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Frank Michael Köhn

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REVIEW

Testosterone and body functions

FRANK MICHAEL KÖHN

Department of Dermatology and Allergy, University of Munich, Munich, Germany

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Abstract
Testosterone supplementation can help reduce many of the symptoms associated with androgen deficiency in the aging male by its effects on various parts of the body. Bone mineral density can decrease in the hypogonadal man and this may contribute to the increased fracture rate in the elderly. Testosterone therapy can improve bone mineral density and bone architecture by increasing bone formation and decreasing bone resorption – the possible benefits on fracture rate are unknown. Testosterone also improves body composition by reducing body fat mass and increasing lean body mass, and by increasing epidermal thickness, but its effects on muscle strength are still debated. In patients with diabetes and androgen deficiency, testosterone supplementation appears to reduce blood glucose and this could have important implications for cardiovascular risk reduction in patients with diabetes or the metabolic syndrome. The wide-ranging benefits of testosterone therapy in young and old men are clear and it appears that the route of administration (intramuscular, oral, or transdermal) does not alter this fact, but future work could illustrate even more profound effects of testosterone (e.g., in reducing cardiovascular risk) that could result in its recommended use in a wider range of patients.

Keywords: *Testosterone, hypogonadism, bone, body composition, metabolic disorders*

Introduction

According to the World Health Organization (WHO), the population over 60 years of age in developing countries will double to 700 million by 2020 and this will account for the majority of the 1000 million people aged over 60 years by 2020 [1]. Problems associated with aging are therefore worldwide and not just associated with the developed world.

For this growing population, life expectancy is continuing to increase (for example, an 80 year-old man can now expect to live for a further 7.5 years) [1] and it is important for the individual that these years are spent with a reasonable quality of life and a reasonable level of physical activity. Any loss of physical activity or age-related illness (such as fractures) also has a major impact on the overall healthcare burden. One of the most important factors in maintaining physical activity and general health in the aging male is testosterone. In men, the reduction in testosterone with age is a major contributor to age-related conditions and the organs affected include the brain, muscle, liver, skin, bone, cardiovascular system, adrenal gland, prostate gland, penis and testicles. Low testosterone has been shown to have a major impact on physical activity such as playing sports (Figure 1) and also decreases strength and endurance in 90 to 100% of men with levels below 10 nmol/l (3.0 ng/ml) [2].

In aging hypogonadal men, testosterone supplementation is therefore justified and can have wide-ranging benefits on a number of body systems. In this review paper we discuss the many effects of testosterone in the body.

Testosterone therapy and the bones

Men who are hypogonadal due to pituitary or testicular disease have lower bone mineral density (BMD) than eugonadal men [3,4]. There are several studies that demonstrate the beneficial effects of testosterone on BMD – bone formation markers increase and bone resorption markers decrease. For example, in 123 hypogonadal men aged 19–68 years given 1% testosterone gel (7.5 or 10 g/day) for 42 months, increases in serum bone markers for bone formation were measured [5]. Serum parathyroid hormone (PTH) increased after 6 months of treatment ($p = 0.0001$), continued to increase up to 12 months ($p = 0.0002$) and then stabilized for the remainder of the study period. Serum skeletal alkaline phosphatase (SALP), serum osteocalcin and serum procollagen showed a similar pattern of

Correspondence: Frank Michael Köhn, Andrologicum München, Burgstrasse 7, 80331 München, Germany. Tel: +49 89 29160655. Fax: +49 89 29160677. E-mail: info@andrologicum.com

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increases or gradually increased over the first 36 months of the study [5]. These changes corresponded to a significant increase in BMD of the hip ($p = 0.0004$) and the spine (3.1% after 18 months and 3.8% after 30 months; $p = 0.0001$ compared with baseline). Furthermore, increased BMD was similar regardless of the dose of testosterone gel used and regardless of the age of the patients [5].

In addition to these quantitative changes in bone, other studies have demonstrated that testosterone supplementation can result in qualitative changes such as improvements in trabecular architecture. This was assessed in 10 hypogonadal men using micro magnetic resonance imaging (μMRI) to measure changes in the distal tibia during 2 years of treatment with 1% testosterone gel (5 g/day) [6]. As well as BMD increases of 7.4% ($p < 0.001$) and 3.8% ($p = 0.008$) in the spine and hip, respectively, trabecular thickness was increased by 1.5% ($p < 0.001$) and the bone volume fraction increased by 5.0% ($p < 0.001$). In addition, the surface-to-curve ratio was used as a measure of the integrity of the trabecular network and this increased by 11.2% ($p = 0.004$) and erosion (measured by the topological erosion index) was reduced by 7.5% ($p = 0.004$) [6]. These findings suggest that testosterone replacement in hypogonadal men not only slows bone resorption but also reverses the deterioration of trabecular architecture caused by the testosterone deficiency.

Various formulations of testosterone have these beneficial effects on bone when administered to hypogonadal men. For example, Testim 1% testosterone gel has been shown to improve BMD of the lumbar spine, as measured by DEXA, by 2.6% ($p < 0.001$) within the first year of treatment (Figure 2) [7]. This increase after 12 months was greater than the 1.3% increase in BMD after 6 months, indicating an ongoing repletion of BMD with continued Testim 1% gel (Testim 50 mg gel) treatment.

Testosterone therapy and body composition

Testosterone supplementation improves the body composition by reducing body fat mass while increasing lean body mass in the form of muscle. However, there is some debate as to whether improvements in muscle mass lead to improved muscle strength. This increase in lean mass is probably due to

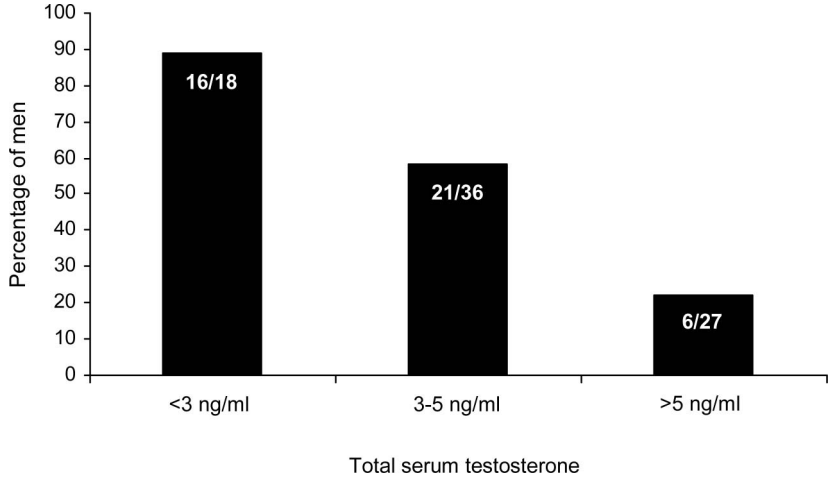

Figure 1. Percentage of aging men with deterioration in their ability to play sports and the relationship to total serum testosterone levels [2].

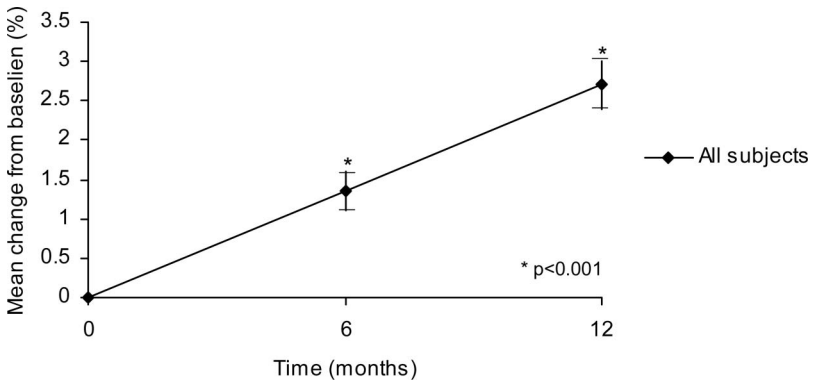

Figure 2. Bone mineral density of the lumbar spine after long-term therapy with Testim 1% testosterone gel (Testim 50 mg gel) [7]. Copyright © MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Dean J, Carnegie C, Rodzvilla J, Smith T. Long-term effects of Testim 1% testosterone gel in hypogonadal men. Rev Urol 2004;6(Suppl. 6);S22–S29. *Reviews in Urology* is a copyrighted publication of MedReviews, LLC. All rights reserved.

muscle fibre hypertrophy, which has been shown to increase when testosterone is administered to healthy men [8]. However, testosterone also stimulates mitosis in myoblasts, stimulates ribosomal activity, stimulates RNA polymerase synthesis and increases synthesis of contractile and non-contractile muscle proteins and all these effects will contribute to its effects on muscle mass.

In the study mentioned in the previous section, administration of 1% testosterone gel (5, 7.5 or 10 g/day) increased lean body mass by approximately 3 kg ($p = 0.0001$) and decreased fat mass by approximately 1.5 kg ($p = 0.0001$) after 36 months, but this did not equate to improved muscle strength – arm and leg strength increased slightly but not significantly after 36 months [5]. Similarly, in 108 men over the age of 65 years treated for 36 months with a testosterone patch that delivered 6 mg/day, fat mass decreased by 3 kg ($p = 0.001$ versus placebo) while lean mass increased by 1.9 kg ($p < 0.001$) [9]. However, leg strength, although increased, did not differ significantly from men who were given placebo.

Several other studies of testosterone replacement in hypogonadal men [10–13] and healthy elderly men [14] have demonstrated increases in muscle strength. One possible explanation for differences between studies is that the different methods used to determine muscle strength have different sensitivities. In addition, in one study showing no increase in muscle strength, the lean mass increase was primarily in the trunk but muscle strength was assessed in the legs, and therefore the results are in fact entirely consistent with the body mass changes measured [9]. Future work may clarify the effect of testosterone on muscle strength and determine whether different formulations have different effects or whether we simply need more standardized and sensitive methods for measuring muscle strength.

As with the effects on bone, the effects of testosterone on body composition are consistently observed with a variety of formulations. A 1% testosterone gel formulation reduced fat mass by 2.1% and increased lean body mass by 2.2 kg after 12 months' treatment [15], and these values are very consistent with the results from intramuscular, patch and other gel formulations in the studies described above. Indeed, a recent comparison between 1% testosterone gel 50 mg/day or 100 mg/day and a permeation enhanced testosterone patch (delivery of 5 mg/day) suggested that the higher dose of the gel may induce greater improvements in body composition [16]. The trial recruited 208 aging men with low testosterone and randomized them to one of the three treatments for 90 days. Lean body mass was significantly increased in all three treatment groups but only testosterone gel 100 mg/day significantly decreased the percentage body fat (Figure 3) [16].

Testosterone therapy – effects on metabolic disorders

In addition to the 'structural' changes to body composition, the level of testosterone in the body is also closely associated with metabolic disorders or an adverse metabolic profile. In 60 men aged 39–69 years (45% with normal glucose tolerance, 20% with impaired glucose tolerance and 35% with type 2 diabetes), there was a 3-fold higher prevalence of the metabolic syndrome in hypogonadal men than in eugonadal men [17]. Furthermore, testosterone levels were correlated with insulin sensitivity ($r = 0.4$; $p < 0.005$) and with genetic and functional markers of mitochondrial function, suggesting that testosterone modulates insulin sensitivity in men [17].

Similarly, low testosterone levels are associated with overt type 2 diabetes. In one cross-sectional study of 746 men (116 were diabetic), more men with diabetes (46%) had low levels of free serum testosterone (<0.043 nmol/l) than men without diabetes (24%). Likewise, 23% of non-diabetic men and 34% of diabetic men had low total serum testosterone (<13.87 nmol/l) [18]. The association is strongest with free testosterone, while total serum testosterone is more closely associated with obesity and central adiposity. Other studies have suggested that the association between diabetes and testosterone levels is a clear predictive relationship – low

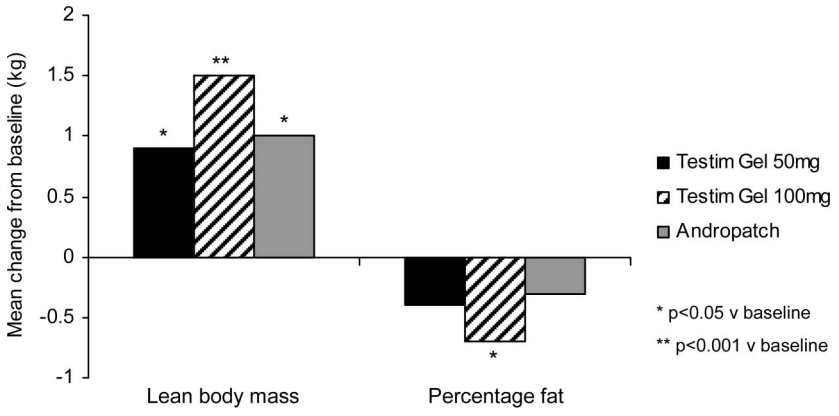

Figure 3. Changes in lean body mass and percentage fat after 90 days' treatment with testosterone gel or a testosterone patch [16].

testosterone levels predicting the development of type 2 diabetes [19–24]. From the Massachusetts Male Aging Study the risk was calculated and the value reached was as follows: for each decrease of 1 SD in free testosterone there was a 1.58-fold increased risk of developing type 2 diabetes after a median of 8.9 years [21].

This wealth of data showing a link between reduced testosterone and type 2 diabetes has led to a recent study investigating the effects of testosterone supplementation in men with type 2 diabetes (and many other studies are ongoing) [25]. Forty-eight men aged between 45 and 65 years (mean age 57 years) with type 2 diabetes, visceral obesity and partial androgen deficiency were recruited into this study and received either oral testosterone (120 mg/day) or no androgen replacement therapy for 3 months. Testosterone significantly reduced weight (by 2.66%) and reduced BMI (by 3.2%) compared with no treatment. A whole host of other measures such as waist-hip ratio and a variety of symptoms such as insomnia, fatigue and libido all improved more in patients receiving testosterone but significantly, in terms of diabetes, testosterone reduced blood glucose – HbA_{1c} levels were reduced by 17.3% (Figure 4) [25]. Fasting blood glucose, postprandial blood glucose and mean daily blood glucose were all reduced significantly with testosterone supplementation compared with no treatment. In other words, testosterone treatment improved many aspects of the metabolic syndrome and may therefore have a favourable effect on cardiovascular risk. However, the mechanisms by which testosterone reduces blood glucose in diabetes are not clear – the effects may be a result of testosterone's effects on visceral fat or insulin sensitivity.

Given the importance of insulin resistance, type 2 diabetes and the metabolic syndrome as risk factors for cardiovascular disease, these data suggest that monitoring testosterone, and if necessary supplementing testosterone levels in diabetics or prediabetics, could be an important aspect in the management of cardiovascular risk in aging men. However, possible atherogenic effects and increased risk of coronary artery disease by supraphysiological peaks of serum testosterone levels after therapy have to be considered.

Other effects of testosterone deficiency

The effects of age-related changes in testosterone levels on the skin include: a reduction in skin elasticity resulting in fragility; a reduction in epidermal thickness resulting in atrophy; reduced rete ridges, keratincoyte size and metabolic activity of keratinocytes; increased elastic degeneration; reduction in collagen content leading to wrinkling; a decreased rate of sebum excretion causing dryness; a reduced epidermal barrier causing irritation; and reduced sweat glands, number of melanocytes and number of hair follicles. Although there is some evidence that testosterone supplementation increases epidermal thickness in hypogonadal men, more data are needed on the effects of testosterone on skin immunology and atopic eczema [26].

There are therefore many other aspects of body composition and mood that are affected by low testosterone and these may benefit from testosterone supplementation. However, more research is needed to investigate these other aspects [27]. Perhaps the most important aspects are fractures and cardiovascular mortality, which are both increased in aging men with hypogonadism. The effects of testosterone replacement on these aspects are not known and have not been extensively studied. The side effects or contraindications of testosterone therapy including those concerning the prostate gland (prostate cancer, obstructive benign prostate hyperplasia) have to be considered.

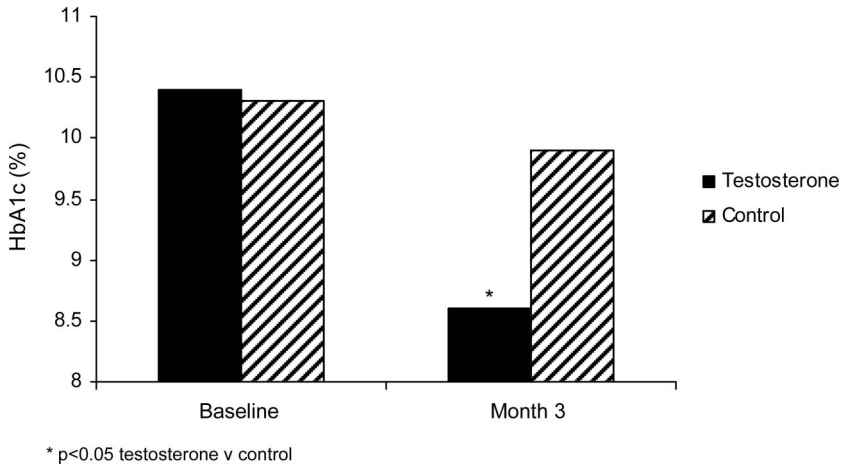

Figure 4. Reduction in blood glucose (HbA_{1c}) after 3 months of treatment with oral testosterone or after no treatment in men with type 2 diabetes [25].

Summary

There is no doubt that testosterone therapy for hypogonadal men has many positive effects on many body functions and many aspects of body composition. Administering testosterone restores serum testosterone levels to normal for most men and this results in increased bone formation and decreased bone resorption, which in turn reverses the deterioration of trabecular architecture. Body composition is improved with a decrease in fat mass and a corresponding increase in lean mass, and this may result in improved muscle strength and increased physical activity. The many effects of testosterone deficiency on the skin should be improved with testosterone replacement, and although there is not a vast amount of evidence on this, epidermal thickness is increased with testosterone administration. Testosterone supplementation also improves several features of the metabolic syndrome such as blood glucose levels in patients with type 2 diabetes and mild hypogonadism, but the longer-term effects of this in reducing cardiovascular risk are as yet unknown. Other patients with chronic diseases such as renal failure and organ transplant recipients may also have general improvements in health when given testosterone replacement therapy. The benefits of testosterone are not restricted to older men or those with severe hypogonadism but can be demonstrated in a wide range of young and old hypogonadal men, and these benefits are achieved when testosterone is delivered by intramuscular injection, orally or transdermally via patches or gels.

References

1. World Health Organization. Men, ageing and health. Aging Male 2000;3:3–36.
2. Kohn FM, Schuppe HC, Schill WB, Elbers J. Treatment of late onset hypogonadism with a new formulation of testosterone undecanoate – baseline data of a multicenter study. Andrologia 2004;36:174–175.
3. Devogelaer JP, De Cooman S, Nagant de Deuxchaisnes C. Low bone mass in hypogonadal males. Effect of testosterone substitution therapy, a densitometric study. Maturitas 1992; 15:17–23.
4. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 1996;81: 4358–4365.
5. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS. 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;89:2085–2098.
6. Benito M, Vasilic B, Wehrli FW, Bunker B, Wald M, Gomberg B, Wright AC, Zemel B, Cucchiara A, Snyder PJ. Effect of testosterone replacement on trabecular architecture in hypogonadal men. J Bone Miner Res 2005;20:1785–1791.
7. Dean JD, Carnegie C, Rodzvilla J. Long-term effects of Testim 1% testosterone gel in hypogonadal men. Rev Urol 2004;6(Suppl. 6):S22–S29.
8. Sinha-Hikim I, Artaza J, Woodhouse L, Gonzalez-Cadavid N, Singh AB, Lee MI, Storer TW, Casaburi R, Shen R, Bhasin S. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. Am J Physiol Endocrinol Metab 2001;283:E154–E164.
9. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999;84:2647–2653.
10. Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. J Androl 1992;13:297–304.
11. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 1997;82:1661–1667.
12. Bhasin S, Storer TW, Berman N, Yarasheski KE, Clevenger B, Phillips J, Lee WP, Bunnell TJ, Casaburi R. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 1997; 82:407–413.
13. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 2000;85:2839–2853.
14. Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol 1995;269:E820–826.
15. Bouloux P. Testim 1% testosterone gel for the treatment of male hypogonadism. Clin Ther 2005;27:286–298.
16. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int 2003;91:69–74.
17. Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care 2005;28:1636–1642.
18. Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int 2005;96:867–870.
19. Tibblin G, Adlerberth A, Lindstedt G, Bjorntorp P. The pituitary-gonadal axis and health in elderly men: a study of men born in 1913. Diabetes 1996;45:1605–1609.
20. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;143:889–897.
21. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. Diabetes Care 2000;23:490–494.
22. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. Diabetes Care 2002;25:55–60.
23. Svartberg J, Jenssen T, Sundsfjord J, Jorde R. The associations of endogenous testosterone and sex hormone-binding globulin with glycosylated hemoglobin levels, in community dwelling men. The Tromso Study. Diabetes Metab 2004;30:29–34.
24. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036–1041.

25. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 2003;6:1–7.
26. Kohn FM, Ring J, Schill WB. [Dermatologic aspects of male hypogonadism]. Hautarzt 2000;51:223–230.
27. O'Connor DB, Archer J, Wu FC. Effects of testosterone on mood, aggression, and sexual behavior in young men: a double-blind, placebo-controlled, cross-over study. J Clin Endocrinol Metab 2004;89:2837–2845.