

# Testosterone – The Male Hormonal Connection Treating Diabetes and Heart Disease

Michael Klentze

Cardiovascular disease (CVD) is the prime cause of death among the elderly in industrialized countries and a principal cause of chronic disability. The number of people in Germany who die a sudden death from myocardial infarction or non-stable plaque runs up to 100,000 per year. In the USA this figure is 1.3 million. A German study of approximately 1 million people showed that obesity increases with age. This is a major public health problem, as we know that body mass index (BMI) is one of the chief factors in the risk of heart disease. The average hip-waist ratio is also on the rise. The mean increase of fat mass from in men between the age of 25 and 70 runs about 15 kg., whereas the mean loss of lean body mass over the same period is approximately 8 kg. The reason for this rise in BMI, hip-waist ratio, and obesity is simple – it all comes down to lifestyle.

## Obesity and Age

Obesity reached epidemic proportions at the beginning of the new millennium. The prevalence of overweight and obesity increases with age. In the very oldest age group

however the BMI tends to decrease. There could be two reasons for this: 1) among the elderly the overweight group at risk has already died, or 2) the eating habits of the elderly change and only small amounts of calories are consumed per day. Aging is associated with visceral fat accumulation in both sexes, with the greatest accumulation found in the oldest age category (> 60 yrs). Therefore, despite the fact that energy intake as well as fat intake is either reduced or unchanged with age, an age-related weight gain can be explained by the decrease in energy expenditure due to a sedentary life style.

Recent figures suggest that Greece has the highest obesity rate in the world. The same study placed Germany and the USA in joint fourth place. However, when USA Americans are obese, they tend to be severely obese with BMI > 32. The reason for that may be a particular American paradox: There was a shift from fat intake to high carbohydrate intake in the United States. After virtually removing cholesterol and fat from the diet something was needed to give people the feeling of fullness. As a result the American diet became chock-full of carbohydrates: bread, noodles, rice, potatoes. This may be the main reason why the weight and obesity problem in the



USA is still on the increase, despite the popularity of low-fat or no-fat diets. As a consequence of this development in the USA 23% of the male population display the metabolic syndrome in which insulin resistance plays a key role.

### **Insulin is a potent stimulator of PAI-1 and SMC proliferation factor**

The endothelium of an average adult man weighs nearly 3 kg. That means that this component of the blood vessels is virtually a complete organ. It is dependent upon a variety of elements especially insulin, IGF-1, GH, testosterone and estrogens, acting via the NOS 3 gene expression. Alterations in the basic levels of these hormones dominate and regulate the endothelial function. In the arterial wall smooth muscle cells are responsible for the extra-cellular matrix, the arterial tone, and the proliferation and migration of SMC. These are important factors in the formation of neointima and stenoses. Apoptosis of SMC contributes to plaque instability and rupture. Macrophages play a key role in atherosclerosis: they can internalize large amounts of exogenous lipids by phagocytosis.

They form foam cells with a high expression of cytokines and growth factors (EGF, platelet-derived factor, IL-1, TNF alpha, IL-6), and act to stimulate the migration and proliferation of SMC (SMC proliferation factor). Insulin incites the SMC proliferation factor, and high insulin levels bring about a high proliferation and migration rate of SMC in the endothelium.

Epidemiological studies indicate that insulin levels and testosterone (T) are inversely correlated. In a study carried out by TIS Hwang in China, which examined the correlation between leptin, sex hormones and fat distribution in middle-aged and elderly men, free T, DHEA-S and SHBG differed significantly between middle-aged men and their older peers, while leptin, T testosterone, and E2 did not exhibit such differences. He found that sex hormones underwent sharp changes during the middle-aged period, whereas among the aged men levels remained rather steady. T and leptin exhibited a strong correlation with BMI and WHR.

Lipoprotein-a (Lpa) levels are affected by levels of thyroxin, human growth hormone (HGH), estrogens, and progestins, but not testosterone. Levels over 30 mg/dL are considered an independent risk factor for coronary, cerebral vascular and peripheral atherosclerotic vessel disease.

**Table 1:** Elevated Values in the following substances signal a heightened risk of acute coronary events

Insulin
S-CRP
IL-6
BMI
DHEA-S
Homocystein
PAI-1
IGF-1
Lipoprotein a

*(Source: International Task Force for the Prevention of Cardiovascular Diseases, The Expert Panel)*

## Testosterone and Diabetes Type II

The aging process is characterized by the decline of most physiological functions. Among these the decline in endocrinal functions plays an important role in the symptomatology of the aging process. In contrast to women, who undergo a rather abrupt termination of the ovarian cyclic hormonal activity, both endocrine (testosterone) and exocrine (spermatogenesis) testicular functions are preserved in men until very old age. Hence, the male equivalent of the menopause, the “andropause”, does not really exist. Nevertheless, both endocrine and exocrine functions do decline with age.

Whereas it has long been debated whether plasma testosterone (T) concentration decreases with age in healthy men, the occurrence of an age-associated decrease in bio-active testosterone concentration is no longer disputed. Normal plasma T levels vary between 11 and 40 nMol/L, reaching their maximum between the ages of 25 to 30. Testosterone circulates in plasma and approximately 50% of

it is bound to Sex Hormone Binding Globulin (SHBG), a  $\beta$ -globulin with a high affinity for T but only a limited binding capacity with T. The remaining approximately 50% of the testosterone is bound to another protein, albumin, which has a low affinity for T, but a high binding capacity with it. In young healthy males, the plasma FT concentration varies between 0,2 and 0,7 nMol/L.

The testosterone only becomes active however when the link to SHBG is broken, and this is a process which occurs at a certain rate all the time. Older men produce relatively more SHBG, as do heavy drinkers and men with thyroid disorders, thus further reducing the amount of ‘free’ testosterone. The significance of SHBG-bound testosterone is poorly understood. It has been shown that some tissues (prostatic cells) carry SHBG receptors, the activation of which leads to a stimulation of cyclic AMP. Due to the high binding affinity of SHBG, only the free and a part of the albumin-bound T is bio-available.

Male sexual function declines with age. It is now clear that the decrease in T levels as a function of age has both a testicular and hypothalamo-pituitary origin, although a decrease in Leydig (interstitial) cell function is not always accompanied by an increase of pituitary hormone LH. In elderly men, however, the LH levels are frequently not increased or only modestly increased, a consequence of the alteration of neuroendocrine control of the gonadal function. Moreover, the circadian rhythmicity of LH and T secretion is blunted in elderly men and the amplitude of LH pulses decreases. The effects of androgens in men and women are very similar and yet different (the interest in sexuality; sebum production; hair growth and loss; EPO- production; the improvement of the lipid profile in men but not in women). Testosterone is a source of estradiol, stimulating bone cells and affecting muscle and fat mass. Controlling the CYP 19 P450 gene (aromatase) has great significance for the prevention of supraphysiological estradiol levels.

In sum, free testosterone probably accounts for only 1-2 per cent of the total. Therefore the measurement of total testosterone is a poor measure of active testosterone. The measurement of free testosterone levels however is expensive and in any case not widely available. The Free Androgen Index (FAI = total testosterone/SHBG x100) is an alternative way of measuring the androgen state; it is not as reliable as measuring free testosterone, but is better than relying solely on total testosterone.

Testosterone deficiency in men is manifested typically by symptoms of hypogonadism, including decreases in erectile function and libido. 25 % of men over 65 have subnormal T levels. Testosterone also has an important role in the regulation of normal growth, bone metabolism and body composition. Men with a testosterone deficiency also display alterations in body composition, including an increase in body fat. Using quantitative CT scans to assess fat distribution, it has been shown that testosterone deficiency is associated with an alteration in site-specific adipose deposition with increased deposits in all areas particularly in the subcutaneous and muscle areas. Because truncal fat correlates with glucose intolerance and cardiovascular risk, hypogonadism may have important implications with regard to overall health and mortality. In one study, the alteration in skeletal muscle composition was associated with a decrease in muscle strength. Therefore testosterone deficiency is associated with an enhanced risk for osteoporosis, an altered body composition including increases in truncal fat, and, possibly, decreases in muscle performance.

As contrasted with women, men display a correlation between low testosterone levels and insulin resistance or Diabetes Type II (FTI). The same inverse relation is known for SHBG and insulin resistance. Low T levels are correlated with carbohydrate metabolism disorders and low levels of FT are correlated with obesity, which is the origin of insulin resistance and Diabetes mellitus Type II. Testosterone is released into the bloodstream in pulses, and levels fluctuate through the day (diurnal variation). In general, the testicles release more testosterone in the morning than later in the day. Blood samples should therefore be taken between 8 and 10 AM; moreover, at least two separate, consistent results are needed to establish that there is a problem with testosterone levels.

Because testosterone levels decline with age, and aging is accompanied by body changes including loss of muscle and an increase in fat, there is a great interest in the potential benefits of testosterone administration in elderly men. There is a role for androgens in improving body composition and function in elderly men, seeing as testosterone is an important modulator of insulin sensitivity in men. The relative hypogonadism in men with insulin resistance is traceable to an impaired Leydig cell secretion of testosterone.

Testosterone increases insulin sensitivity. Plasma FT's apparent protective effects against an atherogenic profile is

probably related to the increase of insulin sensitivity thanks to testosterone. Today there is no doubt about the relationship between androgens, body fat, and insulin sensitivity. That testosterone has an effect upon the development of body fat in men and women is well documented. Testosterone enhances lipolysis in adipocytes by increasing the expression of beta-adrenergic receptors adenylate cyclase, protein kinase A and hormone-sensitive lipase (HSL).

Additionally, T administered even in combination with an aromatase inhibitor suppresses lipoprotein-a levels. Besides the favorable effects on cardiovascular risks by physiological T levels (increasing HDL-C and decreasing LDL), T might have an indirect adverse effect on the vessels (NO- expression): T lowers Lp-a and HDL. But as shown in the Procain Study by Assmann, in which 40,000 men and women were followed for ten years, HDL alone does not seem easily correlatable with cardiovascular risk.

Testosterone improves muscle growth and strength, serum proteins, mood, libido, cognitive functions, and erythropoietin (EPO). Nearly 50% of men over the age of 80 have subnormal testosterone levels. That means total testosterone levels, because total testosterone levels normally don't decrease so much. There are some extremely important reasons for hypogonadism and these should be checked before prescribing testosterone therapy.

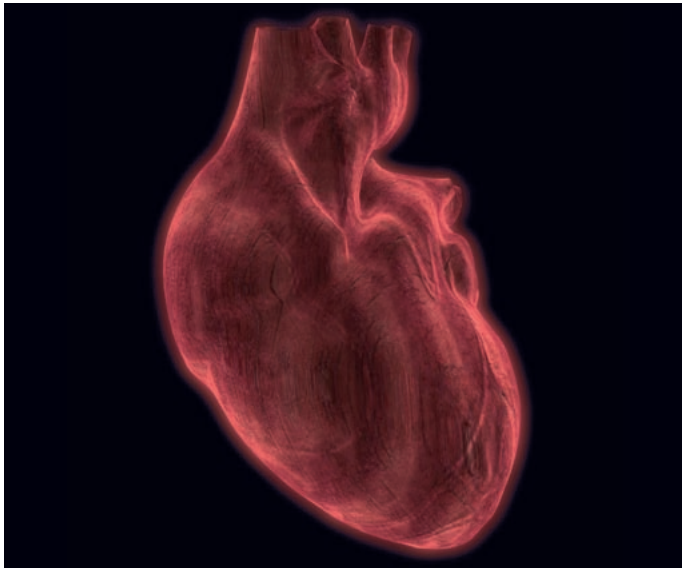
## The PPAR alpha and Gamma receptors display a decline of genetic expression during aging

These receptors are members of the nuclear receptor-transcription-factors super-family, and play an important role in the metabolism of fat (alpha) and in inflammation (gamma). Alpha regulates the genes of Beta-Oxidation, of fatty acids transport system, of Carnitin-Palmitoyl-transferase, of Acetyl-Co A synthetase, and of the 3-Hydroxy-Acyl-Co A dehydrogenase. This PPAR alpha has anti-inflammatory effects (e.g., suppression of the stress-kinases, inhibition of IL -6, IL 12, and TGF-alpha). The age-related decline of PPAR-alpha is associated with a decreased energy in mitochondria and increased inflammatory processes.

The activation of PPAR-gamma stimulates the activation of macrophages, which express the surface factor CD 36 (LDL scavenger). This is the basic condition necessary for macrophages to bind cholesterol and form foam cells.

Furthermore PPAR-gamma inhibits inflammatory cytokines and stimulates the cholesterol transport protein APCA 1, thus eliminating cholesterol. Stimulating the expression of glucose transporter GLUT 4, combined with the RXR receptor, thiazolidines are able to bind to the PPAR-gamma (anti-diabetic and anti-arteriosclerotic effects of thiazolidines by stimulating PPAR gamma). There is evidence that testosterone acts like thiazolidine on the PPAR gamma receptor. Thus it may be that testosterone displays an improved GLUT 4 mechanism.

By administering testosterone to testosterone-deficient men the levels of type 2 muscle fibers increase and glucose metabolism improves. Thiazolidines stimulate the PPAR-gamma receptor, thus improving insulin sensitivity. It has



been shown that exercise and testosterone display similar effects. In men who are within a normal total testosterone-level range the concentration of bio-available testosterone varies. If we find a low level, we will often find a generalized obesity with central subcutaneous and visceral fat distribution.

It seems that free T is not a real predictor for Diabetes type II. But Total T is indeed a predictor, especially the FTI (Free T Index). There is no difference between the concentrations of FT, DHEA, estradiol and SHBG in diabetic and non-diabetic men. In the participants of the Rancho Bernardo Study there were also no significant points found which could explain the correlation between low FT levels and diabetes. However in this same study low levels of

Total T were found to be correlated to Diabetes Type II. Testosterone was shown to increase the coronary blood flow in elderly men with heart disease. When T was administered to men with low T levels who suffered from heart disease, their ECG scores improved. Testosterone has effects on the PQ-interval of the ECG in the form of short PQ intervals. So far we know that testosterone deficiency increases heart rate and rhythmic disorders.

Testosterone deficiency in the aging male is associated with:

- A reduction in high-density lipoprotein (HDL) cholesterol and an increase in low-density lipoprotein (LDL) cholesterol, which increases the risk of developing coronary artery disease.



- An increase in total body fat. (This is due to a decline in the proportion of body weight that is muscle, rather than due to weight gain).
- Increased insulin resistance.
- Increased inflammation.

Because testosterone increases the sensitivity of the PPAR-gamma receptor and has effects similar to those of Rosiglitazone, a deficiency of androgen and an excess of estrogen will incline the carbohydrate metabolism to insulin resistance as well as increasing SHBG.

It is more than merely interesting to equilibrate the androgen deficiency of the aging male. If you have a man aged 55 with an age-related testosterone decrease and you are

considering the administration of testosterone, first give him a neuro-endocrinological exam: It is most important to determine that there is no disease in the pituitary or hypothalamus. Such men will complain about depressive moods, loss of self-confidence, cognitive defects, memory loss, decreased vitality and energy, sleep disturbances, loss of libido, and erectile dysfunction. Some will report flashes, while others will complain about nausea, and some have a very high pulse rate. Night sweating is rare.

In concluding here we can say that testosterone is useful in the treatment of Type II Diabetes since it increases the expression of the glucose transporter gene (GLUT4), and increases the sensitivity of peroxisomal PPAR- $\gamma$  receptor.

### Testosterone and NOS 3

The coronary vessel walls display the highest density of testosterone receptors. Due to the localized endothelial aromatase activity, the coronary vessels can convert testosterone to estradiol, and estradiol is a potent stimulator of nitric oxide Synthase 3 (NOS 3). Then there is the penis. Testosterone has the same effect on the penis vessels as it does on the walls of the coronary vessels – it stimulates NO production. Thus, it works in virtually the same way as Viagra. Arginine is one of the most potent stimulators of nitric oxide production. Administering arginine, which is converted to citrulline, produces NO. The “missense” variant in exon 7 of the eNOS gene is suspected to act synergistically with the promoter T>C-786 polymorphism by further increasing the risk of coronary artery disease. According to a recent meta-study, carriers of this 298Asp/Asp genotype have an increased risk of ischemic heart disease (~30% excess risk). Carriers of the Asp/Asp genotype with at least one C allele of the T-786>C variant have a ~4-fold increased risk of coronary artery disease. Carriers of this genotype should be informed of their particularly high risk if they smoke. This applies especially to men.

If this variant has indeed been detected, it makes sense to administer testosterone to the patient.

T appears to have an important relationship with risk factors for the circulatory system. In men with chronic stable angina low-dose testosterone reduces exercise-induced myocardial ischemia. Exercise is of course important for reducing obesity and lessening cardiovascular risk factors.

Testosterone therapy in hypogonadal men is indicated if the bio-available testosterone is below 30% or the Total Testosterone is below 12 nmol/L with clinically evident signs of androgen deficiency. The goal is to substitute the androgen as physiologically as possible so as to bring it within normal adult male ranges. Natural testosterone preparations are applied either intramuscularly, transdermally or subcutaneously. Oral therapy with testosterone undecanoate is effective in hypogonadal patients only for few hours. Testosterone injections can be administered, e.g. 40 mg intramuscularly every third day. A new testosterone i.m. product guarantees stable levels over 3 months (Nebido). Testosterone gels are also available and show good results in studies and clinical practice. Daily application leads to physiological testosterone serum levels without serious side effects (only rarely are there allergic skin reactions). However before embarking on testosterone substitution therapy contraindications must be excluded; these would include existing prostate cancer or male breast cancer. Therapy must be evaluated regularly: every three months in the beginning; thereafter the effects should be controlled at least once a year. In addition to inquiring into patient satisfaction, control investigations should check for clinical signs of androgen deficiency and include clinical examinations (skin, bone, breast, prostate) and lab parameters such as testosterone, SHBG, Dihydrotestosterone, estradiol, PSA, hemoglobin, hematocrit.

Benefits: Improved muscle mass and strength, decreased fat mass, improved spatial capacities, cognition and memory, improved BMI, improved „Well-Being“, improved sexual function and libido, improved energy and mood, decreased T- Cholesterol and LDL-Cholesterol and CV risk, improved insulin sensitivity and glucose levels.

### Side effects of Testosterone application:

**Gynecomastia:** Gynecomastia refers to the enlargement of the male breast, mimicking female breast appearance. Gynecomastia is not only a cosmetic problem; it also increases the risk of male breast cancer. Some men undergo a surgical intervention which very often brings insufficient results. In contrast to the breast gland of young men, the breast gland of the elderly is dominated by diffuse smooth fat and connective tissue. Although some swellings are more

indurate than others or present more density in an ultrasound examination, no reliable discrimination between true gynecomastia and lipomastia is possible. Also histologically the clinical forms are indistinguishable; there is only a gradual difference in the relation of fat to glandular tissue. G. is suggested if a skin fold below the mammilla or the alveolar mammilla exceeds 3 cm. When the BMI is less than 32, fewer than 30% of men display G.; beyond 32, the percentage increases up to 90%. An important differential diagnosis is mammary gland cancer which occurs in less than 1% of the male population (one-sided gynecomastia). In a study which examined 36 men with gynecomastia, tamoxifene brought a reduction of the gland and decreased pain in 83% of the subjects with few side effects. A complete reduction is possible only if no fibrolization and hyalinization has yet occurred. Tamoxifene blocks and protects the mammary epithelium from estrogenic effects in order to increase the androgenic effects. With regard to estrogen receptor alpha, tamoxifene acts as antagonist, on estrogen receptor beta as agonist. The distribution of both receptor types is organ specific. In breast tissue tamoxifene acts against the alpha receptor; in bone material tamoxifene stimulates the beta-receptor and therefore the bone density.

**Increased Hemoglobin and Hematocrit:** If Hct is over 50% interrupt T administration and lower the dosage.

**Prostate:** The prostate size increases 1.6% per year. There is no difference in testosterone levels between men with BPH and those without. Men with prostate cancer do not have any abnormal hormone levels (testosterone, dihydrotestosterone, Free T, SHBG; or as estradiol, cortisol). There is evidence that estradiol stimulates prostate growth in view of its relation to the uterus (utriculus). The detection of the estradiol alpha receptor and the CYP 19 (aromatase) polymorphism in men could prove especially helpful in estimating the risk of BPH by testosterone or DHEA as precursors of estradiol.

Testosterone exerts its effects on gene expression via the androgen receptor. Modulations of the transcriptional activity influenced by the AR can be assigned to a polyglutamine stretch of variable length within the receptor. This stretch is encoded by a variable number of CAG triplets in exon 1 of the AR gene. Longer triplets' residues lessen the binding of AR co-activators, hence promoting decreased androgenicity. In eugonadal men with CAG repeats' residues

of normal length, an influence of the polymorphism on androgen target tissues such as prostate spermatogenesis, bone, hair, and on metabolic parameters and psychological factors has already been demonstrated. The androgen receptor seems to be the problem. It increases its sensitivity to androgens with age due to its loss of methyl groups which are bound to the CAG triplet repeats and lead to mutations by shortening these repeats. Polymorphisms with short AR repeats are known. In the case of shortened CAG repeats peptide growth factors such as IGF-1 and EGF are expressed in high amounts. Therapy with finasteride, which blocks the 5 alpha reductase, results in a reduction of prostate size as well as PSA. Testosterone substitution should therefore be monitored by detecting the polymorphism of CAG repeats, CYP 17 (17-hydroxylase, which leads to high tissue amounts of androgens) and the polymorphism of 5 alpha reductase (which leads to high dihydrotestosterone levels in the prostate), as well by urological control (TUS) and regular PSA controls. Extending these findings to pharmacogenetic considerations, a possible modulation of androgen effects during T administration has to be considered. This point could have clinical significance especially for older men, as this group is more likely to develop unwanted side effects. In sum, treating men with testosterone should be guided by adjusting the dose to the AR polymorphism.

Epidemiological studies show no constant relation between T levels and prostate cancer. Recently a study carried out by Lunglmayr in Vienna was able to show that low serum testosterone levels were found in high-grade prostate cancers long before cancer was diagnosed, and low serum levels could be considered as an additional marker for PC: Can we administer T to men after PC therapy? Older studies showed that administering T where there is active PC leads to disastrous results. However today, with widespread PSA screening and aggressive treatment, men with early PC are usually cured, as shown by non-detectable PSA. Recent case reports show that men cured of PC who are truly hypogonadal can be carefully treated with the gel-form without activation of their cancer. Recently, T replacement in hypogonadal men at high risk of PC (by virtue of having PIN on the prostate biopsy) was shown not to result in an increased risk of PC or PSA elevation.

## References:

1. Spetz ACE, Frederiksson MG, Hammar ML. 2003. Hot flushes in a male population aged 55, 65, and 75 years, living in the community of Linköping, Sweden. *Menopause* 10:81-87.
2. Atala A, Amin M, Harty JJ. 1992. Diethylstilbestrol in treatment of postorchietomy vasomotor symptoms and its relationship with serum follicle-stimulating hormone, luteinizing hormone, and testosterone. *Urology* 39:108-110.
3. Jeffery SM, Pepe JJ, Papovich LM, et al. 2002. Gabapentin for hot flashes in prostate cancer. *Ann Pharmacother*. 36:433-436.
4. Smith MR. 2004. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology* 63:742-745.
5. Kiratli BJ, Srinivas S, Perkash I, et al. 2001. Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. *Urology* 57:127-132.
6. Hatano T, Oishi Y, Furuta A, et al. 2000. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. *BJU Int* 86:449-452.
7. Center JR, Nguyen TV, Schneider D et al. 1999. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 353:878-882.
8. Smith MR, McGovern FJ, Zietman AL, et al. 2001. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 345:948-955.
9. Smith MR, Eastham J, Gleason DM, et al. 2003. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer *J Urol* 169:2008-2012.
10. Shores MM, Sloan KL, Matsu-moto AM, et al. 2004. Increased incidence of diagnosed depressive illness in hypogonadal men. *Arch Gen Psychiatry* 61:162-167.
11. Pope Jr HG, Cobane GH, Kana-yama G, et al. 2003. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* 160:106-111.
12. Pagotto U, Gambineri A, Pelusi C, et al. 2003. Testosterone replacement therapy restores normal ghrelin in hypogonadal men. *J Clin Endocrinol Metab* 88:4139-4143
13. Khan HN, Rampaul R, Blamey RW. 2003. The use of tamoxifen for gynaecomastia at Nottingham Breast Unit. *Br J Surg* 90(s1):100.
14. Khan HN, Blamey RW. 2003. Endocrine treatment of physiological gynaecomastia. Tamoxifen seems to be effective. *BMJ* 327:301-302.
15. Woodhouse LJ, Gupta N, Bhasin M, et al. 2004. Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. *J Clin Endocrinol Metab* 89:718-726.
16. Moffat SD, Zonderman AB, Metter EJ, et al. 2004. Free testosterone and risk for Alzheimer disease in older men. *Neurology* 62:188-193
17. Quan A, Chakravarty S, Chen J-K, et al. 2004. Androgens augment proximal tubule transport. *Am J Renal Physiol* 287:F452-F459.
18. Littleton-Kearney M, Hurn PD. 2004. Testosterone as a modulator of vascular behavior. *Biol Res Nurs* 5:276-285.
19. Pugh PJ, Jones TH, Channer KS. 2003. Acute haemodynamic effects of testosterone in men with chronic heart failure. *Eur Heart J* 24:909-915.
20. Barras BJR, Thurairaja R, Persad RA. 2004. More should be done to prevent the harmful effects of long-term androgen ablation therapy in prostate cancer. *BJU Int* 00:1175-1176.
21. Thompson CA, Shanfelt TD, Loprin-zi CL. 2003. Andropause: symptom management for prostate cancer patients treated with hormonal ablation. *Oncologist* 8:474-487.

---

### Michael Klentze, M.D., Ph.D.

Specialist for gynecology; specialist for psychotherapeutic medicine. Board certified Physician of the American Board of Anti-Aging Medicine (ABAAM, USA); General Secretary of the European Society of Anti-Aging Medicine, Vienna, Austria; President of the European Council of Aging Research and Education (ECARE), Berne, Switzerland; Director of the American Academy of Anti-Aging Medicine (A4M); member of the Scientific Advisory Board of the German Society of Anti-Aging Medicine (GSAAM) and responsible for quality-certification and external relations; Medical Science Director of the Klentze Institute for Anti-Aging Medicine; member of the Scientific Board of the Medical Council for Aging Research and Education, Chicago USA (MCARE); Chairman of the Ethics Committee of the American Academy of Anti-Aging Medicine.

