

LE Magazine August 2002

## REPORT

GRUMPY NO MORE:  
TESTOSTERONE DEFICIENCY & DEPRESSION  
DOES DHEA RAISE THE LEVELS OF  
BIOAVAILABLE TESTOSTERONE IN MEN?

Postmenopausal depression and cognitive dysfunction in older women have received much attention. Many studies have established a positive impact of estrogen on mood and memory, motor coordination, alertness and cerebral blood flow. But what about depression in hormone-deficient older men? Is the "grumpy old man" syndrome just one of those jokes about aging, like the countless jokes about memory loss and waning sexual potency? Depression is no joke, but research shows that it can be treated.

By Ivy Greenwell



No one wants to be depressed, but it seems depression scores tend to rise with age. Depression is finally being recognized as a widespread and serious problem, not only among the elderly, but also among midlife men (we used to call it "the midlife crisis," but is now referred to as "andropause"). The "grumpy old man" syndrome is only now coming to the fore as a serious, debilitating condition that is potentially easily corrected—not with antidepressants such as Prozac (notorious for causing sexual dysfunction), but with testosterone.

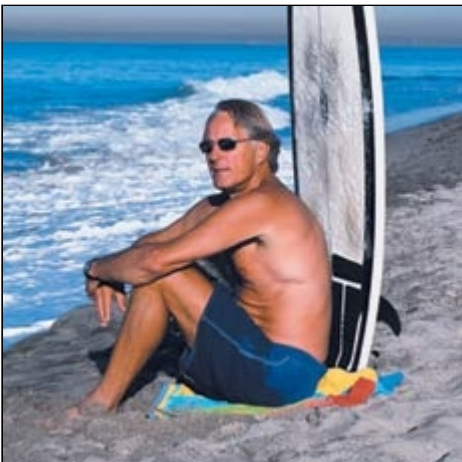
Clinical and anecdotal experience indicates that testosterone is an excellent antidepressant, capable of restoring a lethargic "grump" to his former cheerful, active self. Delighted wives speak of irritable mates turning sweet-tempered again, of couch potatoes rising from their slough of despond and beginning to putter in the garage, whistling as they work. The ad for the new Testoderm patch states, "enhances mood, energy, libido and sexual function." Note that "mood" is mentioned first. "Men who take testosterone typically report that they feel happier, more energetic and more full of life," explained Dr. William Regelson, author of *The Superhormone Promise*. One reason it is so difficult to do placebo-controlled testosterone studies is that men taking the active substance quickly note an enhanced sense of well-being (as well as youthful changes such as more color in the face and lips due to increased red blood cell production).

As testosterone replacement for women is becoming increasingly commonplace, women too report not just restored libido, but also improved mood and greater energy, less anxiety and more assertiveness. The very fact that depression has a large female predominance hints that testosterone may be protecting men against this debilitating disorder. But is there enough research to validate the widely accepted testosterone-mood connection?

#### Free testosterone and depression

A major study was published in the February 1999 issue of the *Journal of Clinical and Experimental Endocrinology and Metabolism*, one of the most respected biomedical journals. Dr. Elizabeth Barrett-Connor, a famous name in the field of hormone replacement research, headed the study. This was part of the Rancho Bernardo Study that yielded much valuable information about postmenopausal women. Now the attention has turned to men.

The subjects in Barrett-Connor's study were 856 men aged 50 to 89, not on testosterone replacement, living in the suburban community of Rancho Bernardo near San Diego. The average age was 70. They completed the Beck Depression Inventory; several physiological variables were measured, including total testosterone and free testosterone, dihydrotestosterone (DHT), total estradiol and free estradiol. The study found a very pronounced drop in free testosterone with age, a smaller drop in free



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estradiol, a relatively small, statistically insignificant decrease in total testosterone and total estradiol; DHT stayed the same (with possible slight trend toward increase with age).

Depression score went up with age, in parallel with the drop in free testosterone. Age, loss of weight (the authors note: "Depressed men, in contrast to depressed women, are likely to lose weight"), and lack of exercise also correlated with the depression score. The strongest connection that emerged was the one between low free testosterone and depression. The researchers state, "After adjustment for age, a significant negative trend in BDI [depression] score was seen only for bioavailable testosterone; the association persisted after additional adjustment for change of body weight and regular exercise." In other words, age alone did not reliably predict depression as assessed by the standard depression inventory; low levels of free testosterone were the best predictor of depression, regardless of age.

Furthermore, it turned out that 25 men in this group suffered from clinical depression (some were actually taking antidepressants). Was this reflected in their levels of free testosterone? The study provided a resounding yes: "These men had lower levels of bioavailable testosterone than all other men." On the average, free testosterone levels were 17% lower in the 25 clinically depressed men.

It is interesting to note that Barrett-Connor and colleagues speculate that the actual correlation between free testosterone and depression scores is even higher than revealed by their study; they suspect that many depressed men were not inclined to participate in this research project. Both depression and declining testosterone are psychologically difficult areas; unlike women, who tend to be much more aware of the hormonal connection, aging men are less likely to be open about their problems.

Discussing their results, the authors point out that in the brain testosterone is partly converted to estradiol and DHT. The improvement in memory and cognitive function associated with testosterone replacement is generally regarded as a consequence of aromatization (when the body converts excess testosterone into estrogen) of testosterone to estradiol. Could it be that the improvement in mood is really due to higher estradiol levels? Barrett-Connor does not think so; after all, the study showed no correlation between depression and free estradiol.

The mood-improving action of testosterone is more likely to be due to the direct action of testosterone on the brain-possibly through raising the levels of dopamine, a very important "reward" neurotransmitter. In addition, a sufficient amount of free testosterone is important for mitochondrial energy production, since some of the Krebs cycle enzymes depend on testosterone. (The Krebs cycle is a series of enzymatic reactions in aerobic organisms that lead to the production of high-energy phosphate compounds.) Like thyroid, testosterone enhances aerobic metabolism. This improved overall energy production may also play a role in creating better mood. (Note that hypothyroidism is also linked to depression.)

Some have also raised the cause-and-effect issue. Could it be that depression comes first, and depressed men produce less testosterone? We know that as cortisol rises, testosterone levels tend to drop. Thus, there seems to be a constant tug-of-war between stress and testosterone. A vicious circle is also likely: lower testosterone leads to depressed mood, depressed mood leads to less exercise and social activity, and also further lowers testosterone production, which in turn leads to more depression.

Continued on Page 2 of 2

[Back to the Magazine Forum](#)

### The Importance of Maintaining Youthful Levels of Free Testosterone

A positive development in endocrinology has been the introduction of tests for "free" hormones, not bound to a protein (in this case, SHBG, the sex hormone-binding globulin). It is the levels of free steroids that matter, since only free hormones are biologically active. This discovery has changed our picture of what really happens to men's testosterone levels as they age. While the levels of total testosterone may remain quite adequate, the levels of free testosterone have been found to decline by as much as 40% between the ages of 40 and 70.

Basically, the drop begins at some point in mid-twenties, but becomes really notable in midlife ("andropause"). This decline in free testosterone is due partially to the increase in sex hormone-binding globulin (SHBG), a protein on which most steroids "ride" in the bloodstream. This rise in SHBG parallels the age-related increase in body fat. As body fat (and thus SHBG) increases, we see more depression, memory problems, atherosclerosis, osteoporosis (yes, men lose bone mass too, especially in the spine), muscle loss and declining sexual function; and yes, we do see more prostate cancer (which is not surprising, considering the rising ratio of free estradiol to free testosterone). Stress, with concomitant conversion of pregnenolone to cortisol rather than testosterone, is also a great enemy of testosterone, as is elevated insulin.

Some (Dr. Barry Sears in *The Anti-Aging Zone*, for example) argue that if men manage to preserve muscle mass while keeping the percentage of body fat as low as it used to be in the early

twenties, they should not need testosterone replacement. Others point out that some free-radical damage to the testes is inevitable over the course of aging, and that sooner or later the production of testosterone is bound to decline.

## REPORT

### Is replacement therapy the answer?

Clinical observation and anecdotal accounts confirm that testosterone replacement has a strong antidepressant effect. Dr. Eugene Shippen, an authority on testosterone replacement, points to the existence of a substantial body of scientific literature that consistently links the decline in testosterone to almost all aging-related diseases, including depression, cognitive dysfunction and neurodegenerative brain disorders. Dr. Regelson quoted a clinician who prescribes testosterone: "I have a number of patients whom I've been treating with testosterone for the past five years, and most of them would not come off it even if you offered them a small piece of the Federal Reserve." Cheerful, energetic, self-confident mood may be a much more important reason for this than enhanced libido.



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Free testosterone has also been found to be the most important biomarker of aging in men. It is insufficient to have your total testosterone tested; men should insist on a blood test for free testosterone. Because of diurnal variations, some suggest early afternoon as the best time for a blood test.

But before we can draw firm conclusions, controlled experimental studies are needed. Predictably, Barrett-Connor concludes by calling for more research on the effects of testosterone replacement. "I would like to stress that since the number of women using testosterone has expanded exponentially in the last few years, we badly need more studies on the effects of testosterone replacement in women as well as in men. Clinicians have observed that women patients respond to correct testosterone replacement with reports of greater zest, energy, assertiveness, and overall improved sense of well-being. The hormone of strength, the hormone of desire apparently has a significant impact on mood and brain function in general in both sexes. Is testosterone the primary hormone of good cheer? Only more research can provide a definite answer."

#### The whole approach

At the 1995 A4M conference in Las Vegas, Dr. Whitaker raised a rhetorical question: "Are we going to give hormones only to women, while men are supposed to just wither away?" Rather than making jokes about grumpy old men, we should keep searching for ways to restore optimal neurochemistry for both sexes. Safe hormone replacement appears to be the key, but may not be the whole answer. Nutrients such as phosphatidyl-serine and acetyl-L-carnitine are also very helpful in preserving a more youthful brain function, and SAME can work wonders as an antidepressant. But depressed midlife and older men would do well to have their free testosterone tested. While weight training and a diet that provides sufficient healthy fat while restricting insulin-raising refined carbohydrates help preserve youthful levels of free testosterone, there eventually comes a time when testosterone replacement needs to be considered.

Dr. Whitaker continued, "Whatever comes first, the eventual effect of the male menopause is an erosion of the underpinnings of our personal strengths. Loss of athletic ability, loss of dynamic executive capabilities, loss of self-confidence, eagerness, aggressive energy-a sense of loss magnified and multiplied by the total unexpectedness of what we are undergoing. This is a change, indeed. The sharp edges of youth are replaced by the well-traveled roads of habit and lethargy.

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While at this point men are far behind women in hormone replacement-some clinicians say men are 15 to 20 years behind-there is an emerging consensus that male hormone replacement is going to become as common as postmenopausal hormone replacement for women. It is routinely offered at anti-aging clinics, and even the more innovative HMO doctors are beginning to prescribe it.

Testosterone replacement does not need to be expensive or inconvenient. You do not have to wear a patch or get shots. Compounding pharmacies, such as Women's International Pharmacy or College Pharmacy, can prepare testosterone gels and creams that are well-absorbed (prescription required) for under \$20 a month. Friendly compounding pharmacists can provide more information to you and your doctor.

Sublingual testosterone is also available from compounding pharmacies, as well as oral testosterone in oil capsules. The transdermal route (cream or gel), however, is widely regarded as the best, producing steady levels and the least stress on the liver. Methyl-testosterone is to be avoided, since it is harmful to the liver; in fact, it has been banned in Europe. The patch (Testoderm or Androderm) uses only natural testosterone.

Studies have shown that neither testosterone shots nor the patch cause a rise in PSA. Some clinicians even suggest that beginning testosterone replacement early prevents prostate cancer by maintaining a youthful androgen/estrogen ratio. Still, every man's greatest fear when it comes to testosterone replacement is the risk of prostate cancer. Life Extension Foundation has written extensively about new findings indicating that it is excess estrogen together with DHT that combine to overstimulate the prostate. Life Extension Foundation's Natural Prostate Formula is a top-of-the-line product. It is unique in that it provides protection not only against excess DHT, but also against excess estrogen. Some innovative physicians would in fact argue that it is testosterone-deficient men who are more in need of various measures to protect the prostate, due to their typically unfavorable androgen/estrogen ratio, which may cause changes in prostate cancer cells that make them more susceptible to mutations that result in prostate cancer.



Zinc (which appears to act as an aromatase inhibitor in the prostate, lowering men's estradiol levels), soy phytoestrogens, green tea, polyphenols in strawberries and other berries, lycopene and conjugated linoleic acid (CLA) have also shown to protect against prostate cancer, and in some cases even reverse it. Finally, keeping the percentage of body fat as low as possible is itself a very effective preserver of a youthful hormonal profile and correct androgen/estrogen ratio.

In some cases DHEA replacement seems sufficient to produce the benefits suggesting increased levels of free testosterone, even though total serum testosterone is unaffected (in women, total serum testosterone does rise after DHEA replacement). Fortunately, a well-controlled study published in the prestigious Journal of Clinical and Experimental Endocrinology and Metabolism did in fact find a significant rise in free testosterone in men aged 60 to 84 years, after three months on 100 mg of DHEA. There was no rise in total testosterone or in PSA. Even at lower doses of DHEA, one would expect a rise in tissue

levels of testosterone, undetectable in the serum but nevertheless of considerable physiological importance.

There is of course every reason for men to take DHEA along with testosterone replacement for enhanced benefits, such as improved immune function. The next five years ought to bring us more much needed information on hormone replacement for men.



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Find out more about DHEA



Cautionary notes: When men use testosterone drugs (even those that provide natural testosterone), there is a propensity for the body to aromatize this testosterone into estrogen. Some men on testosterone drug replacement therapy develop dangerously high estrogen levels. Estrogen can be suppressed by taking an aromatase-inhibiting drug like Arimidex (0.5 mg twice a week) or using a supplement like Super Mira Forte (six capsules daily). Regular blood tests are important to make sure enough aromatase inhibiting drug-nutrient is being taken to keep estradiol levels under 30 (pg/mL).

Life Extension recommends that any man taking testosterone drugs have a blood test every 45 to 60 days during the first six months of use to guard against estrogen-overload or detect an elevated PSA that could rise if there were an occult prostate tumor present. Prostate cancer should be ruled out before testosterone is prescribed by both a blood PSA test and a digital rectal examination. A small percentage of men who have occult prostate cancer will have a normal PSA and show no other signs of the disease until they begin taking testosterone drugs. Annual blood testing to measure free testosterone, estradiol, liver function and PSA is mandatory for those taking testosterone drugs. Refer to Life Extension's "Male Hormone Modulation Protocol" at [www.lef.org](http://www.lef.org) for complete information about safe testosterone replacement therapy.

Resources mentioned in this article:

- Women's International Pharmacy: 800-279-5708
- College Pharmacy: 800-888-9358

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[Back to the Magazine Forum](#)

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