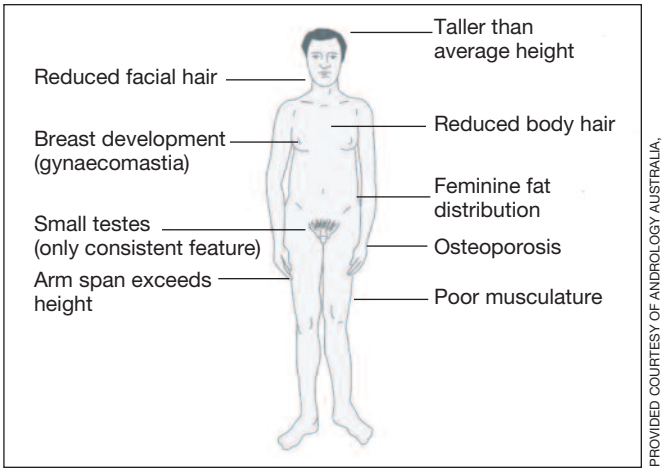
# Raising awareness of a 'hidden' condition: Klinefelter's syndrome

**ROBERT McLACHLAN** MB BS, FRACP, PhD

**Most cases of Klinefelter's syndrome remain undiagnosed and untreated. The key clinical feature of the condition is reduced testicular volume and this should be routinely measured as part of a male physical examination.**




PROVIDED COURTESY OF ANDROLOGY AUSTRALIA, WWW.ANDROLOGYAUSTRALIA.ORG

Figure 1. Clinical features of patients with Klinefelter's syndrome. In a patient with Klinefelter's syndrome, a few, some or all of these features may be present.

Klinefelter's syndrome is a common genetic condition that affects one in 650 men worldwide;[1] however, up to 70% of cases remain undiagnosed and therefore untreated for life.[2] Klinefelter's syndrome results from the presence of an extra X chromosome (47XXY) in the genome of the affected patient.[3] Chromosomal mosaicism (the presence of both 47XXY and 46XY cells) occurs in about 10% of men who usually have milder or fewer features of Klinefelter's syndrome, whereas the presence of additional X chromosomes (e.g. 48XXXY or 49XXXXY) is rare and associated with more severe signs and symptoms.

Professor McLachlan is a Principal Research Fellow of the NHMRC at the Prince Henry's Institute, Deputy Director of Endocrinology at the Monash Medical Centre, Clayton, Vic, and Director of Andrology Australia.

## Clinical features

Defective testicular development is universal in men with Klinefelter's syndrome but other features of the condition are less consistent and relate to testosterone deficiency and/or the presence of the extra X chromosomal material. Classic features of Klinefelter's syndrome in adults include (Figure 1):

- poor pubertal development
- gynaecomastia
- feminine fat distribution
- lack of virilisation
- tall stature
- small firm testes.

These features may be present in affected men, but there is a wide spectrum of signs and symptoms. Not all boys or men with Klinefelter's syndrome will have all of these classic features and symptoms: many have normal sexual function, are of normal height, do not have gynaecomastia and at first glance appear virilised such that a diagnosis of Klinefelter's syndrome may not be considered.

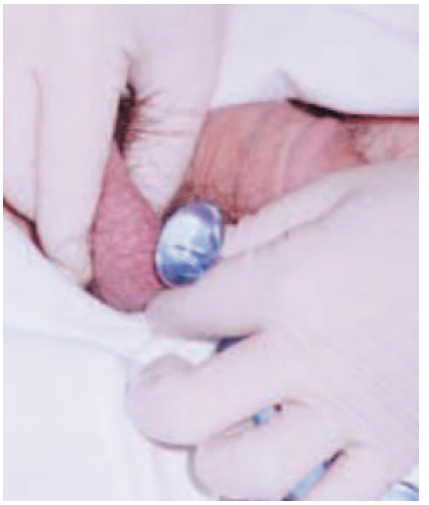
Small firm testes are the only consistent feature of Klinefelter's syndrome. The presence of small firm testes is associated with impaired testosterone secretion by the testicular Leydig cells (a low-normal serum testosterone level and an elevated luteinising hormone [LH] level from mid-puberty) and spermatogenic failure (azoospermia and a markedly elevated serum follicle-stimulating hormone level).

## Clinical diagnosis

Clinical features of Klinefelter's syndrome vary with the age of the affected man (childhood, adolescence [around puberty] or adulthood). In childhood, the features may include learning and/or behavioural difficulties and occasionally undescended testes, but most features of the condition appear at and after puberty. Diagnosis is then readily apparent by a straightforward medical history plus examination of the genitals (including measurement of testicular volume) and secondary sexual characteristics. The diagnosis can then be confirmed on laboratory investigations of reproductive hormone levels and karyotype.

It must be emphasised that reduced testicular volume is the key physical finding in patients with Klinefelter's syndrome and should be assessed using an orchidometer (Figures 2a and b). Normal testicular volume range is less than 3 mL in childhood, 4 to 14 mL in puberty, and 15 to 35 mL in adulthood. Although the testes may start to develop in early puberty,

**continued**



PROVIDED COURTESY OF ANDROLOGY AUSTRALIA, WWW.ANDROLOGYAUSTRALIA.ORG

Figures 2a and b. An orchidometer used to measure testicular volume, showing (a, left) a 10 mL normal testis and (b, right) a 4 mL testis characteristic of Klinefelter's syndrome.

### Useful resources

- A range of education resources are available from Andrology Australia for both health professionals and consumers to improve understanding and diagnosis of Klinefelter's syndrome: www.andrologyaustralia.org
- Tanner stages are available on growth charts on the Australasian Paediatric Endocrine Group website: http://apeg.org.au/Portals/0/1841%20boys%202-18%20years.pdf

the testicular volume soon regresses in men with Klinefelter's syndrome to less than 4 mL by mid-puberty. The finding of small testes despite otherwise well-advanced signs of puberty (e.g. penile size, pubic hair) according to the Tanner stages, suggests a diagnosis of Klinefelter's syndrome. The low detection rate of Klinefelter's syndrome would be improved if testicular examination including measurement of testicular volume became a regular part of a male physical examination.

### Learning and behavioural difficulties

The general intellectual ability of boys with Klinefelter's syndrome is within the normal range; however, these boys have a greater prevalence of difficulties with speech and reading, delayed motor development, reduced attention span and behavioural problems (particularly in adolescence). Consideration and diagnosis of Klinefelter's syndrome in these settings will facilitate educational assistance and guide the management of behavioural difficulties.

### Androgen deficiency

Klinefelter's syndrome is the most common cause of androgen deficiency in young men. The extent of deficiency varies with some men appearing to be normally virilised whereas others show obvious features of poor virilisation. Serum testosterone and LH levels should be determined in the morning because of the circadian nature of testosterone production.[4] Abnormal values should be confirmed with repeat measurement of hormone levels. The majority of patients with Klinefelter's syndrome derive substantial benefit to their quality of life from life-long treatment with testosterone. Testosterone is important for the development and maintenance of bone strength, so men with unrecognised (untreated) Klinefelter's syndrome have a higher risk of developing osteoporosis and fracture, especially in the hips and spine.

### Infertility

A failure of spermatogenesis results from the loss of germ cells and hyalinisation of seminiferous tubules such that the vast majority of men with Klinefelter's syndrome are azoospermic.

### Other features

Klinefelter's syndrome is often associated with various somatic features (Figure 1). Patients with the condition are also at an increased risk of a number of conditions throughout life, such as diabetes, varicose veins, thromboembolic disease, thyroid dysfunction and, rarely, some types of cancers; however, the absolute risk is low. Social and lifestyle factors may also be important health determinants. Yet in spite of these factors, lifespan is only minimally affected.

## Management

As Klinefelter's syndrome is strongly linked with androgen deficiency, life-long testosterone replacement therapy (TRT) is needed to maintain good health and well-being in men with the condition.[5] During evaluation, even if the measured testosterone level is within the low-normal range, the very common finding of a raised LH level indicates a degree of androgen deficiency due to testicular failure. This highlights the need for TRT to benefit bone health and, potentially, other effects of androgenic deficiency on muscle, the cardiovascular system and general quality of life.

A range of treatment options are available, particularly long-acting intramuscular injections, subcutaneous implants and topical gels

Patient convenience and familiarity,

cost and availability will determine the type of treatment prescribed. TRT may be started from mid-puberty, although many boys initially virilise normally. Teenage boys should usually be started on about half the adult dose and increased to a full adult dose as puberty progresses.

Infertility is a major issue in patients with Klinefelter's syndrome because most affected men are azoospermic. Rarely, a few sperm can be found in the ejaculate but couples have a realistic prospect of fertility through the isolation of sperm from testicular biopsy tissue (in about 30 to 50% of cases) and their use for intracytoplasmic sperm injection. As TRT will suppress spermatogenesis, fertility options, if appropriate, need to be considered before TRT is started, and counselling may be necessary (see box of useful resources on page 50).

## Specialist referral

The initial diagnosis and management of a patient with Klinefelter's syndrome can be readily undertaken in general practice, with accompanying specialist referral and support recommended. In children and adolescents, referral to a paediatric endocrinologist is recommended to confirm the diagnosis and help with management and educational and allied health assistance, if needed. In adults, developing a plan in the consultation with an endocrinologist for the management of hormone deficiency, infertility and osteoporosis is recommended. It is also important to refer adults to a fertility specialist, as appropriate, for sperm recovery from the testis (occasionally) or use of donor sperm.

## Follow up

The monitoring of patients who are using TRT requires the standard approach for any condition that causes androgen deficiency. Particular attention should be paid to monitoring bone health given the increased risk of osteoporosis from prior androgen deficiency. Left untreated, men with Klinefelter's syndrome are less likely to be diagnosed with prostate cancer; whereas restoring testosterone levels to the normal range may return their risks to those of their eugonadal peers.[6] Therefore, men with Klinefelter's syndrome should be subject to the same advice about prostate cancer screening (digital rectal examination and measurement of PSA levels) as their peers. When initiating testosterone treatment in men over the age of 40 years with Klinefelter's syndrome, exclusion of significant prostate pathology is essential. Otherwise age-appropriate medical care, with attention to the general health, weight and lifestyle factors of patients with Klinefelter's syndrome

is needed. Some features of Klinefelter's syndrome are specific to the syndrome (e.g. behavioural and cognitive problems) and may require special attention.

## Conclusion

The clinical presentation of a patient with Klinefelter's syndrome may be subtle and the diagnosis can be overlooked unless actively considered. There are three peak times for detection of Klinefelter's syndrome (approximately one-third of cases are detected at each phase): prenatal karyotyping; during childhood and puberty; and in adulthood in association with infertility or androgen deficiency.

The fact that most men with Klinefelter's syndrome remain undiagnosed reflects the lack of awareness about the condition, the flawed assumption that the lack of classic features excludes the diagnosis and, most importantly, that routine assessment of the testes from late puberty onwards is often not performed. Identification of boys and men with Klinefelter's syndrome is rewarding because great benefit will follow treatment in terms of their physical and psychosocial health and that of their families or partners. MT

## References

1. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet 2004; 364: 273-283.
2. Bojesen A, Juul S, Gravholt C. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 2003; 88: 622-626.
3. Jacobs P, Strong J. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature 1959; 183: 302-303.
4. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983; 56: 1278-1281.
5. Allan C, McLachlan R. Androgen deficiency in men. Med Today 2007; 8(4): 47-54.
6. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. J Natl Cancer Inst 2005; 97: 1204-1210.

COMPETING INTERESTS: None.