Testosterone Replacement Therapy and Late-onset Hypogonadism

a report by
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Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age and characterised 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 musculoskeletal 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 comprise an adequate history and physical examination, which also serve to identify any previously unsuspected systemic disease processes. The syndrome is characterised 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, a decrease in lean body mass with an 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, signs and symptoms alone are insufficient for a conclusive diagnosis, with the specificity of screening questionnaires being notoriously low. Biochemical assessment of total testosterone level is therefore essential, preferably performed between 8am and 11am due to the circadian variation in serum levels.[1] The free testosterone level can also be helpful (calculated from measured levels of testosterone and sex-hormone-binding globulin or measured through a reliable equilibrium 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 for a healthy adult male is internationally defined by a serum total testosterone below 12nmol/litre or a free testosterone below 250pmol/litre, with total testosterone levels between 8nmol/litre and 12nmol/litre or free testosterone levels between 180pmol/litre and 250pmol/litre being regarded as borderline.

It is also important to bear in mind reference ranges from the local biochemistry laboratory. Even with apparently clear-cut biochemical hypogonadism, it is advisable to repeat the testosterone determination, with measurement of serum gonadotropins, i.e. luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH are raised in men with a primary disorder of the testis and low or 'inappropriately' normal in men with deficient hypothalamic–pituitary function. A diagnosis of primary hypogonadism or testicular failure is unquestionable if gonadotropin levels are chronically elevated, even if the testosterone level itself seems entirely normal.[1]

Hypogonadal men with low or normal gonadotropins should undergo a more detailed biochemical evaluation, particularly serum prolactin (PRL) level but also cortisol, thyroid and iron studies if more profound hypothalamic–pituitary dysfunction is at all suspected. A therapeutic trial of testosterone treatment can always be considered in men with borderline hypogonadism.[1]

Treatment

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

1 *Nieschlag E, Swerdloff R, Behre H M et al., "Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM and EAU recommendations",* Eur. Urol. *(2005);48: pp. 1–4.*

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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 substanceor 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.

Schering AG, 13342 Berlin, Germany
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Andrology

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A New, Long-acting Formulation of Testosterone Undecanoate for Intramuscular Injection

A new testosterone preparation for intramuscular (IM) injection, 1,000mg testosterone undecanoate (Nebido®), has recently been developed.[2] Testosterone undecanoate is dissolved in castor oil for IM injection, and this depot formulation allows a remarkable extension of the injection interval from one to three 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 IM testosterone undecanoate to have a prolonged duration of action, allowing for the gradual extension of the injection interval from six to 12 weeks.[3] Subsequent clinical studies have shown that one injection of IM testosterone undecanoate 1,000mg maintained serum testosterone concentrations within the normal range for around three months, while avoiding non-physiological peaks.[4,5]

In phase III studies, IM testosterone undecanoate proved to be as efficient as the reference formulation of 250mg testosterone enanthate in improving body composition, bone mineral density, muscle mass and strength, erythropoiesis, libido and potency as well as general wellbeing 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 six-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 that is available in sachets of 50mg of testosterone in 5g of gel, respectively. Doses need to be individually adjusted to between 5g and 10g 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 six-month trial in more than 150 hypogonadal men showed that treatment with testosterone gel – 50mg/day, 75mg/day and 100mg/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, activity and performance scores were significantly improved compared with baseline values and were maintained from six months until the end of treatment.[8] Similarly, mood scores were

2. *Schubert M, Minnemann T, Hubler D 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): pp. 5,429–5,434.*
3. *Behre H M, 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): pp. 414–419.*
4. *Nieschlag E, Buchter D, Von Eckardstein S et al., "Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men",* Clin. Endocrinol. *(1999);51(6): pp. 757–763.*
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): pp. 419–425.*
6. *Hubler D, Schubert M, Minnemann T 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): p. S51.*
7. *Wang C, Swerdloff R S, Iranmanesh A 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): pp. 2,839–2,853.*
8. *Wang C, Cunningham G, Dobs A 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): pp. 2,085–2,098.*

improved, 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 him-/herself and can be interrupted at any time.

Patient Follow-up

It is important that both the physician and the patient are committed to regular follow-ups for the duration of androgen therapy. Follow-up assessments should be performed every three 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 osteopenia or osteoporosis, treatment could 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 three to five 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 LOH occur more frequently after 50 years of age, some men with prostate cancer will have or develop LOH and vice versa. The possible development or unmasking of prostate cancer is a major concern in the treatment of LOH, 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 localised prostate cancer in many men. Indeed, there is an on-going and unresolved debate among urologists as to the real value of PSA screening in the normal male population.

Due to the fact that 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 with the levels in patients with prostate cancer found the mean testosterone levels at diagnosis to be the same in both groups in 15 studies (60%), higher in patients in four trials (16%) and lower in six (24%). Overall, 1,481 patients and 2,767 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 three months for the first year and yearly thereafter has been recommended.[13]

9. *Morales A, "Androgen replacement therapy and prostate safety",* Eur. Urol. *(2002);41(2): pp. 113–120.*
10. *Kaufman J M, "The effect of androgen supplementation therapy on the prostate",* Aging Male *(2003);6(3): pp. 166–174.*
11. *Morales A, Buvat J, Gooren L J et al., "Endocrine aspects of sexual dysfunction in men",* J. Sex. Med. *(2004);1(1): pp. 69–81.*
12. *Slater S, Oliver R T, "Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy",* Drugs Aging *(2000);17(6): pp. 431–439.*
13. *Rhoden E L, Morgentaler A, "Risks of testosterone-replacement therapy and recommendations for monitoring",* N. Engl. J. Med. *(2004);350(5): pp. 482–492.*