

## Review Article

# The Role of Testosterone in the Etiology and Treatment of Obesity, the Metabolic Syndrome, and Diabetes Mellitus Type 2

Farid Saad<sup>1,2</sup> and Louis J. Gooren<sup>3</sup>

<sup>1</sup> Bayer Schering Pharma AG, Scientific Affairs Men's Healthcare, D-13342 Berlin, Germany

<sup>2</sup> Gulf Medical University School of Medicine, Ajman, UAE

<sup>3</sup> Endocrinology, VUmc, Amsterdam, The Netherlands

Correspondence should be addressed to Farid Saad, farid.saad@bayerhealthcare.com

Received 22 March 2010; Accepted 6 July 2010

Academic Editor: A. Halpern

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Obesity has become a major health problem. Testosterone plays a significant role in obesity, glucose homeostasis, and lipid metabolism. The metabolic syndrome is a clustering of risk factors predisposing to diabetes mellitus type 2, atherosclerosis, and cardiovascular morbidity and mortality. The main components of the syndrome are visceral obesity, insulin resistance, glucose intolerance, raised blood pressure and dyslipidemia (elevated triglycerides, low levels of high-density lipoprotein cholesterol), and a proinflammatory and thrombogenic state. Cross-sectional epidemiological studies have reported a direct correlation between plasma testosterone and insulin sensitivity, and low testosterone levels are associated with an increased risk of type 2 diabetes mellitus, dramatically illustrated by androgen deprivation in men with prostate carcinoma. Lower total testosterone and sex hormone-binding globulin (SHBG) predict a higher incidence of the metabolic syndrome. Administration of testosterone to hypogonadal men reverses part of the unfavorable risk profile for the development of diabetes and atherosclerosis.

## 1. Introduction

A major problem is the management of overweight. Obesity is a condition that is reaching epidemic proportions in both the developed and the developing world. In the United States, 63% of men and 55% of women are classified as overweight. Of these, 22% are deemed grossly overweight, with a body mass index above 30 kg/m<sup>2</sup>, and the consequences of this rapid increase are serious [1]. Approximately 80% of obese adults suffer from at least one, and 40% from two or more of the diseases associated with obesity, such as type 2 diabetes, hypertension, cardiovascular disease, gallbladder disease, cancers, and diseases of the locomotor system, such as arthritis [2].

This contribution will highlight the significance of testosterone in the development and treatment of obesity. The reality of life is that the practice of medicine is subdivided into medical specialties, each with its own perspective and problems. Obesity and particularly its sequels, such as diabetes mellitus, cardiovascular disease, and locomotor

problems, are not primarily treated by endocrinologists. Even among endocrinologists the expertise on sex hormones, not to speak of testosterone, is often limited. This contribution will argue that testosterone has a significant role to play in the etiology and treatment of obesity and its sequels in the male.

## 2. Sex Differences in Fat Distribution

Adult men and women differ in their fat distribution; the regional distribution of body fat is a characteristic of masculinity and femininity [3]. In premenopausal women a larger proportion of fat is stored in peripheral fat depots such as breasts, hips, and thighs. Men tend to deposit excess fat in the abdominal regions (both subcutaneous and intra-abdominal or visceral fat depots) and generally have a larger visceral fat depot than (premenopausal) women [4]. As regional localization of body fat is considered a secondary sex characteristic, it is likely that sex steroids are involved in the male and female patterns of fat deposition.

This view is strengthened by the observation that variations in sex steroid levels in different phases of (reproductive) life parallel regional differences in fat storage and fat mobilization, until puberty boys and girls do not differ very much in the amount of body fat and its regional distribution. From puberty onwards, differences become manifest [5, 6]. The ovarian production of estrogens and progesterone induce an increase in total body fat as well as selective fat deposition in the breast and gluteofemoral region. Pubertal boys show a strong increase in fat free mass while the amount of total body fat does not change very much [5]. Adolescent boys lose subcutaneous fat but accumulate fat in the abdominal region, which in most boys, is not very visible in that stage of development but clearly demonstrable with imaging techniques [7]. The sex steroid-induced regional distribution is not an all-or-none mechanism; it is a preferential accumulation of excess fat. Obese men and women still show their sex-specific fat accumulation but store their fat also in the “fat depots of the other sex”. Not only the fat distribution differs between the sexes from puberty on, but also the dynamics of fat cell size and fat metabolism are different. The amount of fat in a certain depot is dependent on the number and size of the fat cells. Fat cells in the gluteal and femoral region are larger than in the abdominal region [8]. The activity of lipoprotein lipase, the enzyme responsible for accumulation of triglycerides in the fat cell, is higher in the gluteo-femoral region than in the abdominal area [9]. Conversely, lipolysis is regulated by hormone sensitive lipase, which in turn is regulated by several hormones and by the sympathetic nervous system. Catecholamines stimulate lipolysis via the  $\beta$ -adrenergic receptor while  $\alpha$ 2-adrenoreceptors inhibit lipolysis. Hormones affect the catecholamine receptors of the adipocytes. Testosterone stimulates the  $\beta$ -adrenergic receptor while estrogens/progesterone stimulate preferentially  $\alpha$ 2-adrenoreceptors [10]. Insulin stimulates fat accumulation. It is not an unreasonable speculation that the sex steroid-dependent fat distribution serves (or from this millennium on has served?) the different roles of men and women in reproduction and caring for their progeny. The visceral fat depot constitutes a quickly available source of calories and energy. By its close anatomical proximity to the liver, it delivers fatty acids through the portal system [11]. The latter may have served a useful function in evolution when there was a more pronounced labour division between the sexes suiting the needs of men in their manual labour and quick physical action.

### 3. The Paradoxical Relationships of Testosterone and Fat Distribution in Adulthood and Ageing

While the evidence that pubertal sex steroids induce a sex-specific fat distribution with preferential abdominal/visceral fat accumulation in males and preferential gluteo-femoral fat accumulation in females is quite solid, later in life a number of paradoxes occur in the relationship between sex steroids and fat distribution.

Acquired adult onset hypogonadism in men is associated with an amount of visceral fat which is not less and mostly more than in a comparison group of eugonadal men [12]. So, apparently while androgens induce visceral fat accumulation, once fat has been stored in the visceral depot it does not need continued androgen stimulation as opposed to maintenance of bone and muscle mass, which are lower in men with adult onset hypogonadism than in eugonadal controls [13]. Induction of androgen deficiency by administration of an LHRH agonist leads to an increase of fat mass [14]. Androgen deprivation treatment of men with prostate cancer increases fat mass, reduces insulin sensitivity, and impairs lipid profiles increasing cardiovascular risk [15, 16] or worsens metabolic control of men with diabetes mellitus considerably [17]. Correlation studies in large groups of subjects have shown that visceral fat increases with ageing. There is an inverse correlation between the amount of visceral fat and plasma insulin on the one hand and levels of testosterone and SHBG on the other [18, 19]. Correlation studies cannot unravel the cause and effect relationships between the correlates whether low testosterone induces visceral fat deposition or whether a large visceral fat depot leads to low testosterone levels. Prospective studies have confirmed that lower endogenous androgens predict central adiposity in men [20] and that these low testosterone levels are significantly inversely associated with levels of blood pressure, fasting plasma glucose, triglycerides, and body mass index but positively correlated with HDL-cholesterol [21]. A five-year follow-up study of Swedish men indicated that elevated plasma cortisol and low testosterone were prospectively associated with increased incidence of cardiovascular-related events and diabetes mellitus type 2 [20]. The fact that androgen deprivation of men with prostate cancer induces a worsening of elements of the metabolic syndrome reveals a role for testosterone in its etiology [15, 22].

### 4. The Metabolic Syndrome

A closer examination of obesity has revealed that a preferential accumulation of fat in the abdominal region is associated with an increased risk of noninsulin-dependent diabetes mellitus and cardiovascular disease, not only in obese subjects but even in non-obese subjects [23]. A large number of cross-sectional studies have established a relationship between abdominal obesity and cardiovascular risk factors such as hypertension, dyslipidaemia (elevated levels of cholesterol, of triglycerides, of low-density lipoproteins and low levels of high-density lipoproteins), impaired glucose tolerance with hyperinsulinaemia, a cluster known as the “insulin resistance syndrome” or “metabolic syndrome” [24–27]. The term metabolic syndrome is now preferred. There is a debate in the literature whether combining these components or conditions has an added diagnostic or prognostic value [28]. In recent years, three main definitions of the metabolic syndrome were used. These definitions overlapped but differ in the points of emphasis of the components. The definition of the National Cholesterol Education program places equal emphasis on the various components of the metabolic syndrome

[29]. The definition adopted by the WHO assigns greater value to insulin resistance as a required component of the metabolic derangements [30]. Increasingly, professional organizations have now proposed definitions. The International Diabetes Federation has drafted a singly unifying definition in 2005. The main emphasis in this definition is central obesity defined by waist circumference: waist circumference in Europids  $\geq 94$  cm and in Asians  $> 90$  cm and two or more of the following four factors: elevated triglycerides  $\geq 1.7$  mmol/L ( $\geq 150$  mg/dL), reduced HDL-cholesterol  $< 1.03$  mmol/L ( $< 40$  mg/dL), elevated blood pressure systolic  $\geq 130$  mm Hg, diastolic  $\geq 85$  mm Hg (or treatment), and dysglycaemia (raised fasting plasma glucose  $\geq 5.6$  mmol/L ( $\geq 100$  mg/dL) (or type 2 diabetes) [31], ([http://www.idf.org/webdata/docs/MetSyndrome\\_FINAL.pdf](http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf)). Recently, several scientific societies have arrived at a joint interim statement to harmonize the approach to the metabolic syndrome [32].

## 5. Testosterone in Men Suffering from the Metabolic Syndrome and Diabetes Mellitus

Numerous studies have found inverse associations between the severity of features of the metabolic syndrome and plasma testosterone [33–38]. For review see [39]. There is an inverse relationship between waist circumference, a reliable indicator of visceral obesity, and testosterone levels over all age groups [40].

The inverse relationship of testosterone and the metabolic syndrome is consistent across race and ethnic groups [41]. Similar to studies in men with the metabolic syndrome, there is in men an inverse relationship between testosterone levels and diabetes. For review: [42]. Men with diabetes have lower testosterone levels compared to men without a history of diabetes [43, 44], and there is an inverse association between testosterone levels and glycosylated hemoglobin [45]. This is no artifact due to medication with, for instance, statins [44]. A systematic review and meta-analysis of cross-sectional studies indicated that testosterone level was significantly lower in men with type 2 diabetes (mean difference,  $-76.6$  ng/dL; 95% confidence interval [CI],  $-99.4$  to  $-53.6$ ) [46]. In men with low plasma testosterone, the likelihood of diabetes mellitus is increased. Prospective studies have shown that men with higher testosterone levels (range 449.6–605.2 ng/dL) had a 42% lower risk of type 2 diabetes (RR, 0.58; 95% CI, 0.39 to 0.87) [46]. In addition, several large prospective studies have shown that low testosterone levels predict development of type 2 diabetes in men. There is persuasive epidemiological evidence from several longitudinal population studies that low testosterone is an independent risk factor for the development of both the metabolic syndrome and type 2 diabetes in later life [43, 47] and their clinical sequels such as stroke or transient ischemic attacks [48]. The Massachusetts Male Aging Study (MMAS) [49] and the Multiple Risk Factor Intervention Trial (MRFIT) [50] have shown that low levels of total testosterone and SHBG (which is associated with insulin resistance) were both independent risk factors

in middle-aged men who later developed diabetes. The Rancho-Bernardo Study based in California demonstrated a significant inverse correlation between baseline total testosterone with long-term (8-year follow-up) fasting glucose and insulin levels as well as glucose intolerance [51]. A Finnish study has shown that low testosterone and SHBG levels also predict the development of the metabolic syndrome as well as diabetes [18], recently confirmed by a German group [52]. Importantly, the MMAS has provided evidence that low testosterone is a risk factor for metabolic syndrome and diabetes in men who were not initially obese [19]. Recently the Third National Health and Nutrition survey (NHANES III) in a population of 1,413 men after adjustment for age, race/ethnicity, and adiposity showed that those men initially in the lowest tertile of either free or bioavailable (but not total testosterone) were approximately four times more likely to have prevalent diabetes compared to those in the third tertile [53]. These findings support those of the MMAS in that the risk is independent of adiposity [49] recently confirmed in Australia [54]. For review see [47, 55].

Interestingly, there is a significant difference in plasma testosterone levels between men with diabetes type 1 (who have normal levels) and type 2 (who have subnormal levels) [56]. This difference was attributed to the differences in circulating levels of insulin (low in type 1 and high in type 2). There is an inverse relationship between insulin levels and sex hormone-binding globulin (SHBG) and, consequently, plasma levels of total testosterone are lower in men with type 2 diabetes. This assumption is confirmed by the observation that men with type 1 diabetes with a high BMI show lower levels of testosterone. Androgen receptor CAG repeat polymorphism appears associated with serum testosterone levels, obesity, and serum leptin in men with type 2 diabetes [57].

## 6. The Vicious Circle of Low Testosterone and the Metabolic Syndrome

Adiposity with its associated hyperinsulinism suppresses sex hormone-binding globulin (SHBG) synthesis and therewith the levels of circulating testosterone [58, 59]. It also may affect the strength of luteinizing hormone (LH) signaling to the testis [60]. Further, insulin [61] and leptin [62] have a suppressive effect on testicular steroidogenesis [45]. So, there are reasons to believe that adiposity is a significant factor in lowering circulating levels of testosterone, even occurring in men under the age of 40 years [63]. For review see [64, 65].

While it is clear that disease, and in the context of this contribution, in particular the metabolic syndrome suppresses circulating testosterone levels, it has also been documented that low testosterone induces the metabolic syndrome [18, 49]. Even in the absence of late-stage consequences such as diabetes and cardiovascular disease, subtle derangements in sex hormones are present in the metabolic syndrome and may contribute to its pathogenesis [66].

The role of testosterone is dramatically demonstrated by findings in men with prostate cancer who undergo

androgen ablation therapy [22, 67], particularly in the longer-term [68]. Another study showed convincingly that acute androgen deprivation reduces insulin sensitivity in young men [69] and strongly impairs glycemic control of men with diabetes mellitus [70].

## 7. Can the Age-Related Decline of Testosterone Be Prevented or Reversed?

As indicated above the age-related changes in neuroendocrine functioning leading to a diminished efficacy of LH stimulation of the Leydig cell and impairments of the steroidogenic process of testosterone synthesis are probably inherent factors in the age-related decline of circulating testosterone levels [58, 71]. But increasingly there is insight that disease significantly contributes to the age-related decline of testosterone [72]. Changes in lifestyle (diet/exercise) might partially prevent or redress the decline of androgen levels with aging [73–75] and should be encouraged.

## 8. Effects of Testosterone Administration on Fat Tissue and Lipid Metabolism

Sex steroid hormones are involved in the metabolism, accumulation, and distribution of adipose tissues. It is now known that estrogen receptors, progesterone receptors, and androgen receptors exist in adipose tissues, so their actions could be direct. Sex steroid hormones carry out their function in adipose tissues by both genomic and nongenomic mechanisms. Activation of the cAMP cascade by sex steroid hormones would activate hormone-sensitive lipase leading to lipolysis in adipose tissues. In the phosphoinositide cascade, diacylglycerol and inositol 1,4,5-trisphosphate are formed as second messengers ultimately causing the activation of protein kinase C [76]. Their activation appears to be involved in the control of preadipocyte proliferation and differentiation. The role of testosterone in regulating lineage determination in mesenchymal pluripotent cells by promoting their commitment to the myogenic lineage and inhibiting their differentiation into the adipogenic lineage through an androgen receptor-mediated pathway has been convincingly demonstrated [77]. In a clinical study, it could be shown that testosterone inhibits triglyceride uptake and lipoprotein lipase activity and causes a more rapid turnover of triglycerides in the subcutaneous abdominal adipose tissue and less so in femoral fat and, maybe, mobilizes lipids from the visceral fat depot. In this study, testosterone administration restoring testosterone levels to midnormal values with a duration of 8–9 months led to a decrease of the visceral fat mass, a decrease of fasting glucose and lipid levels and an improvement of insulin sensitivity; in addition, a decrease in diastolic blood pressure was observed [76].

A meta-analysis of randomized controlled trials evaluating the effects of testosterone (T) administration to middle-aged and ageing men on body composition showed a reduction of 1.6 kg (CI: 2.5–0.6) of total body fat, corresponding to –6.2% (CI: 9.2–3.3) variation of initial

body fat, an increase in fat-free mass of 1.6 kg (CI: 0.6–2.6), corresponding to +2.7% (CI: 1.1–4.4) increase over baseline and no change in body weight. In a placebo-controlled study using long-acting testosterone undecanoate injections, the reduction of fat mass was 5.3 kg with an increase of lean mass of 4.2 kg [78]. Testosterone also reduced total cholesterol by 0.23 mmol/L (CI: –0.37 to –0.10), especially in men with lower baseline T concentrations, with no change in low density lipoprotein (LDL-) cholesterol. A significant reduction of high density lipoprotein (HDL-) cholesterol was found only in studies with higher mean T-values at baseline or when androgens were nonaromatizable (–0.085 mmol/l, CI: –0.017 to –0.003) [79]. This underlines the necessity to use the chemically unmodified molecule of testosterone for treatment.

## 9. Testosterone Administration to Men with the Metabolic Syndrome and Diabetes Mellitus

So, it is clear now that low testosterone levels are a factor in the etiology of common ailments of elderly men such as the metabolic syndrome and its associated diseases such as diabetes mellitus and atherosclerotic disease. The question arises then whether testosterone treatment has a role to play in the treatment of the metabolic syndrome and its sequels such as diabetes mellitus type 2 and cardiovascular disease. There is increasing evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome [80]. Changes in visceral fat appeared to be a function of changes in serum total testosterone [81]. The beneficial effects of androgens on (visceral) fat have been confirmed in other studies [82, 83]. A study investigating the effects of normalization of circulating testosterone levels in men with subnormal testosterone levels receiving treatment with parenteral testosterone undecanoate found favorable effects on body composition (waist circumference) [84]. In another study, 32 hypogonadal (plasma testosterone <12 nmol/L) men with the metabolic syndrome, with newly diagnosed type 2 diabetes mellitus were single-blindly randomized to diet and exercise alone ( $n = 16$ ) or to diet and exercise in combination with testosterone gel 50 mg once daily ( $n = 16$ ) and treated for 52 weeks. No glucose-lowering agents were administered prior to or during the study period. Addition of testosterone significantly further improved these measures compared to diet and exercise alone on glycaemic control, waist circumference, and other parameters of the metabolic syndrome [75].

Testosterone substitution in hypogonadal men improves insulin sensitivity [85]. Furthermore, testosterone reduces insulin levels and insulin resistance in men with obesity. A study in hypogonadal men with type 2 diabetes has shown that testosterone replacement also improves glycaemic control although this study was nonblinded [86]. In a recent Korean study, glucose levels were significantly reduced after 24 weeks of testosterone treatment in men with baseline glucose  $\geq 110$  mg/dL while there was no change in men with baseline glucose <110 mg/dL [87]. By contrast, two studies replacing testosterone in men with diabetes type 2

and hypogonadism found little or no effect on glycaemic control [88, 89], but a more recent study analyzing the effects of testosterone administration to 24 hypogonadal men (10 treated with insulin) over the age of 30 years with type 2 diabetes found that testosterone replacement therapy reduced insulin resistance (as measured by homeostatic model index) and improved glycaemic control in hypogonadal men with type 2 diabetes. So, while the evidence for powerful effects of normalization of circulating levels of testosterone on glucose homeostasis so far is limited, there are studies to prove that administration of testosterone may have favorable effects on glycaemic control and the metabolic sequels of diabetes mellitus.

## 10. New Perspectives on Testosterone

In recent times, the understanding and thinking about the (patho)physiological functions of testosterone have undergone a revolutionary development. The traditional assumption was that hypogonadism in men usually resulted in loss of libido and potency which could be restored by androgen administration. While the significance of testosterone for male reproductive/sexual functioning has been obvious to most physicians, they now need to familiarize themselves with the insight that testosterone is a key player in glucose homeostasis and lipid metabolism.

Physicians will have to make a change of their mindset that testosterone, rather being a dangerous companion to a man's life, bringing joy but exacting its toll, is a vital hormone for men's health, from early prenatal development to the end of a man's life. Earlier it has been questioned whether testosterone has an essential role to play in male physiology. Recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men [90–94]. Obviously, epidemiological studies cannot unravel cause relationships, but the evidence is convincing that the decline in testosterone levels with aging is accounted for rather by (age-related) disease than the calendar age of men [95, 96]. Intervention studies provide potential answers to the causality of the relationship. It is no exaggeration to say that in modern medicine and endocrinology testosterone is no longer a marginal hormone. Neither is it a lifestyle hormone for those men seeking eternal youth. Its deficiency leads to a serious deterioration of the health of men expressing itself in the metabolic syndrome and its sequels: diabetes mellitus type 2 and atherosclerotic disease, osteoporosis and sarcopenia, all strongly limiting physical independence in old age and accelerating morbidity and mortality.

## 11. Measuring Serum Testosterone

There is no generally accepted cutoff value of plasma testosterone for defining androgen deficiency, and in the absence of convincing evidence for an altered androgen requirement in elderly men, Arbitrarily, the normal range of testosterone and free testosterone (fT) levels in young males is considered also valid for elderly men. Then the normal levels of total testosterone are between 12 and 35 nmol/L.

It is of note that the determination of reference values of laboratory parameters is based on statistical analysis of a population of subjects [97]. For the clinician workable criteria are the following: the lower limit of normal of total testosterone is 12 nmol/L and of fT 250 pmol/L. Most authors agree that plasma testosterone levels should be measured in early morning samples in view of the circadian rhythm of plasma testosterone, with shows its lowest values in the late afternoon. (Late) afternoon samples might present unduly low values and not be representative of a man's androgen status [58, 98]. The recommendation also agrees that a single measurement providing a low testosterone value is to be repeated, certain when that value would be enough reason to start testosterone administration. Small ailments, like a cold or other minor stressors, may temporarily suppress circulating testosterone.

It will not be rare to find rather ambiguous, borderline normal/abnormal levels of plasma total testosterone in elderly men, even in those men with clinical symptoms of androgen deficiency. In these cases, assessment of bioavailable or free testosterone might be an asset. Bioavailable testosterone can be measured in the laboratory using the ammoniumsulphate precipitation technique. The gold standard for free testosterone measurement still is the dialysis method, although a mass spectrometry-based assessment of free testosterone in ultrafiltrates was recently proposed as a candidate reference method (for review: [58]). However, both ammoniumsulphate precipitation and the dialysis technique are nonautomated, time-consuming, and expensive techniques and therefore not routinely available in the vast majority of laboratories. There has been a direct radioimmunoassay claiming to measure free testosterone but this assay has been universally criticized because of lack of accuracy and should not be used [58]

The two most widely used equations for calculating bioavailable or free testosterone are those described by Vermeulen et al. [99] and Sodergard et al. [100]. The equations are largely identical apart from the association constants for the binding of testosterone to albumin and sex hormone-binding globulin.

At least two algorithms have been placed on the internet as so-called bioavailable testosterone calculators (<http://www.issam.ch/> and <http://www.get-back-on-track.com/en/tools/kalkulator.php> and <http://www.him-link.com/>) making these algorithms readily available for distant users. It is redundant to measure/calculate bioavailable/free testosterone if plasma total testosterone appeared to be in the truly hypogonadal (<6 nmol/L) or in the truly eugonadal range (>15 nmol/L).

## 12. Safety Concerns

Traditionally, the majority of physicians associate the administration of testosterone, particularly to elderly men, with a serious risk of inducing malignancies of the prostate or exacerbating voiding problems of the elderly male.

Several follow-up studies of men receiving testosterone treatment [101–103] have failed to demonstrate an exacerbation of voiding symptoms due to benign prostatic

hyperplasia. Complications such as urinary retention in therapy groups did not occur at higher rates than in controls receiving placebo.

The occurrence of prostate cancer after testosterone administration to (elderly) men has been reported [104–108] but its causality has not been established. Aging, typically, increases the risk of developing prostate cancer. By contrast, a variety of studies, using various designs and testosterone formulations, over periods ranging from several months to 15 years, in men with a wide range of ages, have not revealed an increased risk of prostate cancer [109–116] see for review [117, 118]. A meta-analysis found that testosterone treatment in older men compared to placebo was not associated with a significantly higher risk of detection of prostate cancer, although the frequency of prostate biopsies was much higher in the testosterone-treated group than in the placebo group [103]. Presently, it is believed that testosterone can be administered to men whose prostate cancer has been radically cured [119].

The above applies also to the assessment of safety of testosterone administration to elderly men. There is no convincing evidence that testosterone is a main factor in the development of prostate cancer in elderly men [120], and guidelines for monitoring have been developed which, if rigorously applied, render testosterone administration to elderly men, an acceptably safe therapy in men without a prior history of prostate carcinoma or without evidence of harboring a prostate carcinoma [121, 122]. There are now at least three publications demonstrating a lack of prostate carcinoma recurrence with testosterone therapy after definitive prostate carcinoma treatment. Two articles have reported no PSA recurrence in a total of 17 men, following radical prostatectomy in men with undetectable PSA [123, 124]. A third study reported that no cancer recurrence was noted in 31 hypogonadal men treated with brachytherapy with a follow-up of approximately 5 years [125]. These small studies suggest that normalization of testosterone in men who have shown no signs of recurrence of prostate cancer after treatment, testosterone replacement could be beneficial.

There is a consensus now that administration of testosterone to elderly men is a responsible practice provided certain guidelines of professional bodies are followed with regard to testosterone administration to elderly men [121, 126].

### 13. Conclusion

In recent times, the understanding and thinking about the (patho)physiological functions of testosterone have undergone a revolutionary development. While the significance of testosterone for male reproductive/sexual functioning has always been obvious to physicians, they now need to familiarize themselves with the insight that testosterone is a key player in glucose homeostasis, lipid metabolism, and cardiovascular pathology. Physicians will have to change their mind-set and accept that testosterone is a vital hormone for many aspects of men's health. The long-held belief that

testosterone has adverse effects on cardiovascular disease explaining the male preponderance in cardiovascular morbidity and mortality appears not to be supported by rigorous scientific testing. Recent epidemiological studies have found that low testosterone levels are a predictor of mortality in elderly men [90–92, 94].

Obviously, epidemiological studies cannot unravel cause relationships. Intervention studies provide potential answers to the causality of the relationship. It is no exaggeration to say that in modern medicine and endocrinology testosterone is no longer a marginal hormone. Neither is it a life-style hormone for those men seeking eternal youth. Its deficiency leads to a serious deterioration of the health of men expressing itself in the metabolic syndrome and its sequels: diabetes mellitus type 2 and atherosclerotic disease accelerating morbidity and mortality. Intervention studies in men with diabetes mellitus are limited in number but hold promise. Normalization of testosterone levels may improve insulin sensitivity and have favorable effects on visceral adiposity and lipid profiles. The fear that testosterone administration to elderly men increases the risk of prostate malignancies is not justified. It only requires prudence in clinical management.

### References

- [1] C. L. Ogden, M. D. Carroll, L. R. Curtin, M. A. McDowell, C. J. Tabak, and K. M. Flegal, "Prevalence of overweight and obesity in the United States, 1999–2004," *JAMA*, vol. 295, no. 13, pp. 1549–1555, 2006.
- [2] I. Janssen and A. E. Mark, "Elevated body mass index and mortality risk in the elderly," *Obesity Reviews*, vol. 8, no. 1, pp. 41–59, 2007.
- [3] K. Blouin, A. Boivin, and A. Tcherno, "Androgens and body fat distribution," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 108, no. 3–5, pp. 272–280, 2008.
- [4] J. C. K. Wells, "Sexual dimorphism of body composition," *Best Practice and Research*, vol. 21, no. 3, pp. 415–430, 2007.
- [5] L. A. Lomba-Albrecht and D. M. Styne, "Effect of puberty on body composition," *Current Opinion in Endocrinology, Diabetes and Obesity*, vol. 16, no. 1, pp. 10–15, 2009.
- [6] R. W. Taylor, A. M. Grant, S. M. Williams, and A. Goulding, "Sex differences in regional body fat distribution from pre- to postpuberty," *Obesity*, vol. 18, no. 7, pp. 1410–1416, 2010.
- [7] J. N. Roemmich, P. A. Clark, V. Mai et al., "Alterations in growth and body composition during puberty: III. Influence of maturation, gender, body composition, fat distribution, aerobic fitness, and energy expenditure on nocturnal growth hormone release," *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 5, pp. 1440–1447, 1998.
- [8] J. O'Connell, L. Lynch, J. Cawood, et al., "The relationship of omental and subcutaneous adipocyte size to metabolic disease in severe obesity," *PLoS One*, vol. 5, no. 4, Article ID e9997, 2010.
- [9] P. Björntorp, "Adipose tissue distribution and function," *International Journal of Obesity*, vol. 15, supplement 2, pp. 67–81, 1991.
- [10] J. S. Mayes and G. H. Watson, "Direct effects of sex steroid hormones on adipose tissues and obesity," *Obesity Reviews*, vol. 5, no. 4, pp. 197–216, 2004.

- [11] M. D. Jensen, "Role of body fat distribution and the metabolic complications of obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 11, supplement 1, pp. S57–S63, 2008.
- [12] L. Katznelson, D. I. Rosenthal, M. S. Rosol et al., "Using quantitative CT to assess adipose distribution in adult men with acquired hypogonadism," *AJR*, vol. 170, no. 2, pp. 423–427, 1998.
- [13] L. Katznelson, J. S. Finkelstein, D. A. Schoenfeld, D. I. Rosenthal, E. J. Anderson, and A. Klibanski, "Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism," *Journal of Clinical Endocrinology and Metabolism*, vol. 81, no. 12, pp. 4358–4365, 1996.
- [14] M. R. Smith, "Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer," *Urology*, vol. 63, no. 4, pp. 742–745, 2004.
- [15] M. R. Smith, H. Lee, and D. M. Nathan, "Insulin sensitivity during combined androgen blockade for prostate cancer," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1305–1308, 2006.
- [16] S. Basaria, D. C. Muller, M. A. Carducci, J. Egan, and A. S. Dobs, "Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy," *Cancer*, vol. 106, no. 3, pp. 581–588, 2006.
- [17] I. H. Derweesh, C. J. DiBlasio, M. C. Kincade et al., "Risk of new-onset diabetes mellitus and worsening glycaemic variables for established diabetes in men undergoing androgen-deprivation therapy for prostate cancer," *BJU International*, vol. 100, no. 5, pp. 1060–1065, 2007.
- [18] D. E. Laaksonen, L. Niskanen, K. Punnonen et al., "Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men," *Diabetes Care*, vol. 27, no. 5, pp. 1036–1041, 2004.
- [19] V. Kupelian, S. T. Page, A. B. Araujo, T. G. Travison, W. J. Bremner, and J. B. McKinlay, "Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 3, pp. 843–850, 2006.
- [20] R. Rosmond, S. Wallerius, P. Wanger, L. Martin, G. Holm, and P. Björntorp, "A 5-year follow-up study of disease incidence in men with an abnormal hormone pattern," *Journal of Internal Medicine*, vol. 254, no. 4, pp. 386–390, 2003.
- [21] J. M. Zmuda, J. A. Cauley, A. Kriska, N. W. Glynn, J. P. Gutai, and L. H. Kuller, "Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men: a 13-year follow-up of former multiple risk factor intervention trial participants," *American Journal of Epidemiology*, vol. 146, no. 8, pp. 609–617, 1997.
- [22] S. Basaria, D. C. Muller, M. A. Carducci, J. Egan, and A. S. Dobs, "Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy," *Cancer*, vol. 106, no. 3, pp. 581–588, 2006.
- [23] W. B. Kannel, L. A. Cupples, R. Ramaswami, J. Stokes III, B. E. Kreger, and M. Higgins, "Regional obesity and risk of cardiovascular disease; the Framingham Study," *Journal of Clinical Epidemiology*, vol. 44, no. 2, pp. 183–190, 1991.
- [24] P. Björntorp and R. Rosmond, "The metabolic syndrome—a neuroendocrine disorder?" *British Journal of Nutrition*, vol. 83, supplement 1, pp. S49–S57, 2000.
- [25] R. O. B. Gans, "The metabolic syndrome, depression, and cardiovascular disease: interrelated conditions that share pathophysiologic mechanisms," *Medical Clinics of North America*, vol. 90, no. 4, pp. 573–591, 2006.
- [26] S. M. Grundy, H. B. Brewer Jr., J. I. Cleeman, S. C. Smith Jr., and C. Lenfant, "Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 24, no. 2, pp. e13–e18, 2004.
- [27] M. C. Carr and J. D. Brunzell, "Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 6, pp. 2601–2607, 2004.
- [28] R. K. Simmons, K. G. Alberti, and E. A. Gale, "The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation," *Diabetologia*, vol. 53, no. 4, pp. 600–605, 2009.
- [29] J. I. Cleeman, "Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III)," *JAMA*, vol. 285, no. 19, pp. 2486–2497, 2001.
- [30] H.-M. Lakka, D. E. Laaksonen, T. A. Lakka et al., "The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men," *JAMA*, vol. 288, no. 21, pp. 2709–2716, 2002.
- [31] E. S. Ford, "Prevalence of the metabolic syndrome defined by the international diabetes federation among adults in the U.S.," *Diabetes Care*, vol. 28, no. 11, pp. 2745–2749, 2005.
- [32] K. G. M. M. Alberti, R. H. Eckel, S. M. Grundy et al., "Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity," *Circulation*, vol. 120, no. 16, pp. 1640–1645, 2009.
- [33] A. Rodriguez, D. C. Muller, E. J. Metter et al., "Aging, androgens, and the metabolic syndrome in a longitudinal study of aging," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 9, pp. 3568–3572, 2007.
- [34] B. A. Mohr, S. Bhasin, C. L. Link, A. B. O'Donnell, and J. B. McKinlay, "The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts male aging study," *European Journal of Endocrinology*, vol. 155, no. 3, pp. 443–452, 2006.
- [35] S. A. Kaplan, A. G. Meehan, and A. Shah, "The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men?" *The Journal of Urology*, vol. 176, no. 4, pp. 1524–1528, 2006.
- [36] C. A. Allan, B. J. Strauss, H. G. Burger, E. A. Forbes, and R. I. McLachlan, "The association between obesity and the diagnosis of androgen deficiency in symptomatic ageing men," *Medical Journal of Australia*, vol. 185, no. 8, pp. 424–427, 2006.
- [37] R. R. Kalyani and A. S. Dobs, "Androgen deficiency, diabetes, and the metabolic syndrome in men," *Current Opinion in Endocrinology, Diabetes and Obesity*, vol. 14, no. 3, pp. 226–234, 2007.

- [38] C. A. Allan, B. J. G. Strauss, and R. I. McLachlan, "Body composition, metabolic syndrome and testosterone in ageing men," *International Journal of Impotence Research*, vol. 19, no. 5, pp. 448–457, 2007.
- [39] F. Saad, "The role of testosterone in type 2 diabetes and metabolic syndrome in men," *Arq Bras Endocrinol Metabol*, vol. 53, no. 8, pp. 901–907, 2009.
- [40] J. Svartberg, D. Von Mühlen, J. Sundsfjord, and R. Jorde, "Waist circumference and testosterone levels in community dwelling men," *European Journal of Epidemiology*, vol. 19, no. 7, pp. 657–663, 2004.
- [41] V. Kupelian, F. J. Hayes, C. L. Link, R. Rosen, and J. B. McKinlay, "Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 9, pp. 3403–3410, 2008.
- [42] F. Saad and L. Gooren, "The role of testosterone in the metabolic syndrome: a review," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 114, no. 1-2, pp. 40–43, 2009.
- [43] R. D. Stanworth and T. H. Jones, "Testosterone in obesity, metabolic syndrome and type 2 diabetes," *Frontiers of Hormone Research*, vol. 37, pp. 74–90, 2009.
- [44] R. D. Stanworth, D. Kapoor, K. S. Channer, and T. H. Jones, "Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes," *Diabetes Care*, vol. 32, no. 4, pp. 541–546, 2009.
- [45] J. Stamler, R. Stamler, W. F. Riedlinger, G. Algera, and R. H. Roberts, "Hypertension screening of 1 million Americans. Community Hypertension Evaluation Clinic (CHEC) program, 1973 through 1975," *JAMA*, vol. 235, no. 21, pp. 2299–2306, 1976.
- [46] E. L. Ding, Y. Song, V. S. Malik, and S. Liu, "Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis," *JAMA*, vol. 295, no. 11, pp. 1288–1299, 2006.
- [47] A. M. Traish, F. Saad, and A. Guay, "The dark side of testosterone deficiency: II. type 2 diabetes and insulin resistance," *Journal of Andrology*, vol. 30, no. 1, pp. 23–32, 2009.
- [48] B. B. Yeap, Z. Hyde, O. P. Almeida et al., "Lower testosterone levels predict incident stroke and transient ischemic attack in older men," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 7, pp. 2353–2359, 2009.
- [49] R. K. Stellato, H. A. Feldman, O. Hamdy, E. S. Horton, and J. B. McKinlay, "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*, vol. 23, no. 4, pp. 490–494, 2000.
- [50] S. M. Haffner, J. Shaten, M. P. Stern, G. D. Smith, and L. Kuller, "Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men," *American Journal of Epidemiology*, vol. 143, no. 9, pp. 889–897, 1996.
- [51] J.-Y. Oh, E. Barrett-Connor, N. M. Wedick, and D. L. Wingard, "Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo Study," *Diabetes Care*, vol. 25, no. 1, pp. 55–60, 2002.
- [52] R. Haring, H. Völzke, S. B. Felix et al., "Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania," *Diabetes*, vol. 58, no. 9, pp. 2027–2031, 2009.
- [53] E. Selvin, M. Feinleib, L. Zhang et al., "Androgens and diabetes in men: results from the third National Health and Nutrition Examination Survey (NHANES III)," *Diabetes Care*, vol. 30, no. 2, pp. 234–238, 2007.
- [54] B. B. Yeap, S. A. P. Chubb, Z. Hyde et al., "Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the health in men study," *European Journal of Endocrinology*, vol. 161, no. 4, pp. 591–598, 2009.
- [55] A. M. Traish, F. Saad, R. J. Feeley, and A. Guay, "The dark side of testosterone deficiency: III. Cardiovascular disease," *Journal of Andrology*, vol. 30, no. 5, pp. 477–494, 2009.
- [56] A. Chandel, S. Dhindsa, S. Topiwala, A. Chaudhuri, and P. Dandona, "Testosterone concentration in young patients with diabetes," *Diabetes Care*, vol. 31, no. 10, pp. 2013–2017, 2008.
- [57] R. D. Stanworth, D. Kapoor, K. S. Channer, and T. H. Jones, "Androgen receptor CAG repeat polymorphism is associated with serum testosterone levels, obesity and serum leptin in men with type 2 diabetes," *European Journal of Endocrinology*, vol. 159, no. 6, pp. 739–746, 2008.
- [58] J. M. Kaufman and A. Vermeulen, "The decline of androgen levels in elderly men and its clinical and therapeutic implications," *Endocrine Reviews*, vol. 26, no. 6, pp. 833–876, 2005.
- [59] R. H. Eckel, S. M. Grundy, and P. Z. Zimmet, "The metabolic syndrome," *The Lancet*, vol. 365, no. 9468, pp. 1415–1428, 2005.
- [60] N. Lima, H. Cavaliere, M. Knobel, A. Halpern, and G. Medeiros-Neto, "Decreased androgen levels in massively obese men may be associated with impaired function of the gonadostat," *International Journal of Obesity*, vol. 24, no. 11, pp. 1433–1437, 2000.
- [61] N. Pitteloud, M. Hardin, A. A. Dwyer et al., "Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 5, pp. 2636–2641, 2005.
- [62] A. M. Isidori, M. Caprio, F. Strollo et al., "Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels," *Journal of Clinical Endocrinology and Metabolism*, vol. 84, no. 10, pp. 3673–3680, 1999.
- [63] N. P. Goncharov, G. V. Katsya, N. A. Chagina, and L. J. Gooren, "Testosterone and obesity in men under the age of 40 years," *Andrologia*, vol. 41, no. 2, pp. 76–83, 2009.
- [64] P. M. Mah and G. A. Wittert, "Obesity and testicular function," *Molecular and Cellular Endocrinology*, vol. 316, no. 2, pp. 180–186, 2010.
- [65] M. Zitzmann, "Testosterone deficiency, insulin resistance and the metabolic syndrome," *Nature Reviews Endocrinology*, vol. 5, no. 12, pp. 673–681, 2009.
- [66] D. E. Laaksonen, L. Niskanen, K. Punnonen et al., "Sex hormones, inflammation and the metabolic syndrome: a population-based study," *European Journal of Endocrinology*, vol. 149, no. 6, pp. 601–608, 2003.
- [67] M. R. Smith, H. Lee, and D. M. Nathan, "Insulin sensitivity during combined androgen blockade for prostate cancer," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1305–1308, 2006.
- [68] M. Braga-Basaria, A. S. Dobs, D. C. Muller et al., "Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy," *Journal of Clinical Oncology*, vol. 24, no. 24, pp. 3979–3983, 2006.
- [69] M. A. Yialamas, A. A. Dwyer, E. Hanley, H. Lee, N. Pitteloud, and F. J. Hayes, "Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 11, pp. 4254–4259, 2007.



- [70] A. Haidar, A. Yassin, F. Saad, and R. Shabsigh, "Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes," *Aging Male*, vol. 10, no. 4, pp. 189–196, 2007.
- [71] F. C. W. Wu, A. Tajar, S. R. Pye et al., "Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European male aging study," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 7, pp. 2737–2745, 2008.
- [72] T. G. Travison, A. B. Araujo, V. Kupelian, A. B. O'Donnell, and J. B. McKinlay, "The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 2, pp. 549–555, 2007.
- [73] A. F. G. Cicero, G. Derosa, M. Bove, V. Di Gregori, A. V. Gaddi, and C. Borghi, "Effect of a sequential training programme on inflammatory, prothrombotic and vascular remodelling biomarkers in hypertensive overweight patients with or without metabolic syndrome," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 16, no. 6, pp. 698–704, 2009.
- [74] K. Esposito, R. Marfella, M. Ciotola et al., "Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial," *JAMA*, vol. 292, no. 12, pp. 1440–1446, 2004.
- [75] A. E. Heufelder, F. Saad, M. C. Bunck, and L. Gooren, "Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone," *Journal of Andrology*, vol. 30, no. 6, pp. 726–733, 2009.
- [76] P. Marin, L. Lönn, B. Andersson et al., "Assimilation of triglycerides in subcutaneous and intraabdominal adipose tissues in vivo in men: effects of testosterone," *Journal of Clinical Endocrinology and Metabolism*, vol. 81, no. 3, pp. 1018–1022, 1996.
- [77] R. Singh, J. N. Artaza, W. E. Taylor et al., "Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with  $\beta$ -catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors," *Endocrinology*, vol. 147, no. 1, pp. 141–154, 2006.
- [78] J. Svartberg, I. Agedahl, Y. Figenschau, T. Sildnes, K. Waterloo, and R. Jorde, "Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip," *International Journal of Impotence Research*, vol. 20, no. 4, pp. 378–387, 2008.
- [79] A. M. Isidori, E. Giannetta, E. A. Greco et al., "Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis," *Clinical Endocrinology*, vol. 63, no. 3, pp. 280–293, 2005.
- [80] T. H. Jones and F. Saad, "The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process," *Atherosclerosis*, vol. 207, no. 2, pp. 318–327, 2009.
- [81] C. A. Allan, B. J. G. Strauss, H. G. Burger, E. A. Forbes, and R. I. McLachlan, "Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 1, pp. 139–146, 2008.
- [82] T. Munzer, S. M. Harman, P. Hees et al., "Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 8, pp. 3604–3610, 2001.
- [83] E. T. Schroeder, L. Zheng, M. D. Ong et al., "Effects of androgen therapy on adipose tissue and metabolism in older men," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 10, pp. 4863–4872, 2004.
- [84] A. Haider, L. J.G. Gooren, P. Padungtod, and F. Saad, "Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate," *Experimental and Clinical Endocrinology and Diabetes*, vol. 118, no. 3, pp. 167–171, 2010.
- [85] N. Pitteloud, V. K. Mootha, A. A. Dwyer et al., "Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men," *Diabetes Care*, vol. 28, no. 7, pp. 1636–1642, 2005.
- [86] M. A. Boyanov, Z. Boneva, and V. G. Christov, "Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency," *Aging Male*, vol. 6, no. 1, pp. 1–7, 2003.
- [87] D. G. Moon, M. G. Park, S. W. Lee et al., "The efficacy and safety of testosterone undecanoate (Nebido®) in testosterone deficiency syndrome in Korean: a multicenter prospective study," *Journal of Sexual Medicine*, vol. 7, no. 6, pp. 2253–2260, 2010.
- [88] J. J. Corrales, M. Almeida, R. Burgo, M. T. Mories, J. M. Miralles, and A. Orfao, "Androgen-replacement therapy depresses the ex vivo production of inflammatory cytokines by circulating antigen-presenting cells in aging type-2 diabetic men and partial androgen deficiency," *Journal of Endocrinology*, vol. 189, no. 3, pp. 595–604, 2006.
- [89] C.-H. Lee, S.-W. Kuo, Y.-J. Hung et al., "The effect of testosterone supplement on insulin sensitivity, glucose effectiveness, and acute insulin response after glucose load in male type 2 diabetics," *Endocrine Research*, vol. 31, no. 2, pp. 139–148, 2005.
- [90] G. A. Laughlin, E. Barrett-Connor, and J. Bergstrom, "Low serum testosterone and mortality in older men," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 1, pp. 68–75, 2008.
- [91] M. M. Shores, V. M. Moceri, D. A. Gruenewald, K. I. Brodtkin, A. M. Matsumoto, and D. R. Kivlahan, "Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men in a geriatric rehabilitation unit," *Journal of the American Geriatrics Society*, vol. 52, no. 12, pp. 2077–2081, 2004.
- [92] M. M. Shores, A. M. Matsumoto, K. L. Sloan, and D. R. Kivlahan, "Low serum testosterone and mortality in male veterans," *Archives of Internal Medicine*, vol. 166, no. 15, pp. 1660–1665, 2006.
- [93] K.-T. Khaw, M. Dowsett, E. Folkard et al., "Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: european prospective investigation into cancer in Norfolk (EPIC-Norfolk) prospective population study," *Circulation*, vol. 116, no. 23, pp. 2694–2701, 2007.
- [94] M. Maggio, F. Lauretani, G. P. Ceda et al., "Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the chianti area (InCHIANTI) study," *Archives of Internal Medicine*, vol. 167, no. 20, pp. 2249–2254, 2007.
- [95] M. Muller, I. den Tonkelaar, J. H. H. Thijssen, D. E. Grobbee, and Y. T. van der Schouw, "Endogenous sex hormones in

- men aged 40–80 years,” *European Journal of Endocrinology*, vol. 149, no. 6, pp. 583–589, 2003.
- [96] T. Mulligan, M. F. Frick, Q. C. Zuraw, A. Stenhagen, and C. McWhirter, “Prevalence of hypogonadism in males aged at least 45 years: the HIM study,” *International Journal of Clinical Practice*, vol. 60, no. 7, pp. 762–769, 2006.
- [97] A. Vermeulen, “Androgen replacement therapy in the aging male—a critical evaluation,” *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 6, pp. 2380–2390, 2001.
- [98] E. Nieschlag, R. Swerdloff, H. M. Behre et al., “Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations,” *European Urology*, vol. 48, no. 1, pp. 1–4, 2005.
- [99] A. Vermeulen, L. Verdonck, and J. M. Kaufman, “A critical evaluation of simple methods for the estimation of free testosterone in serum,” *Journal of Clinical Endocrinology and Metabolism*, vol. 84, no. 10, pp. 3666–3672, 1999.
- [100] R. Sodergard, T. Backstrom, V. Shanbhag, and H. Carstensen, “Calculation of free and bound fractions of testosterone and estradiol-17 $\beta$  to human plasma proteins at body temperature,” *Journal of Steroid Biochemistry*, vol. 16, no. 6, pp. 801–810, 1982.
- [101] D. Schultheiss, S. Machtens, and U. Jonas, “Testosterone therapy in the ageing male: what about the prostate?” *Andrologia*, vol. 36, no. 6, pp. 355–365, 2004.
- [102] A. Morales, “Testosterone treatment for the aging man: the controversy,” *Current Urology Reports*, vol. 5, no. 6, pp. 472–477, 2004.
- [103] O. M. Calof, A. B. Singh, M. L. Lee et al., “Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials,” *Journals of Gerontology*, vol. 60, no. 11, pp. 1451–1457, 2005.
- [104] D. W. Ebling, J. Ruffer, R. Whittington et al., “Development of prostate cancer after pituitary dysfunction: a report of 8 patients,” *Urology*, vol. 49, no. 4, pp. 564–568, 1997.
- [105] K. R. Loughlin and J. P. Richie, “Prostate cancer after exogenous testosterone treatment for impotence,” *The Journal of Urology*, vol. 157, no. 5, p. 1845, 1997.
- [106] M. J. Curran and W. Bihrlle III, “Dramatic rise in prostate-specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate,” *Urology*, vol. 53, no. 2, pp. 423–424, 1999.
- [107] E. L. Rhoden and A. Morgentaler, “Risks of testosterone-replacement therapy and recommendations for monitoring,” *The New England Journal of Medicine*, vol. 350, no. 5, pp. 482–492, 2004.
- [108] S. Sengupta, H. J. Duncan, R. J. Macgregor, and J. M. Russell, “The development of prostate cancer despite late onset androgen deficiency,” *International Journal of Urology*, vol. 12, no. 9, pp. 847–848, 2005.
- [109] H. B. Carter, J. D. Pearson, E. J. Metter et al., “Longitudinal evaluation of serum androgen levels in men with and without prostate cancer,” *Prostate*, vol. 27, no. 1, pp. 25–31, 1995.
- [110] A. W. Hsing, “Hormones and prostate cancer: what’s next?” *Epidemiologic Reviews*, vol. 23, no. 1, pp. 42–58, 2001.
- [111] J. S. Tenover, “Effects of testosterone supplementation in the aging male,” *Journal of Clinical Endocrinology and Metabolism*, vol. 75, no. 4, pp. 1092–1098, 1992.
- [112] L. S. Marks, N. A. Mazer, E. Mostaghel et al., “Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial,” *JAMA*, vol. 296, no. 19, pp. 2351–2361, 2006.
- [113] A. Morgentaler, “Testosterone replacement therapy and prostate cancer,” *Urologic Clinics of North America*, vol. 34, no. 4, pp. 555–563, 2007.
- [114] A. Yassin and F. Saad, “Testosterone treatment in hypogonadal patients does not cause higher incidence of prostate cancer,” *The Journal of Urology*, vol. 179, no. 4, p. 301, 2008.
- [115] A. A. Yassin and F. Saad, “Improvement of sexual function in men with late-onset hypogonadism treated with testosterone only,” *Journal of Sexual Medicine*, vol. 4, no. 2, pp. 497–501, 2007.
- [116] R. M. Coward, J. Simhan, and C. C. Carson III, “Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy,” *BJU International*, vol. 103, no. 9, pp. 1179–1183, 2009.
- [117] R. L. Leibowitz, T. B. Dorff, S. Tucker, J. Symanowski, and N. J. Vogelzang, “Testosterone replacement in prostate cancer survivors with hypogonadal symptoms,” *BJU International*, vol. 105, no. 10, pp. 1397–1401, 2010.
- [118] E. L. Rhoden and M. A. Averbeck, “Testosterone therapy and prostate carcinoma,” *Current Urology Reports*, vol. 10, no. 6, pp. 453–459, 2009.
- [119] H. Isbarn, J. H. Pinthus, L. S. Marks et al., “Testosterone and prostate cancer: revisiting old paradigms,” *European Urology*, vol. 56, no. 1, pp. 48–56, 2009.
- [120] A. Morgentaler, “Rapidly shifting concepts regarding androgens and prostate cancer,” *The Scientific World Journal*, vol. 9, pp. 685–690, 2009.
- [121] S. Bhasin, G. R. Cunningham, F. J. Hayes et al., “Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline,” *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 6, pp. 1995–2010, 2006.
- [122] C. Wang, E. Nieschlag, R. Swerdloff et al., “Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations,” *European Journal of Endocrinology*, vol. 159, no. 5, pp. 507–514, 2008.
- [123] J. M. Kaufman and R. J. Graydon, “Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men,” *The Journal of Urology*, vol. 172, no. 3, pp. 920–922, 2004.
- [124] P. K. Agarwal and M. G. Oefelein, “Testosterone replacement therapy after primary treatment for prostate cancer,” *The Journal of Urology*, vol. 173, no. 2, pp. 533–536, 2005.
- [125] M. F. Sarosdy, “Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy,” *Cancer*, vol. 109, no. 3, pp. 536–541, 2007.
- [126] C. Wang, E. Nieschlag, R. Swerdloff et al., “Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations,” *European Urology*, vol. 55, no. 1, pp. 121–130, 2009.