REVIEW

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Antioxidants and hormones as antiaging therapies: High hopes, disappointing results

ABSTRACT

No single agent has been shown to truly reverse aging or increase longevity in humans. This article reviews the evidence of efficacy (or lack thereof) for two types of agents touted as antiaging therapies: antioxidants (vitamin E, vitamin C, and carotenoids) and hormones (growth hormone, testosterone, dehydroepiandrosterone, and vitamin D).

KEY POINTS

There are not enough data to support the daily use of the antioxidants vitamin A, the vitamin A precursor beta-carotene, vitamin C, or vitamin E as antiaging therapies.

Although these antioxidants may reduce serum cholesterol levels, they had little effect on cerebrovascular and cardiovascular disease in clinical trials and in fact may even increase overall mortality. Data are inconsistent on their effect on cognition.

Although serum levels of many hormones decline with age, additional research is needed to prove that these declining levels are pathologic and that hormone replacement actually affects the aging process.

Vitamin D is indicated in combination with calcium supplementation in osteoporosis treatment; it also has been shown to improve muscle strength and function in older adults.

SCIENTISTS HAVE YET to uncover convincing evidence that any single "antiaging therapy" truly reverses aging or increases longevity in humans, although some interventions have demonstrated these effects in laboratory animals. The antiaging controversy thus leaves it to clinicians to interpret both reputable and questionable data with the hope of improving both quality and quantity of life for patients.

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This article focuses on specific antioxidant and hormonal therapies that are touted as antiaging interventions with respect to their effects on mortality and functional status (in contrast to their use in disease or deficiency states). We also discuss harmful effects of these therapies.

INTEREST IS RISING AS AMERICANS GET OLDER

Over 50% of the American public is aware of antiaging therapies,[1] although only a small percentage of people currently use them.

Interest in this area is growing, however, for several possible reasons. The baby-boomer generation is entering its senior years, and the geriatric population in the United States will increase tremendously in the next few decades. At the same time, the use of alternative therapies is on the rise,[2] progress is being made in understanding aging, and the public has more access to information resources (media and the Internet) than ever before.[3]

TABLE 1

Nutritional supplements with antioxidant properties

Vitamins
- Coenzyme Q10
- Nicotinamide adenine dinucleotide (NADH)
- Vitamin A
- Vitamin B_2
- Vitamin C
- Vitamin E

Minerals
- Copper
- Manganese
- Selenium
- Zinc

Amino acids
- Cysteine
- Glutamine (glutathione precursor)
- Glutathione
- Methionine
- Taurine

Herbs
- Bilberry
- Garlic
- Ginkgo biloba
- Green tea
- Milk thistle
- Sage
- Turmeric

Hormonal
- Alpha-carotene
- Beta-carotene
- Carotenoids
- Melatonin
- Lycopene

Miscellaneous
- Alpha-lipoic acid
- Grape seed extract
- N-Acetylcysteine

In theory, antiaging interventions could modify the biochemical and molecular events causing aging, correct physiological changes responsible for symptoms and signs of aging, or decrease the susceptibility to disease associated with aging.

The American Academy of Anti-Aging Medicine (A4M), an organization that claims a membership of 11,500 physicians and scientists from 65 countries, states on its Web site that "the disabilities associated with normal aging are caused by physiological dysfunction which in many cases are [sic] ameliorable to medical treatment, such that the human life span can be increased, and the quality of one's life improved as one grows chronologically older."[4]

The Palm Springs Life Extension Institute Web site advertises that, "by restoring your hormones to young-adult levels, [the Institute] can help you avoid age-related illnesses, reverse your biological age, extend your life expectancy, and significantly improve the quality of your additional years."[5]

No wonder, then, that the business of antiaging medicine has grown into a multimillion dollar industry that sells products claimed to slow, stop, or reverse human aging.[6]

Thus, primary care physicians may be asked more and more by their aging patients if these therapies will improve their health and prolong their life—an area that receives little attention in the traditional curriculum of medical schools.

ANTIOXIDANTS

Oxidation may play a role in atherosclerosis, cancer, Parkinson disease, and Alzheimer disease

One of the most studied hypotheses about aging is that it is caused by oxidative stress. Oxidation can damage proteins, DNA, and lipids. In humans, oxidation may play a role in atherosclerosis, cancer, Parkinson disease, and Alzheimer disease.[6]

Numerous nutritional supplements have or are claimed to have antioxidant properties (TABLE 1)[7–9]; these substances vary in the exact mechanism and potency of the antioxidant effect. The following section discusses the effects of the most extensively studied antioxidants: vitamin A, its precursor beta-carotene, vitamin C, and vitamin E (TABLE 2).

Cardiovascular and cerebrovascular effects of antioxidants

Three studies found that antioxidants had no effect on cerebrovascular and cardiovascular diseases; one study found that beta-carotene reduced the risk of stroke.

In the Physicians' Health Study, Muntwyler et al[10] analyzed data from a prospective cohort study of 83,639 US male

physicians, of whom 29% were taking vitamin E, vitamin C, or multivitamin supplements on a self-selected basis. The authors concluded that these supplements were not associated with a significant decrease in total cardiovascular diseases or coronary heart disease mortality.

Ascherio et al,[11] in another prospective study in 43,738 men 40 to 75 years old with no cardiovascular disease or diabetes, reported that vitamins E and C and certain carotenoids did not reduce the risk of stroke.

The Heart Outcome Prevention Evaluation (HOPE) trial,[12] a randomized controlled trial in patients 55 years or older who had cardiovascular disease or diabetes, found that taking vitamin E 400 IU daily for an average of 4.5 years had no effect on their cardiovascular outcomes or nephropathy.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study,[13] in contrast, found that dietary intake of beta-carotene was inversely associated with the risk of cerebral infarction (relative risk [RR] 0.47, 95% confidence interval [CI] 0.60–0.91) in a 6.1-year follow-up of 26,593 male smokers 50 to 69 years old.

Effect of antioxidants on lipids

Data are inconsistent on the effect of antioxidants on serum lipid levels.

Rezaian et al,[14] in a randomized, double-blind, placebo-controlled study in 120 subjects age 50 and older with no cardiovascular disease, reported that the antioxidant vitamins C and E alone or in combination decreased the serum cholesterol and low-density lipoprotein cholesterol (LDL-C) levels and raised the serum high-density lipoprotein cholesterol (HDL-C) level.

Brown et al,[15] in a 3-year, randomized, double-blind, placebo-controlled study in 160 patients younger than 70 years with coronary heart disease, low HDL-C, and normal LDL-C, reported that the antioxidants vitamin E, vitamin C, beta-carotene, and selenium attenuated the beneficial effects of the lipid-lowering drugs simvastatin and niacin on lipid levels and coronary stenosis. The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants alone, and 0.7% with antioxidants plus simvastatin and niacin; it regressed by 0.4% with simvastatin and niacin alone.

TABLE 2

Summary of the effects of antioxidants as antiaging interventions

Vitamin E
- No decrease in total cardiovascular mortality[10,22]
- No reduction in risk of stroke[11,12,22]
- Inconsistent data on the effect on lipids[14,15]
- Inconsistent data on the effect on cognition[16–20]
- Insufficient evidence in the treatment of Alzheimer disease[21]
- Inconsistent data on all-cause mortality[22,23]

Vitamin C
- No decrease in total cardiovascular mortality[10]
- No reduction in risk of stroke[11]
- Inconsistent data on lipid profile[14,15]

Carotenoids
- Inconsistent data on risk of stroke[11,13]
- Increase in all-cause mortality[22]
- Increase in cardiovascular mortality[22]

Effects of antioxidants on cognition

Several studies suggested that antioxidants may prevent cognitive decline, while others had inconsistent results.

Zandi et al[16] performed a cross-sectional and prospective study in patients 65 years and older and concluded that the use of vitamin E and C supplements in combination (but not independently) is associated with reduced prevalence and incidence of Alzheimer disease (hazard ratio [HR] 0.36, 95% CI 0.09–0.99). The wide confidence interval and nature of this study design minimize its potential impact for clinicians.

Yaffe et al[17] performed a controlled study in 2,166 elderly people in the Age-Related Eye Disease Study, randomizing them to four regimens: antioxidants (vitamin E, vitamin C, and beta-carotene); zinc and copper; antioxidants plus zinc and copper; or placebo. None of the regimens was beneficial or harmful with respect to cognition ($P > .05$ for all).

The Third National Health and Nutrition Examination Survey[18] assessed memory in 4,809 elderly people and found that the lower the serum level of vitamin E, the greater the degree of memory impairment.

All-cause mortality rates were slightly higher with high-dose vitamin E

TABLE 3

Summary of the effects of hormones as antiaging interventions

Testosterone
- Decrease in fat mass and increase in lean mass[33–35]
- Mixed data on the effect on cognition[39,42–45]

Dehydroepiandrosterone
- Inconsistent data on muscle mass, fat mass, and strength[53–58]
- Insufficient evidence for improvement in cognition[65,66]

Growth hormone
- Increase in lean body mass; decrease in fat mass[71,72]
- Increase in bone mineral density[74–76]
- Increase in mortality[73]

Vitamin D
- May improve muscle function[75,79,80]

Serum vitamin A, vitamin C, beta-carotene, and selenium levels were not associated with poor memory performance. This finding does not prove a causal relationship between low antioxidant levels and memory loss.

Rinaldi et al[19] found significantly lower antioxidant levels of vitamins A, C, and E and carotenoids in 25 elderly people with mild cognitive impairment and 63 people with Alzheimer disease compared with 53 controls.

Testosterone levels decline by about 100 ng/dL per decade

Gray et al[20] studied 2,082 community-dwelling elderly people from the Duke Established Populations for Epidemiologic Studies of the Elderly. The incidence of cognitive decline was 34% lower in those who used vitamins A, C, and E (plus selenium or zinc) (adjusted RR 0.66; 95% CI 0.44–1.00). The nonrandomized design and self-reported dosing and duration of antioxidant use significantly limit the usefulness of these data.

A Cochrane review of randomized double-blind trials of the use of vitamin E at any dose vs placebo in the treatment of Alzheimer disease found only one study of sufficient quality for evaluation. Vitamin E users were less likely to die or experience a decline in function; however, they were more likely to fall than nonusers.[21]

Effect of antioxidants on mortality

Vivekananthan et al[22] performed a meta-analysis to evaluate the effect of vitamin E on cardiovascular mortality. Seven randomized trials of vitamin E (50 to 800 IU) and eight of beta-carotene treatment (15 to 50 mg) were identified. Each study included 1,000 or more patients and had a follow-up of 1.4 to 12.0 years. Vitamin E did not reduce mortality compared with control treatment, did not significantly decrease risk of cardiovascular death, and did not reduce risk of cerebrovascular accidents. Beta-carotene led to a small but significant increase in all-cause mortality and in cardiovascular death.

Miller et al[23] performed a subsequent meta-analysis that included 19 clinical trials (135,967 participants) using vitamin E in doses of 16.5 to 2,000 IU/day. Of these, 11 trials used vitamin E in high doses (≥ 400 IU/day), and in these the rate of all-cause mortality was slightly but significantly higher with vitamin E than with placebo. The 8 trials of low-dose vitamin E did not detect an increased risk of mortality. The risk mechanism is thought to be an anticoagulant effect of high vitamin E levels or disruption of the balance of other protective fat-soluble antioxidants.

HORMONAL THERAPY

Because many hormonal levels decrease with aging, treatment with hormones has often been called the "fountain of youth." Much research is needed to prove the efficacy of hormonal therapy, as data have not demonstrated the expected positive impact of hormones on aging per se (TABLE 3).[24] We will focus on hormone use as supplementation, not as replacement for documented hormonal deficiency in the setting of disease management.

Testosterone

Testosterone therapy has become accepted in the treatment of hypogonadal men, but it is still nonconventional in older men who are not clinically hypogonadal.

Levels of total testosterone and, to a greater extent, free testosterone and bioavailable testosterone (free and albumin-bound testosterone) decline with age but do not necessarily cause a hypogonadal disease state.[25–30] In a longitudinal study, testosterone levels declined by approximately 100 ng/dL per decade.[31]

It is important for clinicians to know that when measuring testosterone, bioavailable or free testosterone should be measured, not just total testosterone.[32]

Effects of testosterone treatment. Although most studies of testosterone therapy have been small and short-term and lacked a control group, three randomized controlled studies, lasting 1 to 3 years, in men with low serum testosterone have shown a significant decrease in fat mass, which was accompanied by statistically significant increases in lean mass and bone mineral density in the testosterone-treated groups.[33–35] None of these studies showed an improvement in measures of muscle strength, overall physical performance, energy, or sexual function, although several smaller studies suggested that testosterone replacement may increase muscle strength in truly hypogonadal men.[36–39]

Although bioavailable testosterone is inversely correlated with cognitive decline,[29,40] and higher levels of testosterone are associated with better mental control and long-term verbal memory,[41] studies of testosterone therapy to enhance cognition have shown mixed results. At least one study demonstrated an improvement in visuospatial memory,[42] and another demonstrated an improvement in verbal fluency,[43] but three other studies found no improvement in cognition with testosterone therapy.[39,44,45]

Potential side effects of testosterone treatment include increases in hematocrit[38,45] and in cholesterol.

Although many believe that testosterone replacement may increase the risk for prostate hyperplasia or cancer, the data are mixed in this regard. A meta-analysis of 19 randomized controlled studies[47] found that the combined rate of all prostate events was significantly greater in men treated with testosterone than in men treated with placebo (OR 1.78, 95% CI 1.07–2.95). The rates of prostate cancer, prostate-specific antigen (PSA) elevations (> 4 ng/mL), and prostate biopsies individually were not significantly higher in treated men than in controls. Other studies vary regarding PSA: some detected no increase in PSA values during short courses of testosterone treatment,[39,45] while others suggested that testosterone may increase serum PSA levels.[48–50] It is still considered prudent to monitor PSA values when treating older men with testosterone.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a metabolic intermediate in the pathway for the synthesis of testosterone, estrone, and estradiol. In men and women, levels of both DHEA and DHEA sulfate (DHEAS, the main circulating form of the hormone) decrease at a rate of about 2% per year. At age 80, levels are only about 20% of those at age 20.[51]

Effects of DHEA supplementation. Although low levels of DHEA have recently been correlated with lower muscle strength and muscle mass, we have little evidence to suggest that DHEA replacement or supplementation prolongs life or prevents disease.[52] It is also unclear whether declining DHEA levels are pathologic, a normal aging phenomenon, or a surrogate marker for other hormonal processes that result in diseases of aging.

Three recent studies reported an increase in muscle mass and a decrease in fat mass with DHEA supplementation of 50 mg/day,[53–55] but this effect was not evident in subsequent studies.[56,57] The two largest placebo-controlled studies evaluating the effects of DHEA on muscular strength in elderly men and women failed to show a benefit from 50 mg/day over 12 months compared with placebo.[35,58]

A meta-analysis found a higher rate of 'prostate events' with testosterone treatment

The data concerning cognitive function are even less convincing. Cognitive dysfunction has been associated with low, normal, and high DHEAS levels.[59–63] One review discussed improvement of learning and memory dysfunction after DHEA supplementation in people with low DHEAS levels,[64] but another study failed to detect any significant cognitive effects after DHEA administration.[65] A recent Cochrane review found no supportive evidence for an improvement in memory or other cognitive functions with DHEA use in normal older people.[66]

Side effects of DHEA. Given the hormonal pathway involved, potential side effects of DHEA have been postulated to include acne, hyperlipidemia, facial hair growth, headache, and increased testosterone and PSA levels and prostate cancer risk. These side effects have been difficult to sub-

stantiate, owing to the lack of large study populations. Serum lipids, testosterone, and PSA values were not substantially increased in several recent investigations.[52,58,67]

The clinician should be aware that DHEA is available at health food stores and through many Web sites on the Internet.

Growth hormone

The most cited antiaging hormone in the lay Internet literature is growth hormone (GH). This hormone has appeal as an antiaging agent because one theory to account for the decline of lean body and bone mass with age is a decline in GH. In fact, GH declines approximately 14% per decade, with an associated decline in insulin-like growth factor 1.[68–70]

Studies of GH supplementation from the 1990s looked promising, with increases seen in lean body mass and decreases seen in adipose tissue mass compared with placebo.[71]

Unfortunately, subsequent studies failed to demonstrate that increasing lean body mass translates to improved strength or aerobic capacity in either men or women. Furthermore, significant side effects of carpal tunnel syndrome, lower-extremity edema, diffuse arthralgia, and diabetes developed in more than one third of GH-treated individuals.[71,72] Most alarmingly, a randomized controlled trial in more than 500 critically ill patients found that the mortality rate was almost twice as high in those receiving GH.[73]

GH levels decline by about 14% per decade, but the risks of GH therapy outweigh the benefits in non-GH-deficient people

Many questions remain unanswered regarding GH as an antiaging therapy. Would a lower dose have positive outcomes without the side effects? Would combining GH treatment with sex steroids (estrogen for women, testosterone for men) improve outcomes with respect to muscle mass or bone density? Sarcopenia of aging (the loss of muscle mass and strength in older adults) seems a prime target for the use of GH or other anabolic agents. However, as mentioned above, GH increases muscle mass without a secondary increase in muscle strength or overall functional status and with significant adverse drug events. There is mounting evidence that GH may have a role in the treatment of osteoporosis for both men and women with or without GH deficiency; however, side effects may ultimately again be limiting.[74–76]

At this point, the use of GH outside of treatment for documented GH deficiency or acquired immunodeficiency syndrome wasting is neither approved by the US Food and Drug Administration nor legal.[76]

Vitamin D

We discuss vitamin D here as an antiaging therapy in the context of muscle strength and function. Vitamin D is essential for the maintenance of calcium homeostasis and is indicated in combination with calcium to prevent and treat osteoporosis. Data suggest that vitamin D may also directly improve functional status in people without osteoporosis by improving muscle strength.

Isaia et al[78] studied 700 women 60 to 80 years old and found that low vitamin D was associated with worsening of performance of daily living activities and with decreased mobility.

Verhaar et al[79] found that 6 months of alphacalcidol (vitamin D) therapy led to significant improvements in isometric knee extensor strength (left leg: 14.6% ± 5.7%, P = .03; right leg: 11.5% ± 5.0%, P = .02). In a subgroup that was deficient in vitamin D at baseline, 6 months of alphacalcidol treatment led to a significant increase in the 2-minute walking distance (from 137.6 ± 12.6 to 151.3 ± 11.2 meters, P = .03).

Visser et al[80] reported that people 65 years old and older with low baseline 25-hydroxyvitamin D levels (< 25 nmol/L) were 2.57 (95% CI 1.40–4.70) times more likely to experience sarcopenia compared with those with high levels (> 50 nmol/L).

OTHER THERAPIES LACK DATA

The following hormones either lack positive data or have not been studied with regard to mortality outcomes and functional (physical and mental) outcomes: melatonin, pregnenolone,[81] and human chorionic gonadotropin.[82]

TAKE-HOME POINTS

Interest in antiaging therapies is growing, but whether the term *antiaging* is accurate is controversial, given that no single therapy has provided a longevity benefit in humans.

According to large prospective studies, antioxidants have little effect on cerebrovascular and cardiovascular diseases and in fact may even increase overall mortality. These agents may reduce serum cholesterol and LDL-C levels and raise serum HDL-C; however, data are inconsistent on their effect on cognition. Based on studies of the antioxidants vitamin A, its precursor beta-carotene, vitamin C, and vitamin E, there are not enough data to support the daily use of antioxidants.

Despite evidence that levels of many hormones decline with age, additional research is needed to prove that these declining levels are pathologic and that hormone replacement actually affects the aging process. Testosterone replacement decreases fat mass and increases lean mass in older men with mildly low levels of testosterone and might increase muscle strength in truly hypogonadal testosterone-deficient men. Routine replacement of DHEA in older adults provides no meaningful benefit, despite measurable declines in the serum level of this hormone with aging. Although initial studies of GH looked promising, according to the available research, the risk of therapy in people who are not GH-deficient outweighs the benefit. Vitamin D, beyond osteoporosis treatment, improves muscle strength and function in older adults.

In the future, research may be better able to explain the aging process, to define antiaging medicine, and to develop novel antiaging interventions. Until then, clinicians should be aware that the two categories of therapies touted as antiaging interventions discussed here, antioxidants and hormonal therapies, have minimal to no effect on improving longevity or functional abilities.

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