Effects of Testosterone on the Metabolic Syndrome

Testosterone inhibits the expression of lipoprotein lipase activity, the main enzymatic regulator of triglyceride uptake in fat cell, preferentially in abdominal fat. Several studies have confirmed that testosterone treatment reduces waist circumference which, in its simplicity, appears to be a valid parameter for visceral obesity. A study of testosterone administration to restore testosterone levels to mid-normal values for 8-9 months found a decrease in visceral fat mass, a decrease in fasting glucose and lipid levels and an improvement to mid-normal values for 8-9 months found a decrease in visceral fat volume. This led to an inverse relationship between plasma testosterone and plasma HDL-cholesterol, as well as an inverse relationship between plasma testosterone and visceral fat volume. 

Introduction

Recent cross-sectional studies on middle-aged men have found a direct, rather than an inverse, relationship between plasma testosterone and plasma HDL-cholesterol, as well as an inverse relationship between plasma testosterone and visceral fat volume. This relationship appears to be independent of age. Earlier cohort studies also linked low testosterone levels to increased cardiovascular risk and type 2 diabetes. Several longitudinal studies confirmed that low testosterone and SHBG (Sex Hormone-Binding Globulin) levels were predictive for metabolic syndrome, not only in obese men but also in men with a BMI (Body Mass Index) <25 kg/m². 

The scientific evidence on association between low testosterone and visceral fat volume, increase in lean body mass, improvement of plasma triglycerides, total cholesterol and LDL-cholesterol level and visceral adiposity which together reduced overall cardiovascular risk. 

While these effects might be indirect (via improvement of body composition: less adipose tissue, leaner body mass), there is also evidence that testosterone directly improves insulin sensitivity. 

For that reason, it is important to screen men at-risk, but currently there is no universal agreement on testosterone level threshold for Testosterone Deficiency Syndrome (TDS) diagnosis or to commence testosterone replacement therapy (TRT). The International Society of Andrology, the International Society for the Study of the Aging Male (ISSAM) and the European Society of Urology has agreed on the following threshold levels for clinical practice: 

- Total serum testosterone (TT) levels <8 nmol/L (<2.31 ng/mL) or free testosterone (FT) levels <<2.31 ng/mL (>72 pg/mL) require TRT 
- TT levels > 12nmol/L (>3.46 ng/mL) or FT levels >250 pmol/L (>7.2 pg/mL) do not require TRT 
- A trial of TRT may be considered in symptomatic men with TT levels 8-12 nmol/L. 

Testosterone Replacement Therapy in Men at Risk

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Pharmacokinetic studies showed that the peak values are higher in single testosterone ester preparations, resulting even larger plasma testosterone levels fluctuations. Therefore, most intramuscular testosterone preparations are not ideal. With the most commonly used testosterone esters, a maximum concentration is reached approximately 72 hours after injection, then showed an exponential decline during the following 10-14 days and reaches the baseline at approximately day 21, resulting low testosterone levels before next injection. The normal circadian rhythm pattern of testosterone is not reached, though it is questionable whether the circadian rhythm has much relevance. Although the level of S-dihydrotestosterone is normal, androgen metabolites are frequently not physiological and estradiol concentrations may become excessive in some men. The fluctuation levels of testosterone may be accompanied by disturbing fluctuations of sexual function, energy level, and mood. High post-injection levels of testosterone predominate androgenic and progestin, and elevated estradiol predispose acne and polycystic ovaries. Long-acting testosterone undecanoate In contrast to short-acting testosterone esters, androgen serum concentrations fluctuations were rarely observed during administration of this agent. If occurs, it is during the last two weeks before the next injection, indicating the possible development of testosterone resistance. The following regimen is recommended for T therapy in hypogonadal men (Schubert, Minnemann, et al.): After the first injection of 1000 mg TU (loading dose), the second injection of 1000 mg TU is administered 6 weeks later, followed by injections every 12 weeks. Significant increase in PSA and prostate sizes were noted; however, this is due to the fact that hypogonadal men have subnormal PSA values and small prostate sizes at baseline; and this increase is observed in every testosterone treatment upon normalization of plasma testosterone levels.

Contraindications

Contraindications to TRT include a history of breast or prostate cancer, a palpable prostate nodule or prostate serum antigen (PSA) >10 nmol/L without urological evaluation, severe low urinary tract symptoms, prostatitis and uncontrolled severe congestive heart failure. Men with obstructive sleep apnea syndrome and a prolactinoma with uncontrolled hyperprolactinemia must receive TRT with caution. As the possible development of a contraindication during treatment (especially prostatic carcinoma) requires rapid discontinuation of TRT, it is recommended to use short-acting (transdermal) oral preparations rather than long-acting (intramuscular, subdermal) depot preparations in older men.

Monitoring

Both physiological effects of treatment and testosterone levels should be monitored. The most sensitive clinical parameters to abnormally low testosterone levels are physical and mental vigour/energy, well-being, libido and sexual thoughts, as well as nocturnal and morning erections. The first effects of TRT may be perceived within 2-4 weeks, but, for sexual function, effects may sometimes take 3-6 months to become apparent and even up to 12 months for the nocturnal erections reaching the normal range in previously untreated hypogonadal patients. In case of oesteoporosis, bone mineral density should be checked after 1-2 years of therapy. Assessment of safety is mainly based on clinical assessment (especially weight, blood pressure, digital retinal examinations) and repeat PSA and haematocrit measurements. Urological consultation becomes mandatory in case of a haematocrit >54%, prostate nodule or prostate serum antigen (PSA) >10.4 nmol/L without urological evaluation, severe low urinary tract symptoms, prostatitis and uncontrolled severe congestive heart failure. Men with obstructive sleep apnea syndrome and prolactinoma with uncontrolled hyperprolactinemia must receive TRT with caution. As the possible development of a contraindication during treatment (especially prostatic carcinoma) requires rapid discontinuation of TRT, it is recommended to use short-acting (transdermal) oral preparations rather than long-acting (intramuscular, subdermal) depot preparations in older men.
To increase the shelf-life, the preparation was recently reformulated to castor oil as solvent. Recent studies showed that serum testosterone levels are proportional with the doses at a dose of 20-80 mg. Over 80% hypogonadal men showed that plasma testosterone levels are in the normal range over 24 hours at a dose of 120-240 mg/day.

Pharmacokinetic studies showed that the peak values are higher in single testosterone ester preparations, resulting even larger plasma testosterone levels fluctuations. Therefore most intramuscular testosterone preparations are not ideal. With the most commonly used testosterone esters, a maximum concentration is reached approximately 72 hours after injection, then showed an exponential decline during the following 10 to 14 days and reaches the baseline at approximately day 21, resulting low testosterone levels before next injection.

The normal circadian rhythm pattern of testosterone is not reached, though it is questionable whether the circadian rhythm has medical relevance. Although the level of Se-dihydrotestosterone is normal, androgen metabolites are frequently not physiologic and estradiol concentrations may become excessive in some men. The fluctuation levels of testosterone may be accompanied by disturbed fluctuations of sexual function, energy level, and mood.

Long-acting testosterone undecanoate

In contrast to short-acting testosterone esters, androgen serum concentrations fluctuations were rarely observed during administration of this agent. If occurs, it is during the last 2 weeks before the next injection, indicating the long duration of therapeutic effects. The following regimen is recommended for TU therapy in hypogonadal men (Schubert, Minnemann, et al). After the first injection of 1000 mg TU (loading dose), the second injection of 1000 mg TU is administered 6 weeks later, followed by injections every 12 weeks.

Significant increase in PSA and prostate sizes were noted; however, this is due to the fact that hypogonadal men have subnormal PSA values and small prostate sizes at baseline; and this increase is observed in every testosterone treatment upon normalization of plasma testosterone levels.

Contraindications

Contraindications to TRT include a history of breast or prostate cancer, a palpable prostate nodule or prostate serum antigen (PSA) >10 ng/ml, without urological evaluation, severe low urinary tract symptoms, polycystic ovary syndrome, and uncontrolled severe congestive heart failure. Men with obstructive sleep apnea syndrome and a prolactinoma with uncontrolled hyperprolactinemia must receive TRT with caution.

As the possible development of a contraindication during treatment (especially prostate cancer) requires rapid discontinuation of TRT, it is recommended to use short-acting (transdermal, oral) preparations rather than long-acting (intramuscular, subdermal) depot preparations in older men.

Monitoring

Both physiological effects of treatment and testosterone levels should be monitored. The most sensitive clinical parameters to abnor- mally low testosterone levels are physical and mental vigor, sleep, libido and sexual thoughts, as well as nocturnal and morning erections. The first effects of TRT may be perceived within 2-4 weeks, but, for sexual function, effects may take 3-6 months to become apparent and even up to 12 months for the nocurnal and morning erections, reaching the normal range in previously untreated hypogonadal patients. In case of osteoporosis, bone mineral density should be checked only after 1-2 years of therapy.

Assessment of safety is mainly based on clinical assessment (especially weight, blood pressure, digital rectal examinations) and laboratory assessment (especially liver function tests, kidney function tests, and full blood count) and clinical assessment (especially weight, blood pressure, digital rectal examinations) and laboratory assessment (especially liver function tests, kidney function tests, and full blood count).

Monitoring is usually started 3 months after initiation of therapy, with clinical, testoster- one levels, hematocrit, and PSA assessments after age 40. Prostate assessments are recom- mended quarterly for 1 year, then at 6-month intervals together with clinical, testosterone and hematocrit assessments.

CONCLUSION

Physicians need to consider testosterone levels measurement in men with metabolic syndrome, as they are actually high-risk group, but low testosterone levels currently are under-recog- nized and under-diagnosed. The combination of typical clinical symptoms and signs, together with treatment history can help identify candi- dates for testosterone screening which may include a testosterone therapy test and potential TRT. TRT can lead to significant improvements in quality of life, and may also improve outcomes in certain associated disorders.

REFERENCES