Male Hypogonadism:
A Review of Three Case Studies

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Hypogonadism presents clinically as failed puberty, gynecomastia, sexual dysfunction, infertility, or osteoporotic fractures in older men. Failed or delayed puberty in a young male points to developmental disorders (Table 1). Pituitary-hypothalamic causes include pituitary tumours or, most commonly, decreasing luteinizing hormone-releasing hormone (LHRH) pulse frequency and amplitude with aging, leading to lower luteinizing hormone (LH) and testosterone. Concomitant with the testosterone decline, its carrier protein sex hormone binding globulin (SHBG) increases, resulting in even greater reduction in the bioactive free testosterone levels.

Meet Paul

Paul is a 45-year-old male. Five years ago, he complained of poor sexual function and fatigue and was found to have a testosterone level of 5.3 nmol/L (normal is 10 nmol/L-29 nmol/L). A luteinizing hormone (LH) was normal.

He was started on replacement therapy by intramuscular testosterone injections. More recently he complains of headaches. A MRI shows a 3 cm pituitary tumour.

Paul's Case

Should a man this age have these test results?

LH levels are critical in determining causes of hypogonadism—an elevated LH indicates irreversible testicular failure from any cause. However, a low testosterone with a "normal" (not elevated) LH indicates the hypothalamus is not properly responding to the low testosterone by increasing LH production and investigation of the pituitary area is mandatory before embarking on therapy. Twenty per cent of men age 60 and 40% of men age 80 have low testosterone levels and probably 95% in these age groups are due to aging rather than tumours. However, in younger men, age-related declines in testosterone are rare and other causes should be sought. Elevated prolactin levels, symptoms of headache or visual disturbance, or clinical features of Cushing's syndrome or acromegaly point to pituitary causes, but a MRI may be needed to exclude tumours. As an approximate guide, men < 55- to 60-years-of-age should have a MRI when this combination of hormonal test results are found.

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Table 1

Common causes of gonadal failure

Testicular failure: low testosterone, high LH	Pituitary-hypothalamic failure: low testosterone, "normal" or low LH
• Developmental: Klinefelter's syndrome, cryptorchidism • Acquired: viral orchitis, trauma, post-radiation/chemotherapy	• Pituitary tumours • Post-pituitary surgery • Age-related decline (andropause, or androgen decline in the aging male) • Developmental: Kallmann's syndrome (LH-releasing hormone deficiency) • Renal failure

Meet Martin

Martin, 52, fell and had a vertebral fracture while running.

He has a low BMD of -2.5 standard deviation T-score at hip and spine. His testosterone is 7.6 nmol/L and LH, prolactin and pituitary MRI are normal.

He denies sexual dysfunction or other symptoms. He has benign prostatic hyperplasia and borderline urine flow.

Martin's Case

Will testosterone replacement improve his osteoporosis, but increase urinary obstruction?

Testosterone therapy will definitely increase his BMD without the need for other therapy. No definite evidence indicates testosterone predictably causes prostatic hypertrophy, but response is variable so that persons with borderline flow may experience growth and obstruction. Treatments with antiandrogens or transurethral resection of the prostate (TURP) would likely worsen Martin's hypogonadism and sexual function. He can avoid these complications by treatment with bisphosphonates, which are effective in increasing BMD in hypogonadal men irrespective of testosterone. It is not clear if testosterone produces a threshold or dose-response effect on bone density.

There is no evidence that testosterone replacement causes prostate cancer.

Would testosterone therapy cause prostate cancer?

There is no evidence that testosterone replacement causes prostate cancer, with the incidence being the same in men with high or low testosterone and both large observational studies and short-term randomized trials do not support a causative relationship. Prostate cancer prevention trials with 5-α-reductase inhibitors demonstrate reduced cancer incidence, but cancers occurring were of higher grade and worse prognosis. Long-term randomized controlled trials of testosterone therapy are planned to address the issue. Nonetheless, men > 40-years-of-age should have a digital rectal examination (DRE) and PSA done prior to and during testosterone therapy to detect and to monitor cancer development.

Meet James

James is a 58-year-old executive with Type 2 diabetes, hypertension, a high LDL-C, a low HDL-C and a BMI of 32.

Gradually, he has noticed some decrease in libido and erectile function, as well as fatigue. His total serum testosterone is 8.4 nmol/L and LH is normal.

He is taking oral hypoglycemic agents, an ACE inhibitor and a statin.

James' Case

Does he have hypogonadism?

Although symptomatic, James' low testosterone may be a test artifact due to obesity causing a low SHBG, the carrier protein for testosterone, thus resulting in an artifactually lowered total testosterone. This is a very common problem in interpretation of testosterone values. He requires a free testosterone or bioavailable (free plus albumin-bound) testosterone to measure the bioactive fraction of testosterone unaffected by SHBG. If this is clearly normal, then his complaints cannot be attributed to testosterone deficiency and replacement is not indicated. Testosterone deficiency causes at most 3% to 5% of cases of erectile dysfunction, the majority being due to drugs or to neurovascular causes, such as diabetes.

Will testosterone therapy be beneficial if he has low testosterone levels?

If he has a definite decrease in free or bioavailable testosterone, then it is indicated to replace his testosterone as he will benefit, regardless of age, from:

- improved sexual function,
- reduction in fat mass,
- increase in muscle mass and strength,
- improved BMD and
- improved mood.

There is an epidemiological association of increased cardiovascular (CV) disease, metabolic syndrome and diabetes with low testosterone. Hence, such patients should be considered for screening for low testosterone and vice versa. Small studies suggest testosterone replacement may be beneficial in reducing insulin resistance and improving exercise-induced ischemic symptoms.

James' CV risk factors should be treated by appropriate directed therapy. If his testosterone is low, then the response rate to a phosphodiesterase type 5 inhibitor is significantly increased by adding testosterone replacement.

James should have baseline DRE, PSA, hematocrit and lipids. These should be repeated every three to six months for the first year, then yearly.

Conclusion

Testosterone replacement produces a threshold effect on mood and sexual function. However, there is a dose-response effect of testosterone on muscle mass and strength and decrease in fat mass, independent of exercise. Current evidence indicates patients with low-normal testosterone levels given replacement therapy experience these changes in body composition, but do not have improved cognitive function or BMD and may have mixed metabolic changes. Thus, the benefit (beyond body composition changes) to important endpoints, such as CV risk and bone of increasing testosterone levels within the normal range, remains unproven.

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Resource

1. Bhasin S, Cunningham GR, Hayes FJ, et al: Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2006; 91(6):1995-2010.