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# Testosterone Deficiency in Men over Ages 25 to 30: Its High Frequency, Adverse Effects, Diagnosis, and Treatment

by **Thierry Hertoghe, MD**  
**President, International Hormone Society**

## At What Age Does Testosterone Deficiency in Men Start, and Should It Be Treated?

Testosterone deficiency may occur at any age. Even a male newborn may be deficient in testosterone. If male babies do not present a higher peak of testosterone in the blood at birth and during the 2 months that follow, they may suffer from genital underdevelopment.<sup>1,2</sup> Cryptorchidism and less “masculine” behavior in boys may reflect very early testosterone deficiency. Adolescents and young adults may be testosterone deficient too, suffering from muscle, body hair, and beard underdevelopment as a result.

In most men, testosterone deficiency appears at a later age. The highest testosterone levels are found at ages 18 to 25. After age 25, testosterone levels slowly decline, especially intracellular testosterone levels.<sup>3</sup>

Why? There are several reasons. First, as an autopsy study showed, the total number of testosterone-producing Leydig cells decreases in adult men from age 18 on. A man goes from having an average of 7 million young and well-working Leydig cells at age 18 to just 2 million old and dysfunctional Leydig cells at age 80. That is a reduction by more than 70%!<sup>4</sup> This decline corresponds to a definitive net loss of 1 testosterone-producing Leydig cell every 4 to 5 minutes on average. Of course, new Leydig cells are formed daily, but after age 25, over time, more Leydig cells disappear than new ones appear.

If you read this article carefully, it might take you 20 to 25 minutes. In that time, the average male reader loses 4 to 5 Leydig cells. (Of course – or at least I hope – it is not due to the reading of this article, as reading other similar-length articles should provide an equivalent loss in Leydig cells.)

Second, Leydig cells decline not only in number but also in function and efficacy with age, so each remaining Leydig cell experiences increasingly greater difficulties with producing testosterone. The remaining Leydig cells at ages 40, 60, or 80 will not produce as much testosterone as an equivalent number of cells at age 18 would.<sup>5</sup>

## Speed of loss of testosterone-producing Leydig cells from age 18 to 80<sup>4</sup>:

115,000 Leydig cells net loss per year  
300 Leydig cells net loss per day  
15 Leydig cells net loss per hour  
1 Leydig cell net loss every 4–5 minutes

Third, the gradual age-related decline in the serum testosterone level worsens by a progressive increase in the serum level of sex hormone-binding globulin (SHBG), the protein that transports testosterone in the blood from the testicles to the target cells. The higher the SHBG level, the more testosterone remains sequestered in blood, tightly bound to SHBG, and the slower and less testosterone (molecules) penetrates the target cells to express their action. The decrease in testosterone bioavailable for the target cells shows up by an age-related decrease in serum-free testosterone levels that is greater than the decline in total (free + bound) testosterone.<sup>6</sup>

Fourth, the target cells for testosterone also age. They react less efficiently to testosterone. This decline in target-cell sensitivity is due to several factors: a decrease in the number and quality of its intracellular testosterone receptors, the accumulation of waste products inside the target cells that hinder metabolic activities, a decrease in functional enzymes to express the effects of testosterone, and so on.<sup>7</sup>

Fifth, as a consequence of previous disorders, the testosterone metabolic effects on the male body gradually decline with age. In laboratory tests, a decrease in testosterone metabolites reflects this decrease in testosterone action.<sup>8–10</sup> A testosterone metabolite is obtained each time a testosterone molecule reaches and binds to a testosterone receptor in the nucleus of a target cell, and it starts the chain of metabolic reactions leading to a testosterone effect. During this interaction, the testosterone molecule becomes converted into a testosterone metabolite. The testosterone metabolites androsterone and etiocholanolone can be measured

in 24-hour urine, while the best androgen metabolites in the serum to assess are dihydrotestosterone and androstenediol glucuronide, which concentration is on the average double that of testosterone.<sup>8-10</sup> The decline in testosterone metabolites is greater than the decrease in the free and total testosterone levels in the serum.

The gradual drop in the serum, urinary, and tissue levels of testosterone and its metabolites, and the consequent drop in the testosterone psychological and somatic effects, beginning at ages 25 to 30, suggest that most men aged 30 to 40 start to suffer from symptoms and signs of testosterone deficiency that are sufficient to justify testosterone supplementation, at least a low dose.

### Who is Affected by ADAM or PADAM Syndrome?

Testosterone deficiency due to the progressive age-related decline in testosterone levels and its effects has received names such as the ADAM (androgen deficiency in aging males) syndrome or PADAM (partial androgen deficiency in aging males) syndrome.<sup>11</sup> The term *aging males* is misleading, as for most people, aging starts around age 45 to 50 or even 60, while in reality, testosterone deficiency due to aging starts at a much younger age, from 25 to 30. At age 30 and over, the PADAM syndrome becomes apparent by slight, almost unapparent, declines in male characteristics.

### Testosterone, the Male Hormone

Testosterone, also called the "male hormone," is the true key to masculinity. It is the hormone that makes a man a real man. Any decrease in testosterone level brings a decrease in manhood, an unbearable thought for some men. To avoid this unnecessary suffering, testosterone levels can be kept at a sufficient level for a man to keep his masculine effects.

### The Real Significance of the Reference Limits and Interval for Testosterone

Many physicians erroneously consider the lower reference limits for total and free testosterone in the serum as thresholds below which there is testosterone deficiency, but above it is OK for them. However, the lower limit, just as the upper reference limit for testosterone, is not a health limit separating healthy and unhealthy testosterone levels. No, the lower reference limit is a purely statistical limit which tells us that 2.5% of male patients who get their testosterone checked at the laboratory have testosterone levels below this limit. A total of 95% of all other male patients will statistically present testosterone levels within the reference interval, between the upper and lower reference limits, while 2.5% have levels above the upper limit.<sup>12</sup> In no way does the lower testosterone reference limit signify that only the 2.5% of patients below this threshold are the ones who are testosterone deficient! Dogmatically relying on these limits to decide whether a testosterone level is healthy or not is a mistake, one that physicians make too often.

### What Is the Frequency of Testosterone Deficiency in Men?

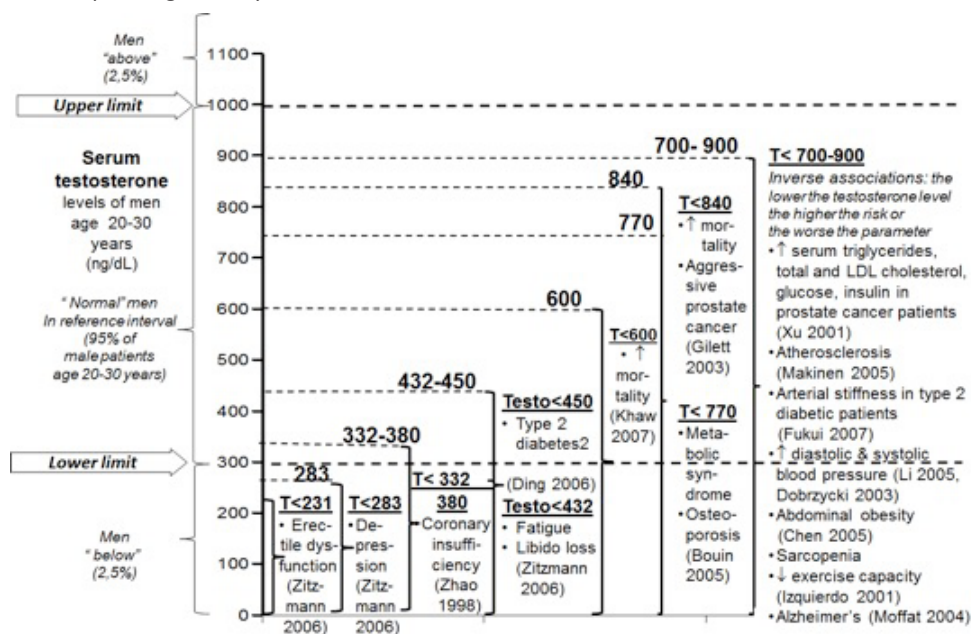
Almost every man aged 30 or over undergoes a slow and progressive decline in testosterone levels. The drop is often barely visible in the beginning and so slow to develop that many men become aware of it only at a far advanced age, 50 or over, when many disorders facilitated by the testosterone deficiency, such as abdominal obesity and cardiovascular disease, may have developed. This could have been prevented by an early testosterone treatment started between ages 30 and 40.

### Adverse Consequences of Testosterone Deficiency at Testosterone Levels Still Within the Reference Range

Small drops in testosterone levels of 10% to 20% within the reference range may pave the way for the development of the first complaints and physical signs of testosterone deficiency.

Research investigations have shown that men with testosterone levels situated in the lower 25%, 33%, 50%, or even 66% of the reference range are at higher risk of developing obesity, metabolic syndrome, diabetes, bone density loss, sarcopenia, dyslipidemia (high serum levels of triglycerides, lipoprotein a, apoB 100, LDL and total cholesterol and high HDL cholesterol), atherosclerosis, arterial hypertension, heart disease – especially coronary heart disease, cognitive dysfunction, including Alzheimer's disease, prostate cancer, in particular aggressive prostate cancer, and premature death.<sup>14-53</sup> According to these studies, 25% to 66% of men aged 30 or older have testosterone levels within those lower portions of the reference interval that are too low to ensure optimal health. The occurrence of these increased risks at these testosterone levels within the reference range strongly suggests that at these levels an intermediate degree of male hormone deficiency, which requires testosterone treatment to revoke the risks, has developed. These studies confirm the inadequacy of considering the lower and upper reference limits for testosterone as sharp limits between health and illness.

The figure below provides an overview of testosterone levels below which there are statistically significantly higher risks of disease and mortality.



# Testosterone Deficiency



## The 'Optimal' Testosterone Level

The data on the adverse health effects of lower (and average) serum testosterone levels within the reference range shown in the above-mentioned figure suggest that the "optimal" serum (total) testosterone level of the average man should be at or – even better – slightly above the mean level of young adults (ages 18 to 30). Thus, the "optimal" testosterone serum level would be 650 to 850 pg/mL (or 6500 to 8500 pg/mL, or 22.5 to 29.5 nmol/L). This concentration should correspond to the patient's highest testosterone level as a young man.

However, these optimal testosterone levels are merely indicative. Taller and more muscular men need higher testosterone levels, as they have built their bodies on higher testosterone levels in young adulthood. They need to keep their levels higher throughout their lives to maintain their bodies' health. Small-sized and thin-muscle men often feel best at lower levels of testosterone, below the average level of young men, because they have always had below-average testosterone levels that fit their body types. Even so, the testosterone level they need to feel best is still (much) higher than the lower reference limit.

## What Are the Benefits of Testosterone for Men?

Testosterone is best known as the male sex hormone that stirs men's sex drive and improves their erectile function, but testosterone produces many other beneficial effects.<sup>54–56</sup>

Testosterone is the hormone for the muscles. A healthy body is a firm body with toned muscles partly due to the correct level of testosterone. In contrast, the typical lax and slumped bodies seen in most men of advanced age are typically testosterone-deficient bodies. The appearance of excess fat and loose muscles indicates that a man's health has declined, partly due to testosterone deficiency. Testosterone has anabolic effects on all types of muscles, not only on the biceps or abdominal muscles. It also builds up the heart, which is mainly made of muscle fibers, and the arteries, each of which is essentially made of a thick layer of smooth muscles, except for a thin inner layer of endothelial cells. A lack of testosterone facilitates the development of atherosclerosis, including coronary insufficiency, by letting the arteries prematurely age.<sup>57–59</sup> Testosterone treatment reverses this condition.<sup>60</sup> Testosterone deficiency is also associated with an increased risk of heart disease due to fiber muscle atrophy of the heart muscle. Testosterone treatment reduces the myocardial ischemia and cardiac dysfunction in male coronary heart disease patients.<sup>61,62</sup>

Testosterone also makes bones stronger and denser with a higher mineral content.<sup>63,64</sup>

Next to cardiovascular diseases, testosterone has also been reported to reduce the occurrence and severity of age-related diseases, such as obesity, diabetes, osteoporosis, and Alzheimer's disease.<sup>65–73</sup>

Mentally, testosterone improves memory by increasing the number of synaptic connections between neurons and by thickening the myelin sheaths around the axons in animals.<sup>74–76</sup> It does not however, increase the number of neurons.<sup>76</sup> This means that testosterone helps individuals to understand complex information more easily. Emotionally, testosterone improves mood, makes men courageous, and may help to reduce

depressive states, such as those experienced by men around age 40 or those that do not respond to antidepressants, although results for depression are not always consistent.<sup>77–81</sup>

Finally, several scientific studies have shown in men that increasingly testosterone treatment of men with low testosterone level reduce the risk of premature death.<sup>82,83</sup>

## How to Diagnose Testosterone Deficiency

In my medical practice, I base my diagnosis of "testosterone deficiency" on the presence in a male patient of typical testosterone deficiency-related complaints and physical signs, and on laboratory tests of testosterone and its metabolites. In testosterone deficiency, the serum and urinary levels of the androgens are sufficiently low to be scientifically linked to higher risks of illness and death, but they might still be situated within the reference range. Also, to confirm the diagnosis, I prescribe a trial of testosterone therapy. If, during this treatment trial, the male patient loses his testosterone-deficiency complaints and physical signs, and he shows no overdose effects at physical examination and in laboratory tests, I consider the diagnosis confirmed and that the testosterone treatment is justified, safe, and efficient.

## Typical Complaints of Male Hormone Deficiency

Table 1 below lists the most common symptoms that show testosterone deficiency in men.

**Table 1: Complaints of Testosterone Deficiency**

- A persistent fatigue from awakening till bedtime, which worsens with physical activity
- Poor or reduced physical performance, including in sports
- Joint pain during physical activities
- A grumpy mood that may develop into depression and is also present from morning to night
- A tendency to quickly run short of breath during physical effort
- Easily inflamed tendons (e.g., in knees and heels – inflamed Achilles tendons)
- An anxiety state wherein details can be dramatized
- A tendency to be overweight with abdominal obesity (belly fat)
- Hot flashes, especially during meetings or at other stressful moments
- Excessive hesitations, difficulty making decisions
- Loose and atrophied muscles
- Lower sex drive
- A lack of determination, initiative
- A lax and obese body
- Erectile dysfunction characterized by a decrease in frequency of erections, especially morning erections<sup>84–86</sup>

What are the typical physical signs of male hormone deficiency?

Table 2 gives examples of the physical signs of testosterone deficiency in men.

## Laboratory Tests Needed and How to Interpret Them

A series of tests confirm the diagnosis of testosterone deficiency.

At the initial assessment, I often ask for the following laboratory tests:

- Total, not free, testosterone serum level. Test kits for free testosterone, which is not bound to a plasma-binding protein in the blood and easily penetrates by diffusion into target cells, are often of poor quality and unreliable. The better, more stable test is that for total testosterone, which measures all of

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the testosterone molecules found in the blood, those bound to transporting proteins and those in free form.

- **Androstenediol glucuronide:** This is the major metabolite of dihydrotestosterone. A metabolite is what remains of a hormone after it has exerted its action. High levels of androstenediol glucuronide signify that dihydrotestosterone activity is abundant in the body and that the male patient may be sexually very active (especially having good ejaculations) and have a clearly defined masculine physical appearance. It may also reflect a higher risk of male pattern baldness and body hair overgrowth.
- **FSH (follicle stimulating hormone),** the pituitary hormone, whose mission is to stimulate spermatogenesis. With age, its level increases to stimulate sperm production, which progressively declines with age. Unfortunately, as FSH also stimulates estradiol production, high FSH levels may produce excessive levels of estradiol. With aging, the increase in the FSH serum level is one of the first strong indicators of testicular failure. It usually precedes the age-related increase in LH (luteinizing hormone, the pituitary hormone that stimulates testosterone production).
- **SHBG (sex hormone-binding globulin):** I absolutely recommend checking the SHBG, the main transporter protein for male hormones. Finding a higher SHBG level (at or above the average level of the reference range) in the presence of a – for young men – average testosterone level signifies that there is a testosterone deficiency, as excessive amounts of this protein in the blood usually bind too strongly to testosterone molecules,

preventing most of the testosterone from leaving the blood and penetrating the target cells.

- In addition, I recommend checking the blood levels of female hormones, especially estrogens, estradiol in particular, and sometimes estrone and progesterone. This is because estrogen excess reduces the efficacy of testosterone by blocking testosterone receptors and by stimulating metabolic reactions that oppose those of testosterone. A low progesterone level allows men to accumulate estradiol. High levels of progesterone are necessary in men to deactivate estrogens by stimulating the conversion of potent estradiol to estrone, which is 3 to 10 times less potent.
- Other tests: LH (luteinizing hormone), the pituitary hormone that stimulates testosterone and progesterone production; prolactin, the pituitary hormone that at high levels reduces testosterone production.

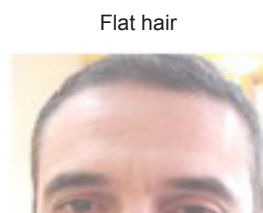
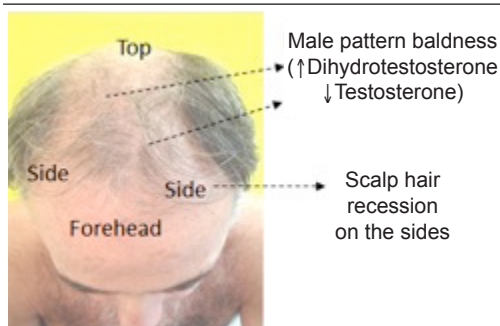
### Treatment of Testosterone Deficiency

There are various types of testosterone formulations to be taken sublingually, orally, transdermal, or intramuscularly. The most common formulation that I prescribe to my patients is a **transdermal liposomal gel of testosterone** at a concentration of 10% (100 mg per gram of testosterone). Doses are between ½ and 3 g/day.

**Table 2: Physical Signs of Testosterone Deficiency**

- Male pattern baldness: hair loss on the sides, near the forehead, and on the top of the scalp\*
- Small wrinkles above the upper lip
- A “worn-out” physical appearance
- A pale face due to poor blood supply to the skin
- Thinner and dry skin
- Hypotonic and atrophied muscles
- Dry eyes and mouth due to a drying out of the mucous membranes
- Overweight with abdominal obesity (belly fat)
- A flabby and obese body<sup>87</sup>

\* Male pattern baldness is caused by excessive levels of dihydrotestosterone, the most masculinizing male hormone, which is derived from testosterone. Dihydrotestosterone produces body hair and beard, but it reduces scalp hair, whereas testosterone makes the muscles firm and the bones strong. The latter effects are nonexistent or poorly achievable with dihydrotestosterone.<sup>88</sup>



Source: Hertoghe T. *The Atlas of Endocrinology for Hormone Therapy*.<sup>87</sup>



# Testosterone Deficiency

## Why not use the pharmaceutical brands of testosterone gel available in prescriptions at any pharmacy?

The usual brands of testosterone gels at 1% take more time to apply (per 5 grams) and are just too poorly concentrated to reach satisfying levels in most patients. The persistence of pharmaceutical companies in keeping concentrations low is explainable: a desire to avoid at all costs getting their names cited with regard to testosterone abuse by athletes.

Liposomal formulation makes testosterone penetrate the skin better.

## Correct use of a transdermal testosterone gel

- **How to proceed?** Apply the testosterone gel to the skin in four successive thin layers by intensively rubbing the testosterone into the skin in between the application of each new layer. When a thin layer of testosterone is applied, the alcohol of the gel easily evaporates, and the evaporation cools the skin, which reacts by the vasodilatation of the arteries and the opening of the capillaries in the skin. This stimulation of the skin's blood vessels helps the skin to absorb the testosterone more effectively. Applying a thick layer of the testosterone gel to the skin does not permit the alcohol to evaporate and open up the blood vessels. Furthermore, the alcohol that remains on the skin – imprisoned in the thick layer – dries the skin and irritates it.
- **Where to apply?** Apply the testosterone gel to hairless skin with high absorption capacity, such as the forehead, the sides of the neck, and above the collarbones – areas where we flush with emotion because of their greater number of blood vessels, thereby facilitating absorption.
- **Avoid hairy areas.** Avoid applying the testosterone gel to areas with a lot of body hair, such as the beard or a hairy chest. Otherwise, the testosterone will turn into dihydrotestosterone, the male hormone that promotes body hair growth but makes men lose scalp hair. Hairy areas, such as the beard and mustache, for example, are rich in 5-alpha-reductase, the enzyme that converts testosterone into dihydrotestosterone.

A second form of testosterone also provides satisfaction: intramuscular (IM) testosterone injections. IM injections are more appropriate for older men (above 60 years), whose skin does not absorb testosterone well. The use of injections assures that all testosterone enters the body. These injections can be applied daily, biweekly, weekly, every 10 days, every 2 weeks, or once every 6 to 8 weeks depending on the preparation.

The best effects are obtained, in my experience, with testosterone enanthate or testosterone cypionate, which both have similar duration in biological activity – 10 to 14 days before the effects die off and testosterone has dropped back to the initial level. However, the effects are even better when the products are injected in divided doses at a higher frequency, every week or twice a week, or in enthusiasts, every day or two days. The logic behind this is that higher-frequency injections provide more stable levels. Most patients learn to self-inject these high-frequency IM injections in the mid-thigh (external side: vastus lateralis muscle). When the 150 to 250 mg of long-acting testosterone are injected every 2 weeks, the first 5 days after injection, testosterone levels are usually excessive with levels well above the upper reference limit and, in some, with overdose

symptoms and signs (erythematous face, oily hair and skin, acne, excessive sensitivity to sexual stimuli, etc.), whereas 10 to 14 days after injection, the testosterone level tends to drop too low, at levels well below optimal levels. Approximately a quarter to a third of patients may feel testosterone deficient on those last days before the next injection.

Men who prefer to get their injections with greater intervals can get testosterone undecanoate injections of 1000 mg every 6 to 8 weeks. The frequency of every 3 months proposed by the pharmaceutical firm that produces them is for most testosterone-deficient men too long, as the testosterone level has then dropped in them back to the initial low pretreatment levels. Male patients feel testosterone deficient during the third month in this situation. Testosterone pellets provide satisfying beneficial effects and are also an alternative for those patients who do not want to bother too much with treatment. A pellet can be implanted every 3 to 4 months and let the patient enjoy stable levels, but this form does not permit the elevating of the dose in transient periods of increased need (intensive sports, for example). In those cases, the daily transdermal testosterone gel is more indicated.

Sublingual testosterone forms are less efficient and need to be taken twice a day. Oral testosterone formulations are often poorly absorbed. Almost all of the testosterone is broken down in the liver after absorption before it can penetrate the blood. To avoid this breakdown, one pharmaceutical company markets oral capsules of testosterone undecanoate, which is for a small part absorbed through lymphatic vessels, avoiding the liver. This form is more active and may provide satisfactory results to young men with milder forms of testosterone deficiency.

## Follow-Up: How to Make Testosterone Treatment Safe

First, avoid overdosing. Overdose symptoms include oily skin, a dominating, aggressive “macho” behavior, an excessive sex drive, and a reddish face and upper torso.<sup>89</sup> The redness is due to cutaneous vasodilatation and an increase in the number of erythrocytes.

Secondly, avoid the excessive conversion of testosterone to estradiol, the main female hormone. Testosterone achieves most of its beneficial effects by being converted in the target cells into either estradiol, the dominant female hormone, or dihydrotestosterone, the most masculinizing androgen. Whenever the conversion of testosterone into estradiol is excessive, the estradiol stimulates the proliferation of excessive amounts of fibrous tissue in the prostate (stromal hyperplasia), an effect that increases the size of the prostate and hardens it. After a year or more of this condition, prostate hypertrophy develops, which progresses into a compression of the urethra, causing dysuria and other signs of prostatism.<sup>90–92</sup> Excess estradiol levels are even able to lift testosterone's protective effects against proliferation of prostate cancer cells.<sup>93</sup> Excessive levels of estrogen may also block testosterone's effects in the target cells by stimulating opposite effects, resulting, for example, in erectile dysfunction and coronary heart insufficiency.<sup>94–102</sup>

## How to Avoid an Excessive Conversion of Testosterone into Estradiol

Avoid the most common causes:

- **Stop drinking daily alcohol or drinks containing caffeine:** One glass of alcohol or 2 cups of coffee or more per day increases the estradiol level by approximately 60%.<sup>102</sup> This is

the reason why the more coffee a man consumes, the greater the likelihood is that he had to undergo surgery for prostate hypertrophy.<sup>103</sup> Stopping the drinking of these beverages or limiting their intake to a maximum of 2 days per week – on weekends, for example – reduces the estradiol level by 30 to 70%.

- **Stop smoking:** Tobacco abuse increases by more than 25% the estradiol level in the serum.<sup>104</sup>
- **Lose weight:** Overweight is characterized by an excess in fat mass. Fat is rich in the enzyme aromatase that converts testosterone into estradiol. This explains why estradiol levels are 30% to 100% higher in obese males.<sup>105</sup> the volume of the prostate is also, for this reason, 30% to 100% greater in obese persons.<sup>106–108</sup> Losing the excessive fat mass can decrease the estradiol level by 30% to 50% in obese men.<sup>108</sup>
- In about 50% of cases of high estradiol, **an aromatase inhibitor, such as anastrozole, at  $-7 \times 0.1\text{--}0.5$  mg/day**, might have to be given to reduce sufficiently the estradiol back to the optimal 20–28 pg/mL. Use of an aromatase inhibitor has been shown to reduce the prostate size.<sup>109</sup> Lower levels than 20 pg/mL and higher levels than 28 pg/mL are linked with increased mortality in male patients with chronic heart failure.<sup>110</sup> If this is true for male patients without disease, the estradiol level should be tightly monitored in the follow-up! Natural inhibitors, such as chrysin and DIM (diindolylmethane), are in most cases inefficient, may be due to their relatively poor absorption and/or bioavailability.<sup>111</sup> Following one of my colleagues' experience, bioidentical progesterone at 100 mg/day reduces the estradiol level by 30% but may occasionally and transiently, due to its calming effects, weaken the quality of an erection a few hours after intake. For this reason, the patient should take it after sex, not just before.

## Conclusion

Research findings suggest that sooner or later all men get testosterone deficient. This age-related decline in testosterone secretion starts early, between ages 25 to 36, usually begins at levels already within the reference range of young adults, and has adverse effects on the male patient's mind and health. These data also suggest that to avoid the development of adverse effects an early treatment with testosterone, starting between age 25 to 35 up to 40 at the latest should be recommended.

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Born in Antwerp, Belgium, Dr. Hertoghe practices his medicine in his clinic in Brussels. With his sister, Dr. Thérèse Hertoghe, they proudly represent the fourth successive generation of physicians working with hormonal treatments – and this since 1892 (after Eugene Hertoghe, former vice president of the Royal Academy of Medicine in Belgium, and Luc and Jacques Hertoghe, endocrinologists). Dr. Thierry Hertoghe devotes his life to the promotion of a better, patient-oriented, and evidence-based medicine.

Author of numerous books, Dr. Thierry Hertoghe also travels a lot to take part in numerous conferences and congresses throughout the world. He co-organizes many of these specialized gatherings and holds important positions in several international and national medical organizations (which usually tend to fight against aging). He is the president of the International Hormone Society (over 2500 physicians), and of the World Society of Anti-Aging Medicine (over 7000 physicians), as well as the supervisor of two important postacademic trainings for doctors.

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