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HealthWatch

Testosterone Update

Low testosterone levels can mean high health risks

After decades of research and hype surrounding female menopause and hormone replacement therapy, men have recently started receiving some attention about their own age-related hormonal decline, known as andropause. Unfortunately, while estrogen replacement for women has been accused of threatening with breast cancer, androgen replacement therapy has been equally incriminated for raising the risk of prostate cancer. A number of studies have tried to relate high testosterone levels with the incidence of prostate cancer, but the preponderance of the evidence shows that maintaining youthful testosterone levels does not affect prostate cancer risk, whereas waning testosterone levels carry their own health threats. Declining testosterone levels can lead to the development of numerous symptoms such as a decrease in virility, libido and sexual activity, general sense of well-being, as well as fatigue, depression and sleep disturbances. In addition to problems such as sexual dysfunction or general malaise, however, low testosterone also translates into decreased muscle mass and strength, as well as a decrease in bone mass and an increase in abdominal fat. Studies show that the latter two lay a role in degenerative diseases such as osteoporosis, cardiovascular disease and diabetes. Moreover, depleted testosterone levels are being linked to the incidence of various lipid disorders and heart disease.



Less bone, more fat

While osteoporosis hasn't always been considered a disease that afflicts males, the rising incidence of bone mass degeneration among aging men points a finger to some age-related cause. As androgen receptors are expressed in osteoblasts (bone-forming cells) researchers now believe that androgens have some direct effect on bone formation and resorption.(1) A Belgian study using an aged rat model examined the effects of partial androgen deficiency and low-dose androgen replacement on bone and lean body mass.(2) Testosterone was administered by implants that released 11.5, 23 and 55 microg/day respectively to 12-month old male orchidectomized rats over the course of 15 weeks. Some rats received an empty implant, thus containing no testosterone. As the researchers expected, the rats that received an empty implant had significantly lower bone mineral content (-7.9%), apparent density (-5.7%), and lean body mass (-10.8%), while cancellous (-50.3%) and cortical (-1.8%) volumetric density also were decreased in the tibia. In addition, measurements of serum osteocalcin and urinary deoxypyridinoline excretion revealed an increase in bone turnover in rats with an empty implant. Meanwhile, rats receiving the smallest dose (11.5 microg/day) were not adversely affected in any of these areas relating to bone mass. This study's results demonstrate that even low-dose androgen therapy can have protective effects for bone mineral content, density and turnover, while also preserving lean body mass.

A growing body of research now suggests that an age-related increase in fat mass, or obesity, can be attributed to a fall in free testosterone and growth hormone levels. Moreover, studies report a connection between abdominal obesity and increased cardiovascular mortality and Type II diabetes mellitus. Recent findings from the University Hospital in Ghent, Belgium illustrate that age is related to a drop in free testosterone levels and free insulin-like growth factor-1, while contributing to an increase in body mass index and fat mass.(3) In fact, write the investigators, such effects make it "tempting to attribute a causal role to the decrease in androgen levels." Their analysis, which consisted of 372 males aged >20-85, revealed that body mass index and age were independent factors in determining testosterone levels. These decreased by about one quarter when researchers compared the young controls to men in the elderly group, while free testosterone levels fell by almost half with age. Likewise, fat-free mass decreased by 18.9%. In a subgroup of 57 men aged 70-80 years, the lower that testosterone levels dropped, the higher the percentage of body and abdominal fat, as well as plasma insulin levels.

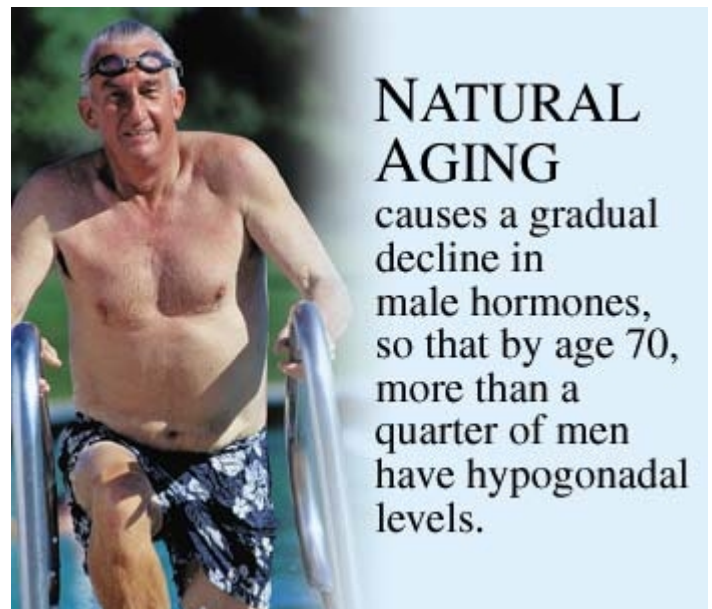
Other findings indicate that low testosterone levels predisposed men to adipose fat which, in turn, seemed to raise their risk of diabetes mellitus.(4) Researchers at the University of Washington's Department of Medicine set out to examine the effects of age-related decreasing serum testosterone levels on intra-abdominal fat in a group of 110 second-generation healthy Japanese-American men. Measurements were taken first to establish baseline levels of glucose, body mass index, visceral adiposity, subcutaneous fat, fasting insulin and C-peptide levels, and overall testosterone levels (which were within the normal range relative to the men's age). When the researchers performed follow-up measurements 7.5 years later, their results indicated that intra-abdominal fat had increased by an average of 8.0 centimeters squared. More importantly, though, they found that the change in

intra-abdominal fat correlated to baseline total testosterone levels, but they were not significantly related to other measurements such as body mass index, total fat or subcutaneous fat. The study authors concluded that, in their sample, “lower baseline total testosterone independently predicts an increase in intra-abdominal fat. This would suggest that by predisposing to an increase in visceral adiposity, low levels of testosterone may increase the risk of type II diabetes mellitus.”

Similarly, another study that analyzed some of the health effects of excess abdominal fat, also referred to as android obesity, reported that individuals exhibiting upper body excess fat distribution tend to have lower levels of plasma testosterone and growth hormone levels, suggesting what the authors describe as “complex hormonal abnormalities”.(5) Abdominal obesity lends itself to an apple-shaped figure and has been related to a heightened risk of conditions such as cancer, diabetes and heart disease. These researchers believe that, “Visceral fat tissue, through its portal drainage, could be an important source for free fatty acids that may exert complex metabolic effects: involvement in hepatic lipogenesis, increase in hepatic neoglucogenic flux, reduction in insulin metabolic clearance and involvement in peripheral insulin resistance through a competition mechanism described by Randle.” They conclude that abdominal obesity may be related to diabetes by means of an enhanced fatty acid made available from fat tissues (visceral and subcutaneous) in individuals who are genetically predisposed to type II diabetes. Research has also pointed to the possibility of a link between abdominal obesity and hypercorticism, or elevated cortisol levels. A reason for this, suggest scientists, might be that excess cortisol opposes testosterone and growth hormone production, both of which are regulators of body fat. Moreover, low testosterone levels also seem to encourage cortisol levels to rise and elicit their many aging effects, including immune dysfunction, brain cell injury, arterial wall damage and other assaults.

Hypogonadism and heart trouble

Low testosterone levels have also been implicated in playing a role in the development of chronic diseases such as atherosclerosis and cardiovascular heart disease. A study from Mahidol University in Bangkok found that, in assessing a group of Thai men and postmenopausal women over 50 years of age for levels of various hormones as they might relate to health conditions, plasma estradiol levels were highest in hypertensive men and testosterone levels were lowest in men with coronary heart disease.(6) The researchers conclude that perhaps, “Decreased testosterone and/or increased estradiol may have an adverse effect on lipid profile in elderly men.” Another study conducted among a Chinese male population likewise reported that low testosterone may be a risk factor for coronary heart disease, which may relate to lipoprotein metabolism by endogenous testosterone.(7) Results showed that mean plasma testosterone levels among patients with coronary heart disease were significantly—about 40%—lower than in healthy subjects. Moreover, there was a negative association between plasma testosterone levels and plasma triglyceride levels and lipoprotein (a), which translated into higher blood lipid levels relative to lower testosterone levels. Contrarily, a positive association between plasma testosterone levels and high-density lipoprotein cholesterol and high-density lipoprotein 3 cholesterol meant that higher testosterone levels equaled higher “good” cholesterol levels.

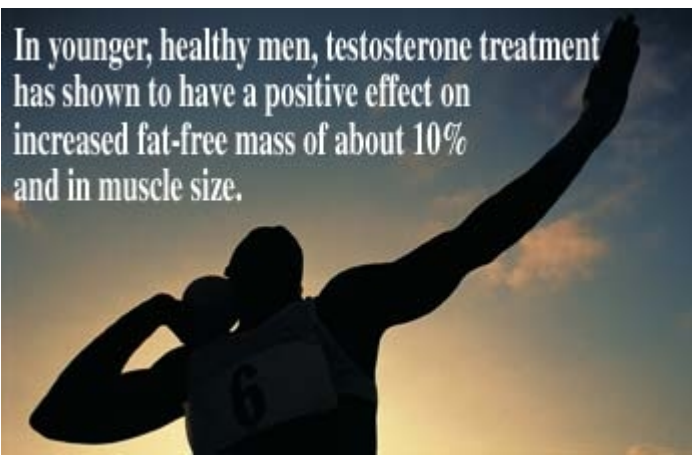


The natural aging factor

It is well documented in research that sex hormones such as testosterone are vital components in the sexual development of pubescent males, as well as contributing to the increase of their muscle and bone mass as they transform from boys into men. Meanwhile, dwindling testosterone levels as a result of metabolic aging trigger the opposite kind of effects, including the loss of body hair and progression of male pattern baldness, loss of muscle and bone mass, and increased fat. Low testosterone levels aren't just the prospect of a small segment of the male population but rather, they tend to affect the male population as a whole. Natural aging causes a gradual decline in male hormones, so that by age 70, more than a quarter of men have hypogonadal levels. (8) Some figures reveal that free testosterone levels start to fall at the rate of 1% per year after age 40.(9) While men with normal testosterone levels sometimes exhibit some of the symptoms, which may very well stem from other causes besides hypogonadism, the fact that androgen therapy usually alleviates these symptoms suggests a hormonal deficiency as the root cause of such deterioration in health.

Researchers suggest that, while it's difficult to pin down the precise role of androgen deficiency in the aging body, many study results do suggest a positive role in maintaining adequate testosterone levels in aging males. In terms of overall body composition, for example, research has demonstrated a measurable increase in lean body mass and in mid-arm circumference and the decrease in waist-to-hip ratio in elderly men, after they received androgen replacement therapy to treat their low testosterone levels. Meanwhile, in younger, healthy men (i.e. athletes), testosterone treatment has shown to have a positive effect on increased fat-free mass of about 10% and in muscle size. More specifically, studies have shown that administering testosterone to older men with low levels can help to ward off atherogenic type diseases. For example, a Polish study of 22 men with baseline serum

testosterone concentrations below 3.5 ng/ml reported that intramuscular injections of testosterone enanthate (200 mg) every two weeks for 12 months resulted in decreased total cholesterol and low-density protein cholesterol levels.(10) In addition, no significant decrease in HDL-cholesterol levels or HDL2- and HDL3-cholesterol subfractions was apparent.



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Such findings seem to indicate a positive therapeutic role for testosterone replacement, particularly in elderly men with hypogonadism at risk of osteoporosis or coronary heart disease. And while some researchers may still contest that raising testosterone levels can present other health threats, some new research is recognizing that testosterone isn't all bad and has some desirable health benefits. For example, a University of Toronto study explored new approaches to treating prostate cancer through androgen ablation therapy while reducing the side effects associated with loss of testosterone.(11) The Canadian researchers examined two new innovative methods, namely 'sequential androgen blockade' and 'intermittent androgen suppression.' The first approach uses a 5 alpha-reductase inhibitor to reduce the conversion of testosterone to dihydro- testosterone, plus an anti-androgen to prevent residual androgen from reaching the androgen

receptor. The latter uses androgen ablation therapy intermittently so as to allow testosterone levels to replenish themselves between cycled treatment periods. Both new methods, which are under current investigation, propose to maintain certain levels of testosterone during ablation therapy, so that men undergoing treatment for prostate cancer won't suffer the side effects of diminished levels, including loss of libido, reduced muscle mass, malaise and psychological upset.* Meanwhile, a University of Connecticut study sought to find out whether short-term administration testosterone would have ill effects on health.(12) After a 9-week period of intramuscular and transdermal testosterone to men over age 70 with low levels, researchers found that the hormonal therapy had effected no changes in bone resorption or formation, prostate symptoms, cholesterol levels or hemoglobin and hematocrit.

The adverse effects of low testosterone levels are apparent, bothersome, and serious enough to warrant further examination of how androgen impacts on various aspects of male health, and how androgen replacement therapy can serve as a means to contain age-related hormonal pitfalls. The biggest challenge may conceivably be to restore the reputation of testosterone, which has been cast as a "bad steroid" for some time. Another task for research will be to continue building a case for the vital role that androgens have with regard to bone, heart, sexual, mental health and general well being. Offering solid proof of testosterone's various functions will help to show that, while testosterone therapy may not be appropriate for every man, it would be a shame for other men to miss out on its merits. —Angela Pirisi

*Please refer to the Life Extension Foundation's Prostate Cancer Protocols (www.lef.org) for a comprehensive review of recommended therapeutic approaches.

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