



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

People are living longer. In 1970, the average life expectancy at birth in the United States was 70.8 years; in 2008, it was 78.0 years; and by 2020, the U.S. Census Bureau projects life expectancy will reach 79.5 years.

Views on aging are also changing. Disease and disability were once considered an inevitable part of growing older, but that is no longer true. While aging does put us at greater risk for health issues, many older adults can be healthy and active well into their advancing years.

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 age-related disease and decline. We have already gained important insights, and what we learn from ongoing and future studies may not only help to increase longevity, but may also promote what is known as "active life expectancy"—the time in late life free of disability. We already know, for example, that healthy eating and exercise and physical activity help promote healthy aging. Are there other interventions that can help? NIA-supported and other studies are taking a look at the possible benefits and risks of a number of approaches, including antioxidants, calorie restriction, and hormone supplements. This tip sheet provides an overview of what we know about these interventions and the research needed to learn more. Until we have a better understanding, it is a good idea to be skeptical of claims that any supplements can solve your age-related problems.

Antioxidants

Antioxidants protect the body from the harmful effects of by-products known as free radicals, made normally when the body changes oxygen and food into energy. The discovery of antioxidants raised hopes that people could slow aging simply by adding them to the diet. So far, studies of antioxidant-laden foods and supplements in humans have yielded little support for this conclusion. Further research, including large-scale epidemiological studies, might clarify whether dietary antioxidants can help people live longer, healthier lives. For now, although the effectiveness of dietary antioxidant supplementation remains controversial, there is positive evidence for the health benefits of fruits and vegetables.

Calorie Restriction, Intermittent Fasting, Resveratrol, and Rapamycin

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 that is lower by a specific percent of calories than the normal diet but includes all needed nutrients. Research in some animals has shown calorie restriction of up to 40 percent fewer calories than normal to have an impressive positive effect on disease, markers of aging, and, perhaps, life span.

Even though calorie restriction appears to work in a variety of species, its effects on longevity are far from universal. It has been found to extend the life of protozoa (very small, one-celled organisms),

yeast, fruit flies, some strains of mice, and rats, as well as other species. However, several animal models, including wild mice, show no lifespan extension by calorie restriction. In some strains of mice, calorie restriction even appears to shorten lifespan. Studies in nonhuman primates have also had conflicting results.

Calorie restriction studies with humans and other primates, such as monkeys, are ongoing. Some studies in nonhuman primates have shown that calorie restriction reduces the incidence of certain diseases such as cancer. Other studies in primates have not yet reached final conclusions.

Findings of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) pilot study in humans showed that overweight adults who cut their calorie consumption by 20 to 30 percent lowered their fasting insulin levels and core body temperature. Both of these changes correlate with increased longevity in animal models. The lower calorie intake also reduced their risk for major causes of mortality such as heart disease and diabetes. CALERIE is currently evaluating a 2-year, 25 percent reduction in caloric intake for feasibility, safety, and effects on factors influencing longevity and health.

Scientists do not yet know if long-term calorie restriction is safe, beneficial, or practical for humans. However, the study of calorie restriction offers 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 and inform the development of treatments for such diseases.

Some studies focus on identifying chemicals that somehow mimic calorie restriction's benefits. Resveratrol, a compound found naturally in foods like grapes and nuts, is of interest. In one study, scientists compared two groups of overweight mice on a high-fat diet. One group was given a high dose of resveratrol together with the high-fat diet. The overweight mice receiving resveratrol

were healthier and lived longer than the overweight mice that did not get resveratrol. In a follow-up study, researchers found that, when started at middle age, resveratrol slowed age-related deterioration and functional decline of mice on a standard diet, but did not increase longevity. A recent study in humans reported that resveratrol may have some similar health benefits to those in animals; however, it is still too early to make any definitive conclusions about how resveratrol affects human health and aging. More research is needed before scientists know if there is a proper and safe dose of resveratrol or if it has any clinical applicability in people.

Rapamycin is also being investigated. This compound is used to help suppress the immune system in transplant patients so that the body does not reject the new organ. Rapamycin has been found to extend median and maximum lifespan of mice, even when fed to the animals beginning at early-old age. This finding suggests that an intervention started later in life may still increase longevity. Researchers are now looking for rapamycin's effects on health span of animal models. Since rapamycin treatment in people is associated with serious toxicities, its potential for human long-term use is uncertain. Researchers do not know if rapamycin has any effect on human aging or if any potential benefit would outweigh risks. But, this discovery in mice has led to an exciting new research direction.

Scientists are also looking at the effect of intermittent fasting or reduced meal frequency. In animals, like mice, reduced meal frequency appears to have a protective effect on the brain and may also help with heart function and regulation of sugar content in the blood. However, here, too, the influence of intermittent fasting on human health and longevity is currently unclear.

While research into these types of approaches continues, it is important to remember 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.

Hormones

Hormones are chemical messengers that set in motion different processes to keep our bodies working properly. For example, they are involved in regulating 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 tissues and organs involved in biological processes. 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 or time of day.

We cannot survive without hormones. As children, hormones help us grow up. In our teenage years, they drive puberty. As we get older, some hormone levels naturally decline. But what does that mean? Scientists do not know exactly.

In order to learn more, NIA is investigating how the administration of hormones to older people affects frailty and function. Many of these studies focus on hormones that naturally decline with age, including:

- Human growth hormone
- Testosterone
- Estrogen and progesterone (as part of menopausal hormone therapy)
- Dehydroepiandrosterone (DHEA)

How Hormones Work

A hormone acts upon a cell much like a key unlocking a door. After being released by a gland, a hormone molecule travels through the blood until it finds a cell with the right fit. The hormone latches onto a cell via the cell's receptor. When this happens 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.

A 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 Therapy

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. These come in many forms such as pills, shots, topicals (gels, creams, and sprays applied to the skin), and medicated skin patches.

You may have read magazine articles or seen television programs suggesting that treatment with hormones can make people feel young again or can slow or prevent aging. That's because finding a "fountain of youth" is a captivating story. The truth is that, to date, no research has shown that hormone therapies add years to life or prevent age-related frailty. And, while some drugs 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 hormones prescribed by a doctor and under a doctor's supervision.

In some cases, the U.S. Food and Drug Administration (FDA) may have approved a hormone (or hormone therapy) 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, demonstrates a drug's usefulness for another condition. However, consumers should be aware that off-label use of any drug may not have been tested and verified to the same degree as the original use of the drug.

Some Dangers of Hormone Therapy and “Anti-Aging” Supplements

Higher concentrations of hormones in your body are not necessarily better. And, a decrease in hormone concentration with age is not necessarily a bad thing. 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. Replacement or supplemental hormones 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 the 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. At this point, scientists do not know all the consequences.

Some hormone-like products are sold over the counter without a prescription. Using them can be dangerous. Products that are marketed as dietary supplements are not approved or regulated by the FDA. That is, companies making dietary supplements do not need to provide any proof that their products are safe and effective before selling them. There is no guarantee that the “recommended” dosage is safe, that the same amount of active ingredients is in every bottle, or that the substance is what the company claims. What you bought 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 largely unknown.

Human Growth Hormone

Growth hormone 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 human growth hormone (hGH) injections in certain circumstances. For instance, hGH injections can help children who do not produce enough growth hormone. 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, growth hormone 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 naturally produced growth hormone 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. They found that reduced growth hormone secretion actually promotes longevity in the tested species.

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—and the evidence suggests that side effects strongly overcome any possible benefits—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, but there is still much to learn. For instance, study findings indicate that injections of 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 buildup leading to high blood pressure or heart failure, remain unanswered, too. A 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. Additional research is necessary to assess the potential risks and benefits of hGH.

Testosterone

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. Testosterone isn't exclusively a male hormone—women produce small amounts as well.

As men age, they often produce somewhat less testosterone, especially 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 increasingly reported about “male menopause,” a condition supposedly caused by diminishing testosterone levels in aging men. There is very little scientific

evidence that this condition, also known as andropause or viropause, exists. 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, but many cases of erectile problems are due to circulatory problems.

For men whose bodies make very little or no testosterone, testosterone replacement may offer benefits. FDA-approved testosterone drugs come in different forms, including patches, injections, and topical gels. Men whose testes (the reproductive glands that make testosterone and sperm) have been damaged or whose pituitary glands have been harmed or destroyed by trauma, infections, or tumors may also be prescribed testosterone. Treatment with testosterone drugs can 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 treatment.

More research is needed to learn what effects testosterone drug therapy 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 are 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 testosterone drugs might have on the aging body. Most epidemiological 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 testosterone drugs increases men's risk for developing prostate cancer or promoting the growth of an existing tumor. There is also uncertainty about effects of testosterone treatment on the cardiovascular system in older men, especially men with mobility limitations and other diseases. Future studies will address this issue to ensure that older men receiving testosterone treatment are not exposed to unnecessary risks.

The bottom line: there is no scientific proof that testosterone treatment 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 treatment 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 may reduce the risk of heart disease and memory problems before menopause. Both estrogen and progesterone are produced naturally by the ovaries. However, after menopause, the ovaries make much less of these hormones. For more than 60 years, millions of women have used estrogen to relieve their menopausal symptoms, especially hot flashes and vaginal dryness. Some women may also be prescribed estrogen to prevent or treat osteoporosis—loss of bone strength—that often happens after menopause. The use of estrogen (by a woman whose uterus has been removed) or estrogen with progesterone or a progestin, a synthetic form of progesterone (by a woman 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 any hormone therapy 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 increase the risk of endometrial cancer. To lessen these risks, doctors now prescribe progesterone or a progestin, in combination with estrogen, 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 NIH Women's Health Initiative (WHI) 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 calcified plaque in their coronary arteries than women not using estrogen. Increased plaque in coronary arteries is a risk factor for heart attacks. Scientists also noted that the risk of heart attack increased in women who started MHT more than 10 years after menopause (especially if these women had menopausal symptoms). There was no evidence of

increased risk of heart attack in women who began MHT within 10 years of going through menopause.

- **Dementia**—Some observational studies have suggested that estrogen may protect against Alzheimer’s disease. However, testing in clinical trials in older, postmenopausal women has challenged that view. In 2003, researchers leading the WHI Memory Study (WHIMS), a substudy of the WHI, reported that women age 65 and older who took one kind of estrogen combined with progestin were at twice the risk for developing dementia compared to women who did not take any hormones. In 2004, WHIMS scientists reported that using the same kind of estrogen alone also increased the risk of developing dementia in women age 65 and older compared to women not taking any hormones. What possibly accounts for the different findings between the observational and clinical studies? One central issue may be timing. The women in the WHIMS trial started treatment a decade or more after menopause. In observational studies that reported estrogen’s positive effects on cognition, the majority of women began treatment soon after menopause. This has led researchers to wonder if it may be advantageous to begin treatment earlier, at a time closer to menopause. Additionally, it appears that progesterone and progestins (progesterone-like compounds) differ in their impact on brain health.

Despite research thus far, there are still many unknowns about the risks and benefits of MHT. For instance, 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 relieve their symptoms during the menopausal transition.

You may also have heard about another approach to hormone therapy for women—“bioidentical hormones.” These are hormones derived from plants, such as soy or yams, that have identical chemical structures to hormones produced by the human body. The term “bioidentical hormones” is now also being applied to the use of compounded hormones. Large clinical trials of these compounded

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 MHT 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 progestin less often be as effective and safe? Does starting MHT around the time of menopause, compared to years later, change the risks? Can we predict which women will benefit or be harmed by using MHT? As these and other questions are addressed by research, women should continue to review the pros and cons of MHT with their doctors. They should assess the benefits as well as personal risks to make an informed decision about whether or not this therapy is right for them. NIA has additional free information on menopausal hormone therapy in the tip sheet *Hormones and Menopause*.

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-20’s 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 estrogen and testosterone is highly individualized. There is no way to predict who will make more or less of these hormones. Having an excess of testosterone or estrogen in your body could be risky.

Scientists do not yet know the effects of long-term (defined as over 1 year) use of DHEA supplements. Early indications are that these supplements, even when taken briefly, may have 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 broader 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.

Many Questions, Seeking Answers

NIA supports research that seeks to learn more about aging and the risks and benefits of potential interventions such as antioxidants, calorie restriction, hormone therapies, and supplements. These studies take time. A great deal of basic

animal and clinical research remains to be done. And, because research is an incremental process, results can move knowledge forward, but it can also take scientists back to basics. Although one goal of NIA research is to determine whether these interventions improve the health of older people, have no effect, or are harmful, don't be surprised if the results of these studies open the door to more questions.

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

People with genuine deficiencies in specific hormones should consult their doctors about appropriate treatments. Talk with your doctor if you are interested in any form of hormone therapy or "anti-aging" approaches beyond a 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.

For more information on health and aging, contact:

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