Chapter 7

Testosterone,
The Male Hormone Connection:
Treating Diabetes and Heart Disease

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ABSTRACT

The purpose of this paper is to examine the links between testosterone, obesity, type II diabetes, and cardiovascular disease. The anti-aging physician approaches and treats obesity, type II diabetes, and cardiovascular disease in a very different way than that of a conventional physician. Here we will focus on testosterone replacement therapy, and will discuss the reasons for recommending a patient for replacement therapy, its benefits and its side effects.

Keywords: testosterone replacement therapy; androgen; cardiovascular disease; obesity; insulin

INTRODUCTION

Is there a link between testosterone, obesity, diabetes, hypercholesterolemia, and cardiovascular disease? Why do men die? What are the leading causes of death in men? What is the relationship between men and women?

Cardiovascular disease (CVD) is the prime cause of death among the elderly in industrialized countries, and a major determinant of chronic disability. Cardiovascular disease, cancer, stroke, accidents, medication, Lyme disease, and murder are the leading causes of death in men.

If a patient gives you $10,000 to estimate his risk of dying from a myocardial infarction (MI) in the next five years, what would you measure? Most doctors would take the patient's blood pressure; others may order an ECG as well. There is a world of difference between how a cardiologist and an anti-aging doctor would respond to such a question. A cardiologist would conduct an invasive exam with a heart catheter, arteriography etc. Anti-aging doctors would turn to the laboratory instead. So what can we do? Insulin is a strong predictor of MI within the next five years. Another is C-Reactive Protein (CRP), a marker of inflammation. CRP is produced in response to interleukin-6 (IL-6). Other predictors of myocardial infarction include DHEA-sulfate, homocysteine, plasminogen activator inhibitor type 1 (PAI1), IGF-1, and lipoprotein-a (Lp(a)).

The lifetime risk of CVD is much larger in men compared to women, suggesting that testosterone or the lack of estrogens play an important role. On the other hand, testosterone levels decrease with age, coincident with the age-related increase in atherosclerotic disease. Results obtained from cross-sectional studies suggest that men with CVD might have lower testosterone levels. While intervention studies with testosterone in older men with CVD suggest an improvement of ECG. In addition, testosterone exerts significant effects on several risk factors for CVD. Studies on intima-media thickness (IMT) of the carotid artery suggest an improvement

by administering testosterone. There is a gap in lifespan and in onset of severity of CVD with a male disadvantage. The higher rate of CVD has been attributed to the decrease of testosterone in aging men. Of significant note is that CVD and unfavourable biochemical CVD risk profiles in men (low HDL-cholesterol, high LDL-cholesterol, high triglycerides, high fibrinogen, and high PAI-1 levels) are associated with low rather than normal levels of testosterone.

The number of people in Germany who die from sudden death by MI or non-stable plaque per year is 100,000. In the US this figure is 1.3 million. A German study of approximately one million people showed that obesity is increasing with age. This is a major public health problem, as we know that body mass index (BMI) is one of the major risk factors for heart disease. The average hip-waist ratio is also on the increase. We know that the mean increase of fat mass in men between the age of 25 and 70 is 15 kg; 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 is attributable to lifestyle.

PLASMINOGEN ACTIVATOR INHIBITOR TYPE 1 (PAI-1)

The physiological role of PAI-1 is the inhibition of fibrinolysis. Therefore, the increase of PAI-1 levels caused by PAI-1 polymorphism is linked to increased blood clotting and decreased fibrinolysis. PAI-1 polymorphism correlates with high risk of CHD, stroke, embolic disease, and myocardial infarction. Women who are affected by this polymorphism should be treated with estradiol replacement, as it reduces PAI-1 levels. It is important to control aromatase activity by monitoring estradiol levels and SHBG (sex hormone binding globulin) during testosterone administration. The risk of acute MI increases with plasma levels of thrombogenetic factors (fibrinogen, PAI-1, factor VII). Those plasma levels are inversely correlated with endogenous testosterone in men.

Insulin is a potent stimulator of PAI-1

In the arterial wall smooth muscle cells (SMCs) form the extracellular matrix, and play an important role in determining arterial tone. Proliferation and migration of SMCs are important steps in the formation of neointima and stenoses. Apoptosis of SMCs contribute to plaque instability and rupture. Macrophages play a key role in atherosclerosis as they can internalise large amounts of exogenous lipids by phagocytosis. They also form foam cells, cytokines, and growth factors (EGF platelet derived factor, IL-1, TNF-alpha), and stimulate the migration and proliferation of SMCs.

Obesity

Obesity reached epidemic proportions at the beginning of the new Millennium. The prevalence of obesity increases with age and reaches a maximum between the ages of 50 and 59 years. There is a tendency for the mean BMI to decrease in the oldest age group.

Aging is associated with visceral fat accumulation in both genders, with the highest prevalence being in the oldest age group (> 60 years). Energy intake, as well as fat intake, either drops or remains unchanged with age, and thus age-related weight gain is associated with a decrease in energy expenditure due to an increasingly sedentary lifestyle.

Recent figures suggest that Greece has the highest obesity rates in the world. The same figures placed Germany and the US in joint fourth place. However, when Americans are obese, they tend to be severely obese. The reason for that is the carbohydrate problem in the United States. You can say that it is an "American paradox": after removing cholesterol and fat from the diet something was needed to give people the feeling of fullness. As a result the American diet became packed-full of carbohydrate: bread, noodles, rice, potatoes, and so on. This is the reason

why the weight and obesity problem in the US is still on the increase, despite the popularity of low-fat or no-fat diets. Of men in the US, 23% have the metabolic syndrome, in which insulin resistance plays a key role. Epidemiological studies indicate that insulin levels and testosterone are inversely correlated.

A study by Hwang examining the correlation between leptin, sex hormones, and fat distribution in middle-aged and aged men, showed that free testosterone, DHEA-S and SHBG levels were significantly different in middle-aged men and their older peers. However, leptin, testosterone, and estradiol levels were similar. The study also revealed that sex hormone levels change steeply during middle-age, but much more steadily in older-age. Testosterone and leptin levels were found to be strongly linked with BMI and waist-hip ratio.

Lipoprotein-a (Lp(a)) levels are affected by levels of thyroxin, human growth hormone (hGH), estrogens, and progestins. Levels of 30 mg/dL and above are considered an independent risk factor for coronary, cerebral vascular, and peripheral atherosclerotic vessel disease. But what about cholesterol? Cholesterol is not a predictive factor of MI. Unfortunately, cholesterol has been relegated to a convenient marketing tool for a lot of industries to sell product. Recent studies suggest that the cardiovascular risk factors we should be concerned about are Lp(a), insulin, homocysteine, fibrinogen, and PAI-1.

Fat Cells

The fat cell, as we know, does not only store fat, it is a very active metabolic cell. Fat cells secrete a number of substances that have a direct effect upon insulin. They also manufacture estradiol, estriol, and estrone by aromatization of testosterone, thus obese people lose their testosterone to their fat cells. Fat cells also secrete angiotensin, which is known to increase blood pressure. Furthermore, there are three hormones that increase the number of fat cells and increase fat storage in these cells, thus making a bad situation worse. These are cortisol, insulin, and estradiol. Estradiol plays a role in pregnancy, and men and women who get high levels of estradiol get fatter and fatter. Estradiol is a fat hormone.

Leptin

Leptin, which stimulates the hypothalamus, is secreted by adipocytes. Leptin by itself is a product of the OB gene, the obesity gene, and is an adipose cytokine. It is secreted by white fat cells, and its primary role is in adaptation to negative energy balance. In normal circumstances, leptin stimulates the hypothalamic satiety center and creates a feeling of fullness. However, obesity increases leptin levels and can cause leptin resistance. If a person has leptin resistance, the concentration of leptin is sufficient to stimulate the hypothalamic satiety center, however, due to the body's resistance to leptin, only some of the leptin stimulates the hypothalamus. This triggers hunger, and thus the person feels the need to eat more.

Leptin also plays a role in the regulation of insulin levels and insulin sensitivity. When we have higher body fat, we also have higher leptin levels and higher insulin levels. This is the correlation between leptin, BMI, and fat. Metformin is used to decrease insulin levels in people with type II diabetes. However, what is interesting is that metformin does not increase leptin levels. Metformin is the only drug that lowers insulin levels without raising leptin levels.

Adiponectin

Another hormone of interest is adiponectin. Adiponectin is interesting because it has a direct correlation with insulin. Adiponectin is an adipose-derived peptide and it acts as a systemic regulator of glucose and lipid metabolism. There is a strong relationship between adiponectin, BMI, and body composition. We also know that adiponectin is a mediator of insulin sensitivity, and an enhancer of fatty acid oxidization. Thus, suggesting that it encourages fat burning and weight loss. If adiponectin levels are low, insulin is not able to phosphorylate the insulin receptor, which normally happens at the tyrosine residuals of the insulin receptors. This

phosphorylation stimulates the starting of the insulin effect. This is why we need adiponectin. Low levels of adiponectin have been linked with an increased risk of cardiovascular disease.

Athlersclerosis

Atherosclerosis is a chronic inflammatory disease. In the early stages of all age-related diseases we find the same pathogenesis: inflammation. Inflammation provides us with a link between Alzheimer's disease, heart disease, and cancer. It takes a long time to build up plaques. A fundamental part of the pathology of atherosclerosis or coronary sclerosis is damage to the endothelial wall of the artery. This causes macrophage-stimulating cytokines to migrate to the damaged endothelium and trigger inflammation. Then we start to see the development of plaques. Atherosclerotic plaques begin to develop when oxidized cholesterol molecules accumulate inside the wall of an artery. However, the problem is not caused by cholesterol itself. The problem is the inflammation and the oxidation.

One of the central mediators for inflammation is cyclooxygenase-2 (COX-2). COX-2 expression is exacerbated by omega-6 fatty acids but inhibited by omega-3 fatty acids. Cytokines, such as interleukin-6 (IL-6), and proliferation factors (SMP) that are produced by macrophages all increase the supersensitive CRP. High CRP levels (2.0 or higher) are a predictor for atherosclerosis. Both COX-2 expression and cytokines are inhibited by testosterone.

Coronary atherosclerosis in most men is a chronic disease. Most men have plaques that are very stable. But plaques that are unstable can erupt tomorrow. This is why you cannot predict sudden death, for example, by bike ergometry. So we have to diagnose very early. What is very interesting is that the whole scientific community is now beginning to turn to preventive medicine after years of focusing on curative medicine.

Atherosclerosis is a multifactorial disease. According to the International Task Force for the Prevention of Cardiovascular Diseases, its pathogenesis is favored by non-modifiable risk factors, such as age, sex, and positive family history, as well as:

- Obesity
- Smoking
- Diabetes mellitus
- Hip-Waist Ratio
- BMI increase
- Arterial hypertension
- High blood levels of LDL-C cholesterol
- Low levels of HDL-cholesterol
- High Lipoprotein-a levels
- High insulin levels

Insulin and Type II Diabetes

Insulin levels are on the rise in obese people. Insulin levels can be elevated even when glucose levels are normal. It is possible for a person to have a glucose level of 90 or 100, which is normal for people of around 50-years of age, and an insulin level of 16 or 20.

Insulin levels, serum glucose and lean body mass are very closely correlated. When insulin is increasing, what happens then? This is called insulin resistance. Insulin affects HDL, and fibrinolysis. It also increases the proliferation of smooth muscle cells, which can lead to the development of atherosclerotic plaques and hypertension.

Type II Diabetes

In the year 2000, the US spent roughly US$2 billion on the treatment of diabetes. There are 20-million people in the US with diagnosed diabetes, and 90% of these people have Type II, not Type I, diabetes. However, there are also a significant number of people with undiagnosed Type II diabetes. Diabetes affects more African-Americans and Hispanics than Caucasians. This is probably due to the fact that African-Americans and Hispanics are more susceptible to obesity.

Type II diabetes mellitus is diagnosed when a person has a fasting glucose of 126 mg/mL or more; and an oral glucose tolerance test result of under 190 mg/mL after one hour, and under 140 mg/mL after two hours. The optimum insulin level is 8 mg/mL or below. People with insulin resistance may present with a fasting glucose of 100mg/mL or more. However, they may also have normal glucose levels. The majority of people affected by insulin resistance are over 30-years old, but the condition is on the increase among younger people, especially in Western countries. They are often overweight by 20% or more of their bodyweight. Typically these people present with high glucose levels, but this is not always the case.

More and more, overweight children are presenting with insulin resistance and this is a real public health problem. These youngsters have increased LDL levels, decreased HDL levels, increased triglyceride levels, raised blood pressure, increased fibrinogen levels, increased CRP levels, increased PAI-1 levels, and increased levels of inflammatory markers. They also have endothelial dysfunction. Basically, they are suffering from metabolic syndrome, which includes obesity, hypertension, hyperglycemia, hyperinsulinemia, and dyslipidemia.

The Role of Anti-Aging Medicine

Anti-aging medicine should start in a child's first year, or possibly even during pregnancy. Studies have shown that children with a low birth weight have a higher risk of insulin resistance. In adults, obesity leads to insulin resistance. However, in adults the beta cells are usually healthy, thus a person with insulin resistance may have normal glucose levels but high insulin levels. But in children the beta cells are not healthy enough to compensate for this insulin resistance so they have high glucose levels and they develop Type II diabetes.

So what can we do? The first thing is to change the lifestyle. Before we start with hormone treatment or any other medical intervention, the patient should be encouraged to start eating healthily and exercising regularly: exercise is far more effective at treating insulin resistance than any medicine. Patients should be advised to switch to a low glycemic diet, which provides carbohydrates that do not rapidly increase glucose levels. This means no potatoes, no rice, no pasta, and no bread. So what can be eaten on a low glycemic diet? Natural rice, full corn, etc. Men should be encouraged to combine aerobic exercise with strength training. Because if you build up muscle, glucose will be burned better when insulin levels drop. Other things to consider are testosterone and metformin.

Human growth hormone (hGH) could be of great benefit but it is very expensive and it is always better to start first with lifestyle changes and testosterone. These steps will increase IGF-1 levels in most cases. HGH is stimulated by a hormone called ghrelin.

Ghrelin

Ghrelin is mainly produced in the stomach, and is the only hormone secreted into the blood that stimulates appetite in order to increase the energy balance of the body. Moreover, ghrelin displays several functions, the exact role of these functions is currently uncertain but they are thought to regulate ghrelin receptors in the periphery. The testicles as well as the ovaries belong to the functional area of ghrelin, and the Leydig cells of the testicles produce ghrelin by themselves. Thus suggesting that ghrelin is the link between reproductive function and metabolism in the human species. A study by Pagotto *et al* examining the correlation between ghrelin and testosterone in hypogonadal men revealed that plasma levels of ghrelin are

significantly reduced in hypogonadal men compared to eugonadal men. The results also showed that administering testosterone to these men causes ghrelin levels to rise to normal levels. Because hypogonadal men have decreased ghrelin levels they should be very slender because of the reduced appetite. However, decreased ghrelin levels actually do the opposite. Obese men also have low ghrelin levels. None of the studies conducted in this area have been able to link low ghrelin levels in obese men to insulin resistance. However, it is very interesting that ghrelin resistance in hypogonadal men and obese men can be responsible for the low levels of the hormone.

Testosterone may activate the androgen receptor, present on the X chromosome, to increase the gene expression of ghrelin. When considering prescribing a patient with testosterone, it is important to consider andropause. Andropause is the decrease in bioavailable or "free" testosterone that occurs with age: this normally occurs at 2% per year starting at around the age of 25. Therefore a 50-year-old man will have lost about 50% of his testosterone, which is a lot. Measuring free testosterone is quite complicated as it changes from lab to lab, and there are only a few good assays available. Therefore, it is easier to measure total testosterone and sex hormone-binding globulin (SHBG), and then determine the free androgen index.

TESTOSTERONE

The aging process is characterized by a decline of most physiological functions. Among these, the decline in endocrine functions plays an important role in the symptomatology of the aging process. In contrast to women, who experience a rather abrupt termination of the ovarian cyclic hormonal activity, in men both endocrine (testosterone) and exocrine (spermatogenesis) testicular functions are preserved until very old age. Hence, the male equivalent of the menopause: the andropause, does not really exist. Nevertheless, both endocrine and exocrine function decline with age. Whereas it has long been debated whether plasma testosterone concentration decreases with age in healthy men, the occurrence of an age-associated decrease in bioactive testosterone concentration is no longer disputed.

Normal plasma testosterone levels range between 11 and 40 nMol/L, and reach their maximum at 25 to 30 years. Approximately 50% of testosterone circulating in plasma is bound to sex hormone binding globulin (SHBG), a ß-globulin with high affinity but limited binding capacity for testosterone, and the remaining 50% is bound to albumin, which has a low-affinity for testosterone but a high binding capacity. In young healthy males, the concentration of free testosterone in plasma varies between 0.2 and 0.7 nMol/L. Because of the high binding affinity of SHBG, only the free testosterone and part of the albumin bound testosterone is bioavailable. 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 the stimulation of cyclic AMP. The formula for determining bioavailable testosterone is as follows. The bioavailable index is the total testosterone divided by SHBG multiplied by 100%.

Male sexual function declines with age. It is now clear that the age-associated decrease in testosterone levels has both a testicular and hypothalamo-pituitary origin, but Leydig cell function decrease does not always occur together with an increase of the pituitary hormone luteinizing hormone (LH). However, LH levels in elderly men frequently remain stable or only increase modestly, because of the alteration of neuroendocrine control of gonadal function. Moreover the circadian rhythmicity of LH and testosterone secretion is blunted in elderly men and the amplitude of LH pulses decrease.

Where are the testosterone receptors? If you ask most doctors they would say testosterone is in the testis, in the penis, perhaps in the brain. Nobody would think that the walls of the coronary vessels have the most testosterone receptors. The coronary vessels can convert testosterone to estradiol, and estradiol is the most potent stimulator of nitric oxide (NO). Therefore the walls of the coronary vessels have the most testosterone receptors, next is the brain,

then bone, then muscle, and then fat. So why don't doctors prescribe testosterone men with problems in the knees or hips? There is no reason why they shouldn't. Measure it and use it.

Then there is the penis. Testosterone has the same effect on the penis 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. If you give a patient arginine it is converted to citraline and then nitric oxide is produced.

Testosterone Deficiency

Testosterone deficiency in men is manifested typically by symptoms of hypogonadism, including decreases in erectile function and libido. One quarter of men over 65 have subnormal testosterone levels. Testosterone also has an important role in the regulation of normal growth, bone metabolism, and body composition. Specifically, testosterone deficiency is an important risk factor for osteoporosis and fractures in men. In men older than 65 years of age, the incidence of hip fracture is 4 to 5 in 1000, and approximately 30% of all hip fractures occur in men. Men with testosterone deficiency have significant decreases in bone density, particularly in the trabecular bone compartment. Testosterone deficiency has been reported in over half of elderly men with a history of hip fracture. Men with testosterone deficiency also have alterations in body composition, which includes an increase in body fat. Quantitative CT scans that assess fat distribution have 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. Therefore, testosterone deficiency is associated with an enhanced risk for osteoporosis, altered body composition including increases in truncal fat, and, possibly, decreases in muscle performance.

Benefits of Testosterone Replacement Therapy

Administration of adequate testosterone replacement therapy leads to improvements in libido and erectile function. Following testosterone replacement, men note an increase in energy and mood, which may reflect either direct behavioral effects of androgens, and/or, an elevation of hematocrit due to rising testosterone levels.

Testosterone therapy in hypogonadal men is indicated if bioavailable testosterone is below 30% or total testosterone is below 12 nmol/L, and clinical signs of androgen deficiency are evident. The aim of testosterone therapy is to substitute the androgen within normal adult male ranges and keep levels as physiological as possible. Natural testosterone preparations are used, applied either intramuscularly, transdermally, or subcutaneously. The most important thing to remember when prescribing testosterone is to always maintain physiological levels. When we have supraphysiological levels we get problems, such as decreasing HDL levels. However, this only happens with supraphysiological levels. Supraphysiological levels tend to arise if testosterone is administered by intramuscular injection. Thus, the best way to deliver testosterone is via testosterone gels, which have proven effective in studies and clinical practice. Daily application of testosterone gels leads to physiologic testosterone serum levels without serious side effects.

There are some very, very important reasons for hypogonadism and these should be thoroughly investigated before prescribing testosterone therapy. It is very important to determine that there is no disease in the pituitary, or hypothalamus. Symptoms of low testosterone levels include:

- Depressive mood
- Lack of self confidence
- Lack of cognition and memory

- Decrease of vitality and energy
- Hot flashes
- Tendency to cry
- Nausea
- Fast pulse rate
- Sleep disturbances
- Night sweating (rare)
- Lack of libido

Prior to beginning testosterone replacement therapy, contraindications must be excluded, such as existing prostate cancer, or male breast cancer. Therapy must be evaluated regularly at intervals every 3 months in the beginning, and at least 12-month intervals thereafter. Control investigations include clinical signs of androgen deficiency and patient satisfaction, clinical examinations (skin, bone, breast, prostate), and lab parameters such as testosterone, SHBG, dihydrotestosterone, estradiol, PSA, hemoglobin, and hematocrit.

Testosterone therapy also leads to important beneficial effects on the skeleton and lean tissue mass. Testosterone replacement increases bone density in hypogonadal men, with the most dramatic effects seen in the trabecular bone compartment. These effects may be seen as early as 6 months following initiation of testosterone therapy. In one recent study of the long-term benefits of testosterone therapy, the greatest benefits in trabecular bone were seen in the first several years of therapy.

With regard to body composition, testosterone replacement therapy results in a dramatic reduction in adipose content, with the greatest effects seen in the subcutaneous and skeletal muscle areas. Testosterone enhances lipolysis in adipocytes by increasing the expression of beta-adrenergic receptors, adenylate cyclase, proteinkinase A and hormonsensitive lipase (HSL). Androgen therapy also leads to a significant increase in lean skeletal muscle mass and strength. Therefore, there are beneficial effects of testosterone replacement on body composition and bone mineral density in adult hypogonadal men that may serve as indications for therapy in addition to libido and sexual function.

Because testosterone levels decline with age, and aging is accompanied by body changes including loss of muscle and increases in fat, there is a great interest in the potential benefits of testosterone administration in elderly men. In a recent randomized, placebo-controlled trial Snyder *et al* administered testosterone via a scrotal patch to 108 elderly men for 3 years. Results showed that testosterone administration had beneficial effects on both lean body and fat mass. Testosterone increases levels of fast-twitch (type 2) muscle fibers, levels of which decrease with age. Thus, if you add testosterone to your intervention, levels of type 2 muscle fibers will increase and glucose burning will improve. Therefore, there may be a role for androgens in improving body composition and function in elderly men.

Testosterone is an important modulator of insulin sensitivity in men. The relative Hypogonadism in men with insulin resistance is due to impaired Leydig cell secretion of testosterone. Testosterone increases Insulin sensitivity. The apparent protective effects of plasma free testosterone against an atherogenic profile in the physiological male concentration range of free testosterone is probably related to increases in insulin sensitivity by caused by testosterone. Additionally, testosterone administered even in combination with an aromatase inhibitor suppresses Lp(a) levels, and physiological testosterone levels have favourable effects on cardiovascular risk factors (increasing HDL cholesterol and decreasing LDL cholesterol). However, testosterone may have a direct adverse effect on the vessels by interfering with nitric oxide (NO) expression and lowering Lp(a) and HDL-cholesterol levels. Although, results of the PROCAM Study by Assmann *et al*, in which 40.000 men and women were followed for ten years, suggested that HDL cholesterol alone is not easily correlated with cardiovascular risk.

HDL-cholesterol levels appear to be more clearly associated with insulin resistance and hypercholesterolemia than coronary risk, whereas Lp(a) is an important risk factor for myocardial infarction, venous thromboembolism, and stroke. More than 25% of all men and women have high Lp(a) levels: that is, an Lp(a) level of 30 mg/dl and above. Lp(a) levels are largely determined by genetics, however levels are also clearly moderated by hormonal status. Testosterone has also been shown to increase coronary blood flow in elderly men with heart disease. Men with low testosterone levels who had heart disease achieved better ECG scores after being treated with testosterone.

In summary, the benefits of testosterone replacement include:
- Improved muscle mass and muscle strength
- Decreased fat mass
- Improved spatial capacities, cognition, and memory
- Improved bone mineral density
- Improved "well-being"
- Improved sexual function and libido
- Improved energy and mood
- Decreased total-cholesterol and LDL-cholesterol levels
- Improved insulin sensitivity and glucose levels

Side Effects of Testosterone Replacement
Gynecomastia

Gynecomastia describes the enlargement of the male breast, to the extent that it mimics female appearance. Gynecomastia is a cosmetic problem and increases the risk of male breast cancer. Some men undergo surgery to correct the problem, however such procedures often produce insufficient results.

In contrast to young men, the breast of the elderly is composed of diffuse smooth fat and dominated by connective tissue. Although some swellings are more indurate than others or present a more dense aspect in ultrasound, no reliable discrimination between true gynecomastia, which is caused by proliferation of glandular tissue, and lipomastia, which is caused by a proliferation of adipose tissue, is possible. Gynecomastia and lipomastia are also very difficult to distinguish between histologically, as there is only a gradual difference in the relation of fat to glandular tissue. Gynecomastia is suggested if a skin fold below the mamilla or the alveolar mamilla exceeds 3 cm. Another aid to diagnosis is the fact that less than 30% of men with a BMI below 32 display gynecomastia, however this rises to 90% in men with a BMI in excess of 32. It is important to exclude mammary gland cancer in patients presenting with gynecomastia.

Khan *et al* treated 36 men with gynaecomasty with tamoxifen. Results showed that the drug caused a reduction of the gland in 83% of participants and decreased tenderness in 84%. Tamoxifen is a specific estrogen receptor modulator (SERM), which blocks the mammary epithelium from the effects of estrogens in order to increase the androgenic effects. Tamoxifen acts on estrogen receptor alpha as an antagonist, and estrogen receptor beta as agonist. The distribution of both receptor types is organ specific. In breast tissue tamoxifen acts against the alpha receptors that dominate breast tissue, and in bone the drug stimulates the dominating beta-receptors, therefore affecting bone density.

Prostate

The prostate increases in size by 1.6% per year. There is no difference in testosterone levels between men with and without benign prostate hyperplasia (BPH), and men with prostate cancer do not have abnormal hormone levels of testosterone, dihydrotestosterone, free testosterone, SHBG, estradiol, or cortisol, However, there is evidence that estradiol stimulates prostate growth. Thus, the detection of the estradiol alpha receptor and the CYP 19 (aromatase)

polymorphism in men could be useful for estimating the risk of a patient developing BPH if they were prescribed testosterone or DHEA, as these are both precursor of estradiol.

Testosterone exerts its effects on gene expression via the androgen receptor (AR). Modulations of the transcriptional activity influenced by the androgen receptor can be assigned to a polyglutamine stretch of variable length within the AR. This stretch is encoded by a variable number of CAG triplets in exon 1 of the AR gene. Longer triplets residues mitigate binding of AR co-activators and, thus, facilitate decreased androgenicity. In eugonadal men with CAG repeat residues of normal length an influence of the polymorphism on androgen target tissues such as the prostate, spermatogenesis, bone, hair, metabolic parameters, and psychological factors has yet been demonstrated. The AR itself seems to be the problem, as it increases its sensitivity to androgens with age due to its loss of methyl groups bound to the CAG triplet repeats, thus shortening the repeats and causing mutations. Polymorphisms with short AR repeats are known. In the case of shortened CAG repeats, peptide growth factors like IGF-1 and EGF are expressed in high amounts. In such cases treatment with finasteride, which blocks 5 alpha-reductase results in a reduction of prostate size as well as a decrease in prostate specific antigen (PSA) levels. Thus it may be of benefit to test patients to see if they have any of the following polymorphisms: CAG repeat, CYP 17 (17-hydroxylase, which leads to high tissue amounts of androgens) and 5 alpha-reductase (which leads to high dihydrotestosterone levels in the prostate). It is also important to regularly check PSA levels and urological controls (TUS). Extending these findings to pharamcogenetic considerations during testosterone administration has to be considered. This aspect could gain clinical significance especially in older men, as they are more likely to develop unwanted side effects. Thus when treating men with testosterone it is important to take into account the AR polymorphism when deciding the dose.

Epidemiological studies show no constant relationship between testosterone levels and prostate cancer. Recently a study by Lunglmayr *et al* showed that low serum testosterone levels were found in patients with high-grade prostate cancers long before cancer was diagnosed, thus suggesting that low serum levels could be considered as an additional marker for prostate cancer.

Can we administer testosterone to men who have undergone treatment for prostate cancer? Older studies showed that administering testosterone to patients with active prostate cancer leads to disastrous results. However today, with widespread PSA screening and aggressive treatment, if prostate cancer is caught early enough it is often curable, as shown by no-detectable PSA. Recent case reports show that men who have been cured of prostate cancer and who are truly hypogonadal men, can be treated carefully with gel without activation of their cancer. Recently, testosterone replacement in hypogonadal men deemed at high risk of prostate cancer (by virtue of having a high-grade PIN (prostatic intraepithelial neoplasia) on prostate biopsy) was shown not to result in an increased risk of prostate cancer or PSA elevation.

Increased Hemoglobin and Hematocrit

Testosterone replacement can lead to increased hemoglobin levels and hematocrit (Hct). If Hct rises by more than 50%, testosterone administration should be interrupted and the dosage should be lowered.

Testosterone and Type II Diabetes

How do modern antidiabetic drugs, like rosiglitazone (Avandia) work? Avandia stimulates the PPR gamma receptor, thus improving insulin sensitivity. Thus it does the same as exercise and testosterone. Pioglitazone and metformin have virtually the same effects. Men in contrast to women display a correlation between low testosterone levels and insulin resistance and type II diabetes, while the same inverse relation is known for SHBG and insulin resistance. Low testosterone levels are correlated with type II diabetes and carbohydrate metabolism disorders, and low levels of free testosterone are correlated with obesity, which is the origin of insulin resistance and type II diabetes. It is important to remember that free testosterone is not a

real predictor for type II diabetes. When calculating a patient's risk of developing type II diabetes total testosterone and the FTI (free testosterone index) should be considered. There is no difference between the concentrations of free testosterone, DHEA, estradiol, and SHBG in non-diabetic and diabetic men.

To summarize, testosterone administration in men with type II diabetes has shown the following benefits:

- Lowered insulin levels
- Lowered glucose levels
- Lowered HbgA1c levels and decreased glycated endproducts
- Saved insulin in the late stages of the disease

Testosterone is useful in the treatment of Type II diabetes, because it increases the expression of the glucose transporter gene (GLUT4), and increases the sensitivity of peroxisomal PPAR-alpha and gamma receptors. Approximately 85% of the population have PPAR-alpha receptor mutations, and these people develop insulin resistance very, very quickly. The PPAR-alpha and gamma receptors show 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 inflammation (gamma). The alpha receptor has anti-inflammatory effects (via suppression of Nfkappa B, and stress-kinases, and inhibition of IL-6, IL-12, and TGF-alpha). Thus, the age-related decline of PPAR alpha results in increased inflammatory processes as well as a decrease of energy levels in mitochondria. The activation of PPAR gamma stimulates the activation of macrophages, which express surface factor CD 36 (LDL scavenger), and foam cells are formed. Furthermore, PPAR gamma inhibits inflammatory cytokines, and stimulates the cholesterol transport protein APCA 1, which eliminates cholesterol.

Because testosterone increases the sensitivity of the peroxisomal PPAR gamma receptor and has similar effects as rosiglitazone, androgen deficiency and estrogen excess shifts the carbohydrate metabolism to insulin resistance and increases SHBG levels. The loss of testosterone in middle and older-age, which in turn increases the risk of obesity and insulin resistance and increases SHBG levels, also increases the risk of type II diabetes.

What happens to the concentration of free testosterone and estradiol as we age? Estradiol levels normally increase, while testosterone levels decrease. Diabetic men typically have lower testosterone levels than non-diabetic men. Hyperandrogenemia is associated with high BMI, high waist-hip ratio, high blood pressure, higher glucose and insulin levels, and higher levels of LDL-cholesterol and triglycerides. One of the reasons why obese men tend to have low levels of bioavailable testosterone, and higher levels of estradiol or estrogens is because they are aromatising a lot of testosterone in the fatty cells. Another is that estradiol increases SHBG levels. SHBG levels increase with age and free testosterone levels decrease with age.

Estradiol is an important hormone and sometimes it is necessary to give men estradiol. If a man is very small, and if he has nearly no fat mass, his estradiol level is typically below 12, which is not measurable. Such low levels of estradiol can lead to osteoporosis. Studies in men with a lack of aromatase enzyme found that men with no estradiol, but normal testosterone levels suffered from osteoporosis. Estradiol is responsible for the inhibition of bone mass loss.

The breakdown mechanism of estradiol has a significant impact upon testosterone. If we are looking at estradiol levels, and we have a patient with high estradiol levels and normal SHBG levels, the problem is likely to be down to breakdown enzymes. If there is a slow breakdown of estradiol it tends to, accumulate in tissues. Estradiol is broken down into water-soluble compounds that can be excreted in the urine. Normally, you would prescribe testosterone to increase estradiol levels, however this will not work in men with not enough aromatase. So in some cases it may well be necessary to prescribe estradiol.

CONCLUSION

The potential benefits of androgen therapy for older men, include maintenance or improvement in bone density, improved body composition (that is, ratio of fat to lean muscle mass), improved strength, improved libido and sexual function, improved mood, and improvement or maintenance of cognitive function.

Current data on cardiovascular risk suggest that it is better for men to have a high rather than a low testosterone level. In general, higher serum testosterone levels correlate with lower metabolic cardiovascular risk factors, including higher high-density lipoprotein (HDL) cholesterol levels, lower blood pressure, and lower levels of plasma fibrinogen, fasting insulin, and lipoprotein. Nonetheless, concerns about this issue tend to raise basic questions about why men have more cardiovascular disease than premenopausal women: Are estrogens protective, are androgens causative, or both? Recent well-controlled data are insufficient to provide a definitive answer. Generally, parenteral testosterone therapy in older men results in a decline in serum levels of total cholesterol and low-density lipoprotein (LDL) cholesterol, and no change in HDL cholesterol, although a few new studies show a decline in HDL cholesterol with treatment.

Thus, most of the available evidence suggests that testosterone replacement is potentially beneficial to aging men, particularly in the areas of bone density and body composition. However, the magnitude and longevity of the beneficial effects of testosterone replacement are currently uncertain.

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