



September 11, 2013

Middle-Aged Men, Too, Can Blame Estrogen for That Waistline

By [GINA KOLATA](#)

It is the scourge of many a middle-aged man: he starts getting a pot belly, using lighter weights at the gym and somehow just doesn't have the sexual desire of his younger years.

The obvious culprit is testosterone, since men gradually make less of the male sex hormone as years go by. But a surprising new answer is emerging, one that doctors say could reinvigorate the study of how men's bodies age. Estrogen, the female sex hormone, turns out to play a much bigger role in men's bodies than previously thought, and falling levels contribute to their expanding waistlines just as they do in women's.

The discovery of the role of estrogen in men is "a major advance," said Dr. Peter J. Snyder, a professor of medicine at the University of Pennsylvania, who is leading a big new research project on hormone therapy for men 65 and over. Until recently, testosterone deficiency was considered nearly the sole reason that men undergo the familiar physical complaints of midlife.

The new frontier of research involves figuring out which hormone does what in men, and how body functions are affected at different hormone levels. While dwindling testosterone levels are to blame for middle-aged men's smaller muscles, falling levels of estrogen regulate fat accumulation, according to a [study published](#) Wednesday in The New England Journal of Medicine, which provided the most conclusive evidence to date that estrogen is a major factor in male midlife woes. And both hormones are needed for libido.

"Some of the symptoms routinely attributed to testosterone deficiency are actually partially or almost exclusively caused by the decline in estrogens," said Dr. Joel Finkelstein, an endocrinologist at Harvard Medical School and the study's lead author, in a news release on Wednesday.

His study is only the start of what many hope will be a new understanding of testosterone and estrogen in men. Dr. Snyder is leading another study, the [Testosterone Trial](#), which measures levels of both hormones and asks whether testosterone treatment can make older men with low testosterone levels more youthful — by letting them walk more quickly, feel more vigorous, improve their sexual functioning and their memories, and strengthen their bones. Smaller studies have been promising but unreliable, and estrogen has not been factored in.

"We had ignored this hormone in men, but we are studying it now," said Dr. Alvin M. Matsumoto, a testosterone and geriatrics researcher at the University of Washington School of Medicine and the V.A. Puget Sound Health Care System, who is a Testosterone Trial researcher. "We are just starting out on this road."

Both men and women make estrogen out of testosterone, and men make so much that they end up with at least twice as much estrogen as postmenopausal women. As levels of both hormones decline with age, the body



changes. But until now, researchers have focused almost exclusively on how estrogen affects women and how testosterone affects men.

Dr. Finkelstein's study provides a new road map of the function of each hormone and its behavior at various levels. It suggests that different symptoms kick in at different levels of testosterone deficiency. Testosterone, he found, is the chief regulator of muscle tone and lean body mass, but it takes less than was thought to maintain muscle. For a young man, 550 nanograms of testosterone per deciliter of blood serum is the average level, and doctors have generally considered levels below 300 nanograms so low they might require treatment, typically with testosterone gels.

But Dr. Finkelstein's study found that muscle strength and size turn out to be unaffected until testosterone levels drop very low, below 200 nanograms. Fat accumulation, however, kicks in at higher testosterone levels: at 300 to 350 nanograms of testosterone, estrogen levels sink low enough that middle-aged spread begins.

As for sexual desire and performance, both require estrogen and testosterone, and they increase steadily as those hormone levels rise. Researchers say it is too early to make many specific recommendations, but no one is suggesting that men take estrogen, because high doses cause feminine features like enlarged breasts.

Although doctors prescribe testosterone gels for men whose levels fall below 300 nanograms per deciliter, that cutoff point is arbitrary, and there is no clinical rationale for it, Dr. Finkelstein said. Often men take the hormone to treat complaints like fatigue, depression or loss of sexual desire, which may or may not be from low levels of testosterone. The data suggest that men with levels around 300 nanograms who complain of sexual problems may want to try testosterone, but those who complain of flagging muscle strength should not blame testosterone deficiency, Dr. Finkelstein said. But, he added, "symptoms of low testosterone tend to be quite vague."

Today, millions of men are using testosterone gels, fueling a nearly \$2 billion market.

For their study, Dr. Finkelstein and his colleagues recruited 400 men aged 20 to 50 who agreed to have their testosterone production turned off for 16 weeks. Half then received varying amounts of testosterone, while the other half also got a drug that shuts off estrogen synthesis so the researchers could assess the effects of having testosterone but not estrogen.

It turned out to be surprisingly easy to recruit subjects, Dr. Finkelstein said. One, Ben Iverson, joined in part for the \$1,000 subjects were paid. "That, to me, was enticing," he said. He was a 28-year-old Harvard graduate student at the time and is now an assistant professor of finance at Northwestern University.

Although Mr. Iverson's wife looked askance at the injections to block testosterone production, Mr. Iverson ended up getting enough testosterone in the gel he was assigned to use. The worst were the testosterone-suppressing injections, which required him to use a huge needle in his abdomen once a month, he said.

He found out when the study ended that he was in a group that got enough testosterone to keep his levels in a normal range. "I literally did not notice any difference at all," Mr. Iverson recalled.

The worst symptoms were in men whose estrogen production was shut down — they got intense hot flashes.

Now Dr. Finkelstein is repeating the study with older men. The Testosterone Trial is looking at them too.

For that study, Dr. Snyder and his colleagues recruited nearly 800 men aged 65 and older who have low testosterone levels. The men take either a placebo or enough testosterone to bring their level to between 400



and 800. Investigators are assessing walking speed, sexual functioning, vitality, memory, red-blood-cell count, bones and coronary arteries. The yearlong study will be completed next year.

Next, researchers said, they want to do a large study [like one conducted with thousands of women](#) in 2002 that asked about long-term risks and benefits of hormone therapy. Does testosterone therapy lead, for example, to more prostate cancer? Does it prevent heart attacks?

“We still don’t know the answers to the clinical questions,” Dr. Matsumoto said. “Does it prevent things that are really important?”