberty. Some groups also have used weight-based dosing for oxandrolone and have rules to lower the dose if bone age advancement greater than 12 months occurs in a 6-month duration and bone age is older than chronologic age; progression of Tanner stage higher than 2 if younger than 8 years; systolic or diastolic blood pressure above the 95th percentile for age, height, and sex; low-density lipoprotein increasing above 159 mg/dL; high-density lipoprotein decreasing below 20 mg/dL; or alanine aminotransferase liver enzyme increasing beyond twice the upper limit of normal. Although other groups report T enanthate dosage to be individualistic and based on the paediatric endocrinologist's clinical judgement, serum T levels are not typically measured before or after injections. (42) Furthermore, response to androgen replacement is individualistic. Based on our clinical experience, boys with KS demonstrate a weaker response to T replacement therapy compared with boys without KS. Biologically, it has been shown that men with KS have impaired trafficking of androgen receptor from the cytoplasm to the nucleus, and thus boys with KS might require greater T replacement than those without KS.

It is also important to note that the FDA has not approved T administration to those younger than 18 years. In early adulthood, it is important to discuss and counsel these men regarding fertility potential and the possible role for fertility preservation through microdissection testicular sperm extraction. Reports have been shown that topical gel-based therapies have less effect of decreasing gonadotropin levels (luteinizing hormone and follicle-stimulating hormone) and thus likely have less of a negative effect on spermatogenesis compared with

injectable T, which typically has a higher peak level. In our practice, the senior author sees children, adolescents, and adults with KS. However, among institutions that have separate designations of paediatric or adult clinicians, it is essential to establish open communication of past, present, and future care needs for each patient at the transition from child to adult. A multidisciplinary transition program, when possible, can optimize clinical care and an effective transition to adulthood as their therapeutic goals evolve.

CONCLUSION

KS is commonly known for the classic constellation of features such as tall stature, gynecomastia, gynoid hips, small firm testes, hypergonadotropic hypogonadism, and infertility. However, many of these individuals have abnormal neurocognitive development and subsequently altered psychosocial functioning. Some of these abnormalities might be due in part to abnormal androgen exposure in utero, infancy, and adolescence to promote normal neural development. Few studies have reported their experience using early androgen supplementation. Results suggest improved speech, language, reading, intellectual functioning, behaviour, and social functioning in children treated with androgens. However, the evidence is currently limited to retrospective results and 1 prospective trial; further prospectively designed studies are necessary to make firm conclusions on the timing and intricacies of androgen supplementation in children with KS

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