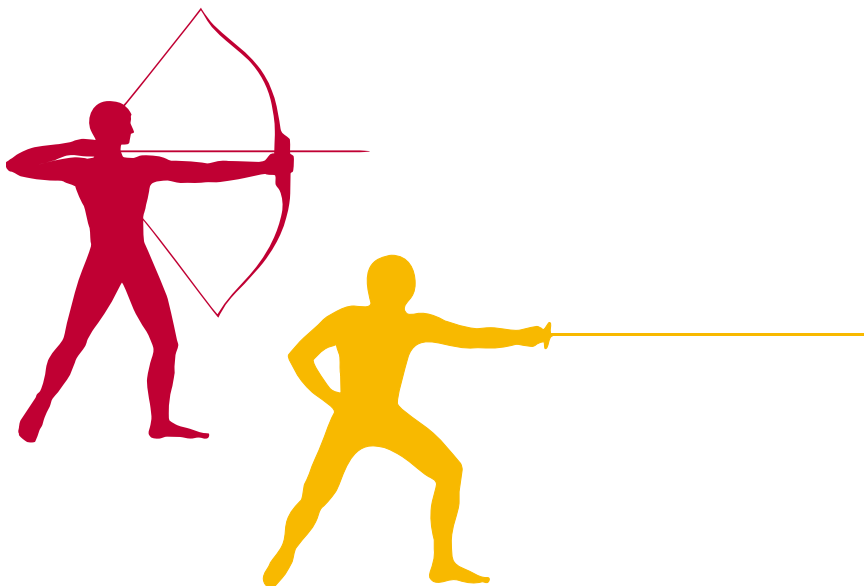


Short Review

Late-onset hypogonadism

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Abstract

An interesting article published in JMHG (Friedrich Jockenhövel, Joel M. Kaufman, Gerald H. Mickisch, Alvaro Morales and Christina Wang: The good, the bad, and the unknown of late onset hypogonadism: the urological perspective . Journal of Men's Health and Gender (2005) 3(1): 292–301) reviews late-onset hypogonadism. It reviews the definition and diagnosis of late-onset hypogonadism (LOH) and describes its treatment with both established and newer testosterone formulations. However, clinicians do need to be vigilant when assessing men presenting with apparent LOH to identify those with (a) wider anterior pituitary dysfunction (eg. secondary to iron overload, hyperprolactinaemia and/or structural pituitary lesions), (b) non-endocrine chronic disease states such as sleep apnoea syndrome and (c) hitherto undiagnosed or untreated congenital hypogonadism, eg. late presenting Kallmann's or progressive multiple pituitary hormone deficiency.

Testosterone therapy can be administered by intramuscular injection, by implant into subcutaneous fat, orally, transdermally or through buccal administration. Newer testosterone formulations include a long-acting 3-month depot injection of testosterone undecanoate (Nebido®) and a once-daily testosterone gel (Testogel®) preparation. Both of these have been shown to be effective in re-establishing normal testosterone levels and improving libido, potency, lean body mass, muscle strength and general well being and mood. In older men, the possible development or unmasking of prostate cancer is a theoretical concern, although the actual evidence for this is surprisingly sparse. Indeed, it has even been suggested that testosterone therapy can be safely administered to hypogonadal patients who have been successfully treated for non-metastatic prostate cancer and who have no detectable disease.

Definition

Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. LOH may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems, particularly the musculo-skeletal system.¹ In a proportion of patients presenting in this way, no specific cause can be identified apart from the ageing process itself, but the case-mix will include individuals with systemic diseases and lesions of the hypothalamic-pituitary region, as well as late-presenting congenital hypogonadism.

Diagnosis

Clinical diagnosis of LOH should be based on an adequate history and physical examination. The syndrome is characterized by diminished sexual desire and erectile quality and frequency, particularly nocturnal erections. Changes in mood with concomitant decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability may also be identified. Other characteristics include sleep disturbances, decrease in lean body mass with associated reduction in muscle volume and strength, increased visceral fat, reduced body hair, skin alterations, and decreased bone mineral density resulting in osteopenia, osteoporosis and increased risk of bone fractures. However, neither the signs

nor the symptoms are specific enough for a conclusive diagnosis. Screening questionnaires are limited in their usefulness and their diagnostic specificity is low. Therefore biochemical assessments are necessary and blood sampling should ideally take place between 08.00 and 11.00 hours due to the circadian rhythm of testosterone production.¹ The most widely accepted parameters to establish the presence of hypogonadism are the measurement of total testosterone and free testosterone calculated from measured total testosterone and sex hormone binding globulin or measured by a reliable free testosterone dialysis method.

Assessment of testosterone levels

It is important to know the adult male range of serum testosterone, bioavailable or free testosterone of the clinical laboratory. The lower limit of normal is internationally defined with total testosterone below 12 nmol/L or serum free testosterone below 250 pmol/L.¹ A diagnosis of primary hypogonadism or testicular failure is unquestionable if serum total testosterone levels are clearly below the reference ranges and gonadotrophin levels are chronically higher than the normal range. If testosterone levels are below or at the lower limit of the accepted normal adult male values, it is recommended to perform a second determination together with assessment of luteinizing hormone and prolactin.¹ Total testosterone levels between 8 and 12 nmol/L or free testosterone levels between 180 pmol/L and 250 pmol/L are regarded as borderline hypogonadal levels. A trial of testosterone treatment can be considered in those patients.¹ Serum gonadotrophins should also be measured to differentiate individuals with a primary disorder of the testis (eg. Klinefelter's), from those with deficient hypothalamic-pituitary function.¹

Treatment

Commonly used testosterone formulations include injectable testosterone (testosterone cypionate, testosterone enanthate and testosterone undecanoate), oral testosterone (testosterone undecanoate), transdermal testosterone (testosterone patch or gel) and buccal testosterone.

A new, long-acting formulation of testosterone undecanoate for intramuscular injection

A new testosterone preparation for intramuscular injection, 1000 mg testosterone undecanoate (Nebido®), has recently been developed.² Testosterone undecanoate is dissolved in castor oil for intramuscular injection and this depot formulation allows a remarkable extension of the injection interval from the 1–3 weeks with testosterone enanthate (i.e. 17–52 injections a year) to 10–14 weeks (i.e. usually four injections a year in long-term therapy). These characteristics of testosterone undecanoate can substantially improve both the acceptability and tolerability of testosterone injection therapy, as well as contributing to far more stable serum testosterone levels within the physiological normal range. Pharmacokinetic studies have shown intramuscular testosterone undecanoate to have a prolonged duration of action, allowing for the gradual extension of the injection interval from 6 weeks to 12 weeks.³ Subsequent clinical studies showed that one injection of intramuscular testosterone undecanoate 1000 mg maintained serum testosterone concentrations within the normal range for around 3 months whilst avoiding non-physiological peaks.^{4,5}

In phase III studies, intramuscular testosterone undecanoate proved to be as efficient as the reference formulation of 250 mg testosterone enanthate in improving body composition, bone mineral density, muscle mass and strength, erythropoiesis, libido and potency as well as general well being and mood.^{2,6} Lipid metabolism showed favourable changes with slight decreases in total cholesterol and low density lipoprotein (LDL) cholesterol, whereas the mean high density lipoprotein (HDL) levels decreased slightly but remained within normal limits.²

Based on the pharmacokinetic data, the most rational and simple dosing scheme is a 6-week interval between the first and second injection followed by injections every 12 weeks. It is important to inject slowly and deeply into the gluteus maximus. After 12 weeks, the dosing interval can be adapted based on clinical symptoms and the trough testosterone level determined prior to the following injection. The trough level should be at the lower limit of the normal range.

Long-term experience with testosterone gel therapy

Testosterone gel (Testogel®) is a transparent colourless gel, which is available in sachets of 50 mg of testosterone in 5 g of gel, respectively. Doses need to be individually adjusted to between 5 and 10 g gel daily. Administration should be daily, preferably in the morning, to the skin of the upper arms, shoulder and/or abdomen and the gel is absorbed by the skin within a few minutes.

Pharmacokinetic studies have shown testosterone gel to provide steady serum testosterone concentrations within the physiological range. A 6-month trial in more than 150 hypogonadal men showed that treatment with testosterone gel, 50, 75 and 100 mg/day, significantly improved sexual function, mood, lean body mass and muscle strength and decreased fat mass and body fat.⁷ In an extension of this study, subjects continued treatment for up to 42 months and sexual desire, sexual activity and performance scores were significantly improved compared with baseline values and were maintained at the same level from 6 months until the end of treatment.⁸ Similarly, mood scores were improved, and lean body mass and bone mineral density were increased and fat mass was decreased with long-term treatment. Advantages of testosterone gel are that it is unobtrusive, can be administered by the patient himself and can be interrupted at any time. Skin irritation is a significantly smaller problem with testosterone gel than with testosterone patches.

Patient follow-up

It is important that both the physician and patient are committed to regular follow-ups for the duration of androgen therapy. Follow-up assessments should be performed every 3 months for the first year of therapy and once a year thereafter if no adverse effects occur. Improvement in signs and symptoms of testosterone deficiency should be sought and, if no benefit in clinical manifestations is apparent and there is no evidence for osteopaenia or osteoporosis, treatment could then be stopped.¹ Assessment should include evaluation for possible adverse effects. Prostate health should be reviewed, including alterations in voiding pattern, the determination of prostate specific antigen (PSA) level and, possibly, digital rectal examination. Testosterone therapy is relatively contraindicated in

patients with severe symptoms of lower urinary tract obstruction or clinical findings of bladder outflow obstruction due to an enlarged clinically benign prostate.¹ Laboratory analyses should include assessment of haemoglobin and haematocrit: a modest elevation of haemoglobin and haematocrit from a low baseline is a frequent effect of no consequence (indeed, it is probably a therapeutic target), but supraphysiological elevations can be serious, particularly in the elderly. Assessment of bone mineral density every 3–5 years can also assist the physician in judging the adequacy of androgen replacement. Although the lipid profile should be checked for detrimental changes in HDL, testing for liver function is optional.

Testosterone therapy for hypogonadal men with prostate cancer

As both prostate cancer and late-onset hypogonadism occur more frequently after 50 years of age, some men with prostate cancer will have or develop late-onset hypogonadism and vice versa. The possible development or unmasking of prostate cancer is a major concern in treating late-onset hypogonadism, although evidence that testosterone therapy is causative is strikingly lacking.

A history of prostate cancer has been considered a contraindication for testosterone therapy.¹ In recent years, however, widespread PSA screening and transrectal ultrasound-guided biopsies have resulted in the diagnosis of localized prostate cancer in many men. Indeed, there is an ongoing and unresolved debate among urologists as to the real value of PSA screening in the normal male population. Because many men are now apparently cured of their early stage prostate cancer, it has been suggested that the pros and cons of androgen therapy should be carefully considered in men without a recurrence.⁹ Furthermore, recent evidence suggests that selected men with hypogonadism and a past history of prostate cancer can safely receive testosterone replacement.¹⁰ However, this evidence, as established at the Consensus Conference on sexual dysfunction, is still limited and such men should be particularly carefully monitored.¹¹

A review of 25 studies comparing testosterone levels in healthy volunteers and patients with prostate cancer found the mean testosterone levels at diagnosis to be the same in both groups in 15 studies (60 %); testosterone to be higher in patients in 4 trials (16 %) and lower in 6 (24 %). Overall, 1481 patients and 2767 healthy volunteers were included in this review.¹²

Recommendations for androgen therapy to ensure prostate safety

Before initiating testosterone therapy in a man over the age of 40 years, documentation of a normal PSA level and probably also a digital rectal examination would be sensible. Follow-up monitoring at intervals of 3 months for the first year, then yearly thereafter has been recommended.¹³

The opinion of the author may not necessarily reflect the opinion of the company Schering AG.

References

- 1 Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros J-J, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM and EAU recommendations. *Eur Urol* 2005;48:1–4.
- 2 Schubert M, Minnemann T, Hubler D, Rouskova D, Christoph A, Oettel M, et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab* 2004;89(11):5429–34.
- 3 Behre HM, Abshagen K, Oettel M, Hubler D, Nieschlag E. Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. *Eur J Endocrinol* 1999;140(5):414–9.
- 4 Nieschlag E, Buchter D, Von Eckardstein S, Abshagen K, Simoni M, Behre HM. Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men. *Clin Endocrinol* 1999;51(6):757–63.
- 5 von Eckardstein S, Nieschlag E. Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. *J Androl* 2002;23(3):419–25.
- 6 Hubler D, Schubert M, Minnemann T, Christoph A, Oettel M, Ernst M, et al. Effect of longterm treatment with a new sustained-action testosterone undecanoate (TU) formulation for intramuscular androgen replacement therapy on sexual function and mood in hypogonadal men. *Int J Impot Res* 2002;14(Suppl. 4):S51.
- 7 Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men. *J Clin Endocrinol Metab* 2000;85(8):2839–53.
- 8 Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 2004;89(5):2085–98.
- 9 Morales A. Androgen replacement therapy and prostate safety. *Eur Urol* 2002;41(2):113–20.
- 10 Kaufman JM. The effect of androgen supplementation therapy on the prostate. *Aging Male* 2003;6(3):166–74.
- 11 Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM, et al. Endocrine Aspects of Sexual Dysfunction in Men. *The Journal of Sexual Medicine* 2004;1(1):69–81.
- 12 Slater S, Oliver RT. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. *Drugs Aging* 2000;17(6):431–9.
- 13 Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004;350(5):482–92.

Nebido® (Testosterone undecanoate) Prescribing Information

Therapeutic indications: Testosterone replacement in male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. **Composition:** 4 ml solution containing: 1000 mg testosterone undecanoate as active ingredient and benzyl benzoate and castor oil as excipients. **Contraindications:** Cases of known or suspected androgen-dependent carcinoma of the prostate or of the male mammary gland; past or present liver tumors; hypersensitivity to the active substance or to any of the excipients. **Side effects:** Administration site: pain and/or hematoma. Possible systemic side effects: diarrhea, leg pain, arthralgia, dizziness, increased sweating, headache, respiratory disorder, acne, breast pain, gynecomastia, pruritus, skin disorder, testicular pain, prostate disorder. Other known adverse drug reactions of treatments containing testosterone are: rare cases of polycythemia, weight gain, electrolyte changes, muscle cramps, nervousness, hostility, depression, sleep apnea, in very rare cases jaundice and liver-function-test abnormalities, various skin reactions including acne, seborrhea, and balding, libido changes, increased frequency of erections, persistent, painful erections (priapism). Treatment with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; high-dosed or long-term administration of testosterone occasionally increases the occurrences of water retention and edema, urinary obstruction, prostate cancer (although data on prostate cancer risk in association with

testosterone therapy are inconclusive). In prepubertal/pubertal boys testosterone, besides masculinization, can cause accelerated growth and bone maturation and premature epiphyseal closure, thereby reducing final height. The appearance of common acne has to be expected. **Precautions:** Nebido® might result in a positive finding in doping tests. Older patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia. Carcinoma of the prostate has to be excluded before starting treatment with testosterone preparations. Regular examinations of the prostate are recommended. Hemoglobin and haematocrit should be checked periodically in patients on long-term androgen treatment to detect cases of polycythemia. In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of testosterone compounds. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in men using Nebido®. Patients predisposed to edema, patients who have had elevated blood pressure, disturbance in renal function, epilepsy or migraine should be closely monitored. The product may elevate blood pressure and is not recommended for patients with cardiac insufficiency. Preexisting sleep apnea may be potentiated. Nebido® has to be used with caution in patients with hypercalcemia due to bone metastases. Serum calcium concentrations have to be

monitored regularly in these patients. Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability. **Posology and method of administration:** Nebido® is injected every 10 to 14 weeks. Injections in these intervals lead to and maintain testosterone levels in the physiological range and do not lead to accumulation. Nebido® is strictly for intramuscular injection and must be injected very slowly. Special care must be given to avoid intravascular injection. The first injection interval may be reduced to a minimum of 6 weeks. With this loading dose, steady-state levels will be reached quickly. **Special warnings:** The use of the product in prepubertal children is not recommended. In unavoidable cases the treatment should be conducted under the supervision of the doctor specialized in pediatric endocrinology. Nebido® is not indicated for use in women and must not be used in pregnant or lactating women. **Please refer to the Summary of Product Characteristics for more detailed information.** For further details contact your local Schering organisation.

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Testogel® Prescribing Information

Therapeutic indications: Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and 2 separate blood testosterone measurements. Testogel® should be used only if hypogonadism (hyperandrogenotrophic) has been demonstrated. **Composition:** Active ingredient: one sachet of 5 g contains 50 mg of testosterone. Pharmacologically inactive ingredients: Carbomer 980, isopropyl myristate, ethanol 96%, sodium hydroxide, purified water. **Contraindications:** Cases of known or suspected prostatic cancer or breast carcinoma, known hypersensitivity to testosterone or to any other constituent of the gel, skin conditions prohibiting the topical application of medication, male sterility or impotence. **Side effects:** Possible local side effects: erythema, acne, dry skin. Possible systemic side effects: prostatic disorders, gynecomastia, mastalgia, dizziness, hyperparesthesia, amnesia, mood disorders, hypertension, diarrhea, alopecia, polycythemia, increased serum lipids. Other known adverse drug reactions of treatments containing testosterone are: prostatic changes and progression of sub-clinical prostatic cancer, urinary obstruction, pruritus, arterial vasodilatation, nausea, cholestatic jaundice, changes in liver function tests, increased libido, nervousness, myalgia and, during high dose prolonged treatment, electrolyte changes (sodium, potassium, calcium, inorganic phosphate and water retention), oligospermia and priapism (frequent or prolonged erections). **Precautions:** Exclusion of risk of pre-existing prostatic cancer, monitoring of the prostate gland and breast. Regular

monitoring of serum calcium concentrations is recommended in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Testogel® may cause oedema with or without congestive cardiac failure in patients suffering from severe cardiac, hepatic or renal insufficiency. In this case, treatment must be stopped immediately. Testogel® should be used with caution in patients with ischemic heart disease. Testosterone may cause a rise in blood pressure and should be used with caution in patients with hypertension. Beside laboratory tests of the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should be checked periodically: hemoglobin, hematocrit (to detect polycythemia), liver function tests. Testogel® should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated. Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment. In case of severe application site reactions, treatment should be reviewed and discontinued if necessary. This proprietary medicinal product contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests. Testogel® should not be used by women. If no precaution is taken, testosterone gel can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and possibly adverse effects in case of repeat contact (inadvertent androgenization). Testogel® should not be prescribed in patients with a major risk of non-compliance with

safety instructions (e.g. severe alcoholism, drug abuse, severe psychiatric disorders). **Posology and method of administration:** Cutaneous use. The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily. The daily dose should not exceed 10 g of gel per day. The adjustment of posology should be achieved by 2.5 g of gel steps. The gel should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders, or both arms or abdomen. Allow drying for at least 3-5 minutes before dressing. **Warnings:** Testogel® is not indicated for use in children and has not been evaluated clinically in males under 18 years of age. Pregnant women must avoid any contact with Testogel® application sites. This product may have adverse virilizing effects on the foetus. **Please refer to the Summary of Product Characteristics for more detailed information.** For further details contact your local Schering organisation.

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