



Can We Prevent Aging? *Tips from the National Institute on Aging*

People are living longer. In 1970, the average life expectancy at birth was 70.8 years; in 2000, it was 76.9 years; and by 2030 it is estimated that the “oldest-old,” age 85 and older, could grow to 10 million people.

Views on aging are also changing. It no longer necessarily means physical decline and illness—in the last two decades, the rate of disability among older people has declined dramatically.

The National Institute on Aging (NIA), part of the Federal Government’s National Institutes of Health (NIH), investigates ways to support healthy aging and prevent or delay the onset of diseases that disproportionately affect us as we age. These studies not only may increase what is known as “active life expectancy”—the time of advancing years free of disability—but also may promote longevity. NIA’s research includes hormone and dietary approaches, including calorie restriction.

Results from NIA-sponsored studies and others are likely to improve our understanding of the benefits and risks of hormone supplements, calorie restriction, and other interventions to promote healthy aging. This tip sheet provides an overview of what we know about hormone supplements and calorie restriction and the research needed to learn more. Until we have a better understanding, it is a good idea to be skeptical of claims that hormone or other supplements can solve your age-related problems. Instead, focus on what is known to help promote healthy aging: healthy eating and physical activity.

What Is a Hormone?

The word “hormone” comes from the Greek word, hormo, meaning to *set in motion*. Hormones are chemical messengers that set in motion different processes to keep our bodies working properly. For example, they are involved in our metabolism, immune function, sexual reproduction, and growth. Hormones are made by specialized groups of cells within the body’s glands. The glands—such as the pituitary, thyroid, adrenals, ovaries, and testes—release hormones into the body as needed to stimulate, regulate, and control the function of other various tissues and organs involved in biological processes.

We cannot survive without hormones. As children, hormones help us “grow up.” In teenagers, they drive puberty. As we get older, some of our hormone levels naturally decline. But what does that mean? Scientists do not know exactly. In order to know more, NIA investigates how replenishing hormones in older people affects frailty and function. Many of these studies focus on hormones that decline with age, including:

- Growth hormone
- Melatonin
- Dehydroepiandrosterone (DHEA)
- Testosterone
- Estrogen and progesterone (as part of menopausal hormone therapy)

How Hormones Work

Most hormones are typically found in very low concentrations in the bloodstream. But a hormone's concentration will fluctuate depending on the body's activity. Like a key that unlocks a door, a hormone molecule is released by a gland and travels through the blood until it finds a cell with the right fit, a "receptor." The hormone latches onto a cell's receptor and a signal is sent into the cell. These signals may instruct the cell to multiply, make proteins or enzymes, or perform other vital tasks. Some hormones can even cause a cell to release other hormones.

One hormone may fit with many types of cells but may not affect all cells in the same way. For example, one hormone may stimulate one cell to perform a task but it might also turn off a different cell. Additionally, how a cell responds to a hormone may change throughout life.

Hormone Supplements

Levels of some hormones change naturally over the lifespan. Some hormones increase with age, like parathyroid hormone that helps regulate the amount of calcium in the blood and bone. Some tend to decrease over time, such as testosterone in men and estrogen in women. When the body fails to make enough of a hormone because of a disease or disorder, a doctor may prescribe hormone supplements. As opposed to hormones produced naturally by the body, hormone supplements come in many forms such as pills, shots, topical (rub-on) gels, and medicated skin patches.

You may have read magazine articles or seen television segments suggesting that hormone supplements can make people feel young again or can slow or prevent aging. That's because finding a "fountain of youth" is an attractive story that captivates us all. The truth is no research to date has shown that hormone supplements add years to life or prevent age-related frailty. And, while some supplements have real health benefits for people with clinical hormone

deficiencies due to a disease or disorder, they also can cause harmful side effects. That's why people who have a diagnosed hormone deficiency should still only take hormone supplements under a doctor's supervision.

In some cases, the U.S. Food and Drug Administration (FDA) may have approved a hormone supplement for one purpose, but it is prescribed by physicians for another. This "off-label" use may occur when physicians believe that research, such as clinical studies done on other groups of people, demonstrates a supplement's usefulness for another condition. While this is the normal process for evaluating drugs already approved by the FDA, consumers should be aware that a particular off-label use of a drug may not have been tested and verified to the same degree as the original use of the drug.

Dangers of Hormone Supplements

Higher concentrations of hormones in your body are not necessarily better. The body maintains a delicate balance between how much hormone it produces and how much it needs to function properly. Natural hormone production fluctuates throughout the day. That means that the amount of hormone in your blood when you wake up may be different 2, 12, or 20 hours later.

If you take hormone supplements, especially without medical supervision, you can adversely affect this tightly controlled, regulated system. Hormone supplements cannot replicate your body's natural variation. Because hormonal balance is so intricate, too much of a hormone in your system may actually cause the opposite of your intended effect. For example, taking a hormone supplement can cause your own hormone regulation to stop working. Or, your body may process the supplements differently than the naturally produced hormone, causing an alternate, undesired effect. It is also possible that a supplement could amplify negative side effects of the hormone naturally produced by the body. Scientists may not know the consequences.

Some hormone-like products are sold over-the-counter without a prescription. Self-medicating with them can be dangerous. Products that are marketed as dietary supplements are not regulated by the FDA. This means that companies making dietary supplements do not need to get FDA approval or provide any proof that their products are safe and effective before selling them. There is no guarantee that the “recommended” dosage is safe, that there is the same amount of active ingredients in every bottle, or that the substance is what the company claims. Because there are no standards, the hormone-like dietary supplements sold over-the-counter may not have been thoroughly studied and potential negative side effects may not be understood or defined. In addition, these over-the-counter products may interfere with your other medications. NIA does not recommend taking any supplement touted as an “anti-aging” remedy because there is no proof of effectiveness and the health risks of short and long-term use are unknown.

Human Growth Hormone

Human growth hormone (hGH) is important for normal growth and development, as well as for maintaining tissues and organs. It is made by the pituitary gland, a pea-sized structure located at the base of the brain.

Research supports supplemental use of hGH injections in certain circumstances. For instance, hGH injections can improve the growth of children who do not produce enough hGH. Sometimes hGH injections may be prescribed for young adults whose obesity is the result of having had their pituitary gland surgically removed. These uses are different from taking hGH as an anti-aging strategy. As with other hormones, hGH levels often decline with age, but this decrease is not necessarily bad. At least one epidemiological study suggests that people who have high levels of hGH are more apt to die at younger ages than those with lower levels of the hormone. Researchers have also studied animals with genetic disorders that suppress growth hormone production and

secretion and found reduced growth hormone secretion may actually promote longevity in those species that have been tested.

Although there is no conclusive evidence that hGH can prevent aging or halt age-related physical decline, some clinics market hGH for that purpose and some people spend a great deal of money on such supplements. Shots can cost more than \$15,000 a year. These shots are only available by prescription and should be administered by a doctor. But, because of the unknown risks, it is hard to find a doctor who will prescribe hGH shots. Over-the-counter dietary supplements, known as human growth hormone releasers, are currently being marketed as low-cost alternatives to hGH shots. But claims of their anti-aging effects, like all those regarding hGH, are unsubstantiated.

Research is starting to paint a fuller picture of the effects of hGH supplements, but there is still much to learn. For instance, study findings indicate that supplemental hGH can increase muscle mass; however, it seems to have little impact on muscle strength or function.

Questions about potential side effects, such as diabetes, joint pain, and fluid build-up leading to high blood pressure or heart failure remain unanswered, too. A recent report that children who were treated with pituitary growth hormone have an increased risk of cancer created a heightened concern about the dangers of hGH injections. Whether or not older people treated with hGH for extended periods have an increased risk of cancer is unknown. To date, only small, short-term studies have looked specifically at hGH as an anti-aging therapy for older people. Before supporting the use of hGH as an anti-aging therapy, the potential benefits and risks should be assessed through additional research.

Melatonin

Melatonin is a hormone involved with our daily sleep/wake cycle. It is made by the pineal gland located in the brain. Despite some claims to the contrary, melatonin production and release does not necessarily decrease with age. Instead, a

number of factors, including light exposure and use of some common medications can affect melatonin secretion in people of any age.

As with other hormones, melatonin is marketed as a dietary supplement. Consumers should look with caution at claims about melatonin supplements' effects.

One claim for melatonin supplements is that they are an anti-aging remedy, but research on the anti-aging effects has been very limited and focused on animals, not humans. There are also claims that melatonin helps with sleep. Research findings have shown that melatonin supplements, in amounts ranging from 0.1 to 0.5 milligrams, can improve sleep in some cases; however, if taken at the wrong time, melatonin can actually disrupt the sleep/wake cycle. And, melatonin's benefits as an antioxidant have been touted. Antioxidants protect the body from the harmful effects of by-products, known as free radicals, made when the body changes oxygen and food into energy. Early test-tube studies suggested that, in large doses, melatonin might be an effective antioxidant. More research is needed to know if using melatonin supplements as an antioxidant will decrease the amount of antioxidants cells produce naturally.

Side effects of melatonin supplements may include confusion, drowsiness, and headache. Animal studies suggest that melatonin may cause some blood vessels to constrict, a condition that could be dangerous for people with high blood pressure or other cardiovascular problems.

The usual dose of melatonin sold without a prescription in stores is 3 milligrams. This dose is much larger than the 0.1 to 0.5 milligrams of melatonin researchers used to study its effects on sleep. People who take these supplements may have a 10- to 40-times higher blood concentration of melatonin than normal. Long-term effects of such high concentrations of melatonin on the body are still unknown. Use caution when considering taking these supplements until researchers learn more.

DHEA

Dehydroepiandrosterone, or DHEA, is made from cholesterol by the adrenal glands, which sit on top of each kidney. It is converted by the body into two other important hormones: testosterone and estrogen.

For most people, DHEA production peaks in the mid-20s and then gradually declines with age. The effects of this decline including its role in the aging process are unclear. Even so, some proponents claim that over-the-counter DHEA supplements can improve energy and strength and boost immunity. Claims are also made that supplements increase muscle and decrease fat. To date, there is no conclusive scientific evidence that DHEA supplements have any of these benefits.

The conversion of naturally produced DHEA into a different amount of estrogen and testosterone is highly individualized. There is no way to predict whose body will make more and whose will make less of these hormones. Having an excess of testosterone and estrogen in your body can be risky.

Scientists do not yet know the effects of long-term use (over 1 year) of DHEA supplements. Early indications are that these supplements, even when taken briefly, may have several detrimental effects on the body, including liver damage. But the picture is not clear. Two short-term studies showed that taking DHEA supplements has no harmful effects on blood, prostate, or liver function. However, these studies were too small to lead to conclusions about the safety or efficacy of DHEA supplementation.

Researchers are working to find more definite answers about DHEA's effects on aging, muscles, and the immune system. In the meantime, if you are thinking about taking DHEA supplements, be aware that the effects are not fully known and might turn out to cause more harm than good.

Testosterone

Most people know testosterone as the hormone that transforms a boy into a man and is somehow associated with sex drive. That may be why some men are concerned about a possible decrease in testosterone production as they age.

Testosterone is a vital sex hormone that plays an important role in puberty. In men, testosterone not only regulates sex drive (libido), it also helps regulate bone mass, fat distribution, muscle mass and strength, and the production of red blood cells and sperm. But testosterone isn't exclusively a male hormone—women produce small amounts, as well. In men, testosterone is produced in the testes, the reproductive glands that also produce sperm. The amount of testosterone produced in the testes is regulated by the hypothalamus and the pituitary gland.

As men age, their testes often produce somewhat less testosterone, especially when compared to years of peak testosterone production during adolescence and early adulthood. Normal testosterone production ranges widely, and it is unclear what amount of decline or how low a level of testosterone will cause adverse effects.

In recent years, the popular press has reported frequently about male menopause, a condition supposedly caused by diminishing testosterone levels in aging men. There is scant scientific evidence that this condition, also known as andropause or viropause, exists. And the likelihood that an aging man will experience a major shutdown of testosterone production similar to a woman's menopause is very remote. In fact, many of the changes that take place in older men often are incorrectly attributed to decreasing testosterone levels. For instance, some men experiencing erectile difficulty (impotence) may be tempted to blame it on lowered testosterone, when in many cases erectile problems are due to circulatory problems.

In certain cases, such as in men whose bodies make very little or no testosterone, testosterone

supplementation may offer benefits. FDA-approved testosterone supplements come in different forms, including patches, injections, and topical gels. Men whose testes have been damaged or whose pituitary glands have been harmed or destroyed by trauma, infections, or tumors may be prescribed testosterone. Supplements can also help men with exceptionally low testosterone levels maintain strong muscles and bones and increase their sex drive. It is unclear if men who are at the lower end of the normal range for testosterone production would benefit from supplementation.

More research is needed to learn what effects testosterone replacement may have in healthy older men without these extreme deficiencies. NIA is investigating the role of testosterone therapy in delaying or preventing frailty and helping with other age-related health issues. Results from preliminary studies involving small groups of men have been inconclusive. Specifically, it remains unclear to what degree testosterone supplements can help men maintain strong muscles and sturdy bones, sustain robust sexual activity, or sharpen memory.

There are also concerns about the long-term harmful effects that supplemental testosterone might have on the aging body. Some epidemiologic studies suggest that higher natural levels of testosterone are not associated with a higher incidence of prostate cancer—the second leading cause of cancer death among men. However, scientists do not know if taking supplemental testosterone increases men's risk for developing prostate cancer or promoting the growth of an existing tumor. There is also concern about a potential increased risk for stroke based on studies that suggest that testosterone supplementation might trigger excessive red blood cell production, which thickens the blood.

The bottom line: Although some older men who use testosterone therapy may report feeling more energetic or younger, there is no scientific proof that testosterone therapy in healthy men will help them age better. Until more scientifically rigorous studies are conducted, it is not known if the

possible benefits of testosterone therapy outweigh any of its potential risks. NIA continues to conduct research to gather more evidence about the effects of testosterone supplements in aging men.

Hormones in Women

Estrogen and progesterone are two hormones that play an important part in women's menstrual cycle and pregnancy. Estrogen also helps maintain bone strength and might prevent heart disease and protect memory before menopause. Both estrogen and progesterone are produced naturally by the ovaries. However, after menopause, the ovaries stop making these hormones. For more than 60 years, millions of women have used estrogen supplements to control for menopausal symptoms, especially hot flashes and vaginal dryness. Women also take it to prevent or treat osteoporosis—loss of bone strength—that often happens after menopause. The use of estrogen (by women whose uterus has been removed) or estrogen with progesterone or a progestin, a synthetic form of progesterone (by women with a uterus), to treat the symptoms of menopause is called menopausal hormone therapy (MHT), formerly known as hormone replacement therapy (HRT).

There is a rich research base investigating estrogen. Many large, reliable long-term studies of estrogen and its effects on the body have been conducted. Yet, much remains unknown. In fact, the history of estrogen research demonstrates why it is important to examine both the benefits and risks of a hormone before it becomes widely used. Here's what scientists know:

■ **Endometrial problems**—While estrogen helps some women with symptom management during and after menopause, it can raise the risk of certain problems. Estrogen may cause a thickening of the lining of the uterus (endometrium) and a slightly increased risk of endometrial cancer. To lessen these risks, doctors now prescribe progestin to women with a uterus to protect the lining.

■ **Heart disease**—The role of estrogen in heart disease is complex. Early studies suggested MHT could lower postmenopausal women's risk for heart disease—the number one killer of women in the United States. But results from the Women's Health Initiative (WHI), a study of MHT by the NIH, suggest that using estrogen with or without a progestin after menopause does not protect women from heart disease and may even increase their risk.

In 2002, WHI scientists reported that using estrogen plus progestin actually elevates some postmenopausal women's chance of developing heart disease, stroke, blood clots, and breast cancer, but women also experienced fewer hip fractures and cases of colorectal cancer. In 2004, WHI scientists published another report, this time on postmenopausal women who used estrogen alone, which had some similar findings: women had an increased risk of stroke and blood clots, but fewer hip fractures. Then, in 2007, a closer analysis of the WHI results indicated that younger women, ages 50 to 59 at the start of the trial, who used estrogen alone had significantly less plaque in their coronary arteries than women not using estrogen. Increased plaque in coronary arteries is a risk factor for heart attacks. Scientists also determined that the risk of heart attack might not be increased in women who started MHT less than 10 years after menopause, but that there is increasing risk in women who begin MHT more than 10 years after menopause.

■ **Dementia**—Some studies suggest that estrogen may protect against Alzheimer's disease. However, this has not yet been proven. In 2003, researchers in a sub-study of the WHI, called the WHI Memory Study (WHIMS), reported that women age 65 and older who take a combination of estrogen and progestin were at twice the risk for developing dementia than women who do not take any hormones. In 2004, these WHIMS scientists reported that using estrogen alone could also increase the risk of developing dementia in women age 65 and older compared to women not taking any hormones.

For all the research findings, there are still many unknowns about the risks of MHT. For instance, scientists have not yet determined if risks differ between women who have menopausal symptoms and those who don't. Also, because women in their early 50's were only a small part of the WHI, scientists do not yet know if certain risks are applicable to younger women who use estrogen to control symptoms during the menopausal transition.

You may also have heard about a relatively new approach to hormone therapy for women—bioidentical hormones. These are man-made hormones (from plants such as soy or yams) that have the same chemical structure as hormones produced by the human body. The term “bio-identical hormones” is now also being applied to the practice of compounding or combining hormones such as estrogen and progesterone, theoretically based on a woman's individual hormonal needs. Large clinical trials of these compound hormones have not been done, and many bioidentical hormones that are available without a prescription are not regulated or approved for safety and efficacy by the FDA. FDA-regulated bioidentical hormones, such as estradiol and progesterone, are available by prescription for women considering MHT.

For middle age and older women, the decision to take hormones is far more complex and difficult than ever before. Questions about menopausal hormone therapy remain: Would using a different estrogen and/or progestin or different dose change the risks? Would the results be different if the hormones were given as a patch or cream, rather than a pill? Would taking the progestin less often be as effective and safe? Does starting menopausal hormone therapy around the time of menopause compared to years later change the risks? Can we predict which women will benefit or be harmed by using menopausal hormone therapy? As these and other questions are addressed by research, women should re-review the pros and cons of menopausal hormone therapy with their doctors, assess the personal risks and

benefits, and then make an informed decision about whether or not this therapy is for them.

NIA has additional free information on menopausal hormone therapy. Call 1-800-222-2225 (toll-free) or visit the NIA website at www.nia.nih.gov/HealthInformation.

Calorie Restriction, Intermittent Fasting, and Resveratrol

Scientists are discovering that what you eat, how frequently, and how much may have an effect on quality and years of life. Of particular interest has been calorie restriction, a diet comprised by generally 25 to 40 percent fewer calories than normal but including all needed nutrients. Research in animals has shown calorie restriction to have an impressive effect on disease and markers of aging. It has been found to extend the life of protozoa (very small, one-celled organisms), yeast, fruit flies, mice, and rats. Recent calorie restriction studies with humans and other primates, such as monkeys, are ongoing. However, early findings of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) study, show that adults who cut their calorie consumption by 25 percent lowered their fasting insulin levels and core body temperature, both of which correlate with increased longevity in animal models. In other studies with non-human primates, researchers have found that calorie restriction reduced incidence of heart disease and cancer.

Scientists do not know if long-term calorie restriction is safe for humans. It is unclear whether or not a calorie-restricted diet will ever be recommended for people. However, studying calorie restriction may offer new insights into the aging process and biological mechanisms that could influence healthy aging. This research may also provide clues about how to prevent or delay diseases that become more prevalent with age.

Other ongoing studies focus on identifying chemicals that mimic calorie restriction's benefits. Resveratrol, found naturally in very small amounts in grapes and nuts, is one of the compounds being studied. Scientists compared two groups of overweight mice on a high fat diet. One group was given a high dose of resveratrol. The overweight mice receiving resveratrol were healthier and lived longer than the other overweight group. In a follow-up study, scientists found that, when started at middle age, resveratrol slowed age-related health problems in mice on a standard diet but did not increase longevity. More research is needed before scientists know if resveratrol is safe for people or even if it has the same effects as it has in mice.

Scientists are also studying the effect of intermittent fasting or reduced meal frequency. In animal models, like mice, reduced meal frequency appears to have a protective effect on the brain and may also help with heart function and regulating sugar in the blood. However, the influence of intermittent fasting on human health and longevity is currently unclear.

While research into calorie restriction and intermittent fasting continues, there is already plenty of research supporting the value of a healthy, balanced diet and physical activity to help delay or prevent age-related health problems.

Many Questions, Seeking Answers

NIA supports research that seeks to tell us more about aging and the risks and benefits of potential interventions such as hormone therapies, supplements, and calorie restriction. One goal is to determine whether DHEA, melatonin, and other hormonal supplements improve the health of older people, have no effect, or are harmful. Researchers are also trying to determine if calorie restriction is safe for humans and if there are any compounds that could replicate

in humans the benefits of calorie restriction seen in animals.

These studies will take some time. Research on supplements and calorie restriction is ongoing and a great deal of basic animal and clinical research is yet to be done. Don't be surprised if these studies open the door to more questions as well as answers. Research is an incremental process; results can move knowledge forward, but can also take you back to basics.

Until more is known about DHEA, melatonin, hGH, and resveratrol, consumers should view these types of supplements with a good deal of caution and doubt. Despite what advertisements and media, like television and magazines, may claim, there are no specific therapies proven to "prevent" aging. Some harmful side effects already have been discovered and additional research may uncover others.

People with genuine deficiencies of hormones should consult with their doctors about supplements. Talk to your doctor if you are interested in any form of hormone supplementation or "anti-aging" approaches beyond healthy diet and physical activity. Meanwhile, people who choose to take any hormone supplement without a doctor's supervision should be aware that these supplements appear to have few clear-cut benefits for healthy individuals and no proven influence on the aging process.



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