[Primary Care]

Pharmacologic Approaches to the Aging Athlete

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As America's baby boomer population matures, there is an increasing interest in supplements that can delay or oppose the aging process. This antiaging movement has exploded over the past decade. While most supplements are not supported by scientific literature or government controls, a number of products have been the subject of significant scientific inquiry. Hormone replacement therapy, including testosterone and growth hormone, has mixed results, and antioxidative strategies are supported by basic science but lack clinical evidence-based outcomes. While the process of aging has become better understood leading to more rational approaches to combat its effects on health, the clinician is reminded to carefully discern between the science and marketing that is available in this area.

Keywords: baby boomer; performance-enhancing drugs; ergogenic aids; antiaging

Americans born between 1946 and 1964 compose the largest segment of our society. These 76 million so-called baby boomers have begun to reach retirement age, and the youngest among them will turn 50 years old next year. A generation known for protest has begun to age and, true to form, is not taking it lightly. Boomers spent more than $72 billion on products and services designed to slow the aging process in 2009 alone,[76] and this figure is projected to grow to $114 billion by 2015.[12] There is considerable controversy, however, as to the safety and efficacy of these products. Many are not controlled by the Food and Drug Administration; therefore, the industry suffers from a lack of scientific data and quality control in support of the claims that these products make. There is, however, a growing body of evidence available for review of antiaging products and an understanding that science can assist clinicians in separating science from marketing hype.

TESTOSTERONE AND ANABOLIC STEROIDS

While the performance-enhancing effects of testosterone have been known in athletic populations since the 1950s, there has recently been a considerable amount of work investigating its role in aging populations. The justification behind this work is logical: Many of the more apparent changes of aging, such as loss of muscle and bone mass, libido, and energy,[36,53,62,74] are often the inverse of what is reported in testosterone users. Furthermore, it is well understood that testosterone levels decrease with normal aging.[21,24,70,72] Thus, it follows that replacing testosterone in an older population may lead to reversal of some of these negative effects.

One of the earliest reports of testosterone supplementation came from the French neurologist Brown-Sequard, who injected testicular extracts into himself to reverse the aging process. He reported in 1889 that these treatments restored his "old powers,"[7] and while subsequent experiments on his extract showed it to be nearly devoid of androgenic potential, his reported findings set off a fad of injections of similar extracts from human, monkey, and goat sources.[60] Testosterone itself was first synthesized in 1935, and further studies documented the ability to successfully administer synthetic testosterone in 1944.[28] In the 1950s and 1960s, testosterone derivatives were extensively used in athletic competitions such as the Olympic games,[90] and despite their banning by all major sports governing bodies, as well as an aggressive international antidoping campaign, their use continues to increase. Since 1993, testosterone prescriptions have increased at an annual rate of 25% to 30%, and overall there has been a 500% increase in prescription use over the past decade.[81]

It is well understood that testosterone levels decline with age. Around 20% of 60-year-olds and 50% of 80-year-olds exhibit total serum testosterone levels below the normal range for young men.[27] Such low levels are commonly associated with erectile dysfunction, loss of libido, muscle weakness, lower bone mass, and frailty.[37] But defining who is truly hypogonadal remains somewhat controversial. The most common method is the measurement of total testosterone, which is reported by

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Table 1. Published effects of testosterone replacement therapy[25,37,84]

Outcome of Interest[a]	Effect	Comment
Total body fat ↑	↓ 1.6 kg (6.2%)	
Lean body mass ↓	↑ 1.6 kg (2.7%)	
Muscle strength ↓	↑ 6%	Seen in dominant muscle groups only
Bone density ↓	↑ 4%	Lumbar spine only
Bone markers ↑	↓ Resorption markers 18%	No effect on bone formation
LDL cholesterol ↑	No effect	
HDL cholesterol ↓	↓ 4%-6%	Predominantly in more hypogonadal subgroups
PSA ↑	↑ 0.6-1 ng/dL	Considered clinically insignificant by all authors
Hematocrit ↓	↑ 2%-5%	
Time to exercise-induced ST segment depression[b] ↓	↑ 22%-24%	

LDL, low-density lipoprotein; HDL, high-density lipoprotein; PSA, prostatic specific antigen.
[a]Arrow shows effect of normal aging.
[b]Measure of cardiac protection.

some authors as low when serum concentrations are less than 200 ng/dL regardless of age.[88] Total testosterone, however, includes a significant portion that is bound to sex hormone–binding globulin, which is biologically inactive, leading some authors to suggest measuring bioavailable, or "free," testosterone as a more accurate reflection of the hormone's active concentration.[3] Furthermore, because of variability in assays, diurnal and situational variation, and a range of normal values, it is difficult to make a diagnosis of hypogonadism on the basis of a laboratory value alone. Thus, most authors suggest combining a low testosterone level with clinical symptoms such as loss of libido, erectile dysfunction, and loss of muscle mass or sarcopenia for an accurate diagnosis.

Testosterone replacement therapy can be delivered in a variety of vehicles, including intramuscular,[79] transdermal,[88] oral,[40] and sublingual routes, each with advantages and drawbacks, and newer vehicles continue to be developed in an effort to provide a stable circulating testosterone level while minimizing adverse side effects.

There is extensive research available on the effects of testosterone in the aging man and several major reviews of these studies[25,37,84] (Table 1). These data suggest that testosterone replacement designed to restore levels similar to the normal young man results in increased lean body mass, muscle strength, bone density, and decreased body fat, without much in the way of side effects. One underappreciated aspect to testosterone replacement in older men is its psychological effects. Some studies show that supraphysiologic supplementation results in improvement in spatial cognition, spatial and verbal memory, and working memory.[10,38,39] It should be noted, however, that very few of these studies went beyond 3 months; therefore, longer term studies are needed to determine the effects of testosterone on cognitive function. Furthermore, the dosing used in these studies was designed to restore testosterone levels to physiologic levels, and it is unclear whether supraphysiologic supplementation would have increased results.

Side effects are generally mild in the doses applied in study populations. Dermatologic reactions,[42] erythrocytosis,[81] and lipoprotein profile shifts[26,81] are generally of minimal clinical consequence. Benign prostatic hypertrophy or prostate cancer is a real area of concern, though in doses reported, testosterone therapy has minimal effects on prostate health.[3] Testosterone supplementation can lead to modest increases in prostate-specific antigen, and there are guidelines for its safe administration.[81] Testosterone therapy is contraindicated in anyone with a history of prostate cancer.[4]

Since many tissues throughout the body are targets for testosterone, it follows that supplementation may have unwanted side effects on some of these systems. The ideal androgen would be selective in which receptors it targeted. To this end, selective androgen receptor modulators (SARMs) are being developed that help testosterone to more selectively target desirable effects.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Estrogens are a family of related molecules that stimulate the development and maintenance of female characteristics and

sexual reproduction. Most estrogenic responses are mediated by estrogen receptors. Selective estrogen receptor modulators (SERMs) are ligands of these estrogen receptors that, in some tissues, act like estrogens but block estrogen action in others.[18]

One of the oldest and most widely studied SERMs is clomiphene. Structurally similar to estrogen, clomiphene citrate (CC) and its effects in ovulation are well documented. Its effectiveness in ovulation induction can be attributed to actions at the hypothalamic level. Depletion of hypothalamic estrogen receptors prevents correct interpretation of circulating estrogen levels. Reduced levels of estrogen feedback trigger normal compensatory mechanisms that alter gonadotropin-releasing hormone secretion to stimulate increased pituitary gonadotropin release that drives ovarian follicular activity.[45]

Until recently, clomiphene was not touted for use in male hypogonadism or testosterone deficiency. Clomiphene, as an alternative therapy, has been investigated because of the adverse effects of exogenous testosterone therapy. With the objective of raising endogenous testosterone levels and improving the testosterone:estrogen ratio, without reported side effects, CC is proving itself an acceptable alternative.[44,77,82] In a 2012 prospective study of 125 men with low sexual desire and testosterone levels below 400 ng/dL, participants were selected to receive 25 mg of CC daily for 3 months. Mean age in the cohort was 62 years. The results demonstrated that CC was effective in stimulating the endogenous production of testosterone with a significant increase in serum testosterone levels and posttreatment quality-of-life scores.[15]

The benefits of SERMs, particularly CC, in raising serum testosterone are well reviewed.[15,77,82] However, there are little data demonstrating CC therapy resulting in other ergogenic advantages to include an increase in lean muscle mass and improvements in lipoprotein profile, muscle strength, and bone density.

SELECTIVE ANDROGEN RECEPTOR MODULATORS

The first SARMs were reported in 1998.[16,19] The advent of SARMs arose from the concept of SERMs. Androgen receptors play a key role in the functions of sexual organs, skeletal muscle, and bone. SARMs bind to the androgen receptor and subsequently demonstrate myoanabolic activity.[61] To this end, SARMs are being developed that help testosterone to more selectively target desirable effects. Side effects are generally mild in the doses applied in study populations. In a recent pharmaceutical study, a SARM demonstrated significant improvement in the ability of healthy elderly men to climb stairs and obtain significant increases in lean body mass and decreases in fat mass after 86 days.[16,19] Dermatologic reactions,[42] erythrocytosis,[81] and lipoprotein profile shifts[26,81] are generally of minimal clinical consequence. Benign prostatic hypertrophy or prostate cancer is a real area of concern, though in doses reported, testosterone therapy has minimal effect on prostate health.

It should also be noted that sex hormones play a role in cognitive function. Multiple studies have described a relationship between Alzheimer disease and low circulating levels of sex steroids in the aging population.[30,31,55,59,65,89] Optimizing the benefits of testosterone replacement while minimizing the potential side effects of this therapy will continue to drive further investigation of specific tissue targeting.[1]

HUMAN GROWTH HORMONE

Human growth hormone (hGH) is a peptide secreted by the pituitary gland that stimulates growth and cell production. Deficiencies in growth hormone result in small stature, increased adiposity, and decreased lean body mass, and treatment in children with growth hormone deficiency can be successful.[57] Its potential for use in antiaging lies in the age-related decline in activity of the hypothalamic growth hormone–insulin-like growth factor axis, a phenomenon referred to as "somatopause."[52] Pituitary hGH production reaches a peak around puberty and then declines steadily.[49] After age 40 years, hGH secretion declines approximately 14% per decade of adult life.[83] Numerous studies show that hGH replacement in young adults with severe deficiency leads to improvement in body composition, muscle strength, bone density, physical function, and quality of life.[9,20,41,71] A 1990 study on growth hormone therapy in otherwise healthy elderly men reported that treatment could reverse decades of age-related changes and sparked the beginning of hGH's use as an ergogenic aid.[73] Annual sales of hGH worldwide now exceed $1.5 billion, and one-third of this may be "off-label" illegal use.[51] Despite this popularity, however, the scientific community continues to be reticent of hGH as a treatment for antiaging and is generally opposed to its use.[22] Furthermore, the distribution of hGH for use as an antiaging therapy in the United States is illegal.[68]

Several well-done meta-analyses have evaluated hGH as an ergogenic aid in healthy young and elderly populations (Table 2). Taken as a whole, hGH supplementation results in a modest decrease in fat mass but with no improvements in muscle strength, lipoprotein profiles, bone density, or insulin sensitivity.[52] Furthermore, no study has demonstrated hGH to have a performance-enhancing effect.[34,66]

Side effects with hGH use include a 42% incidence of soft tissue edema, an 18% incidence of carpal tunnel syndrome, a 16% increase in arthralgias, and a 4% incidence of new onset diabetes.[52] Across studies, 27% of patients treated with growth hormone required a dose decrease because of side effects associated with its use. It should be noted that most studies limited dosing to therapeutic ranges; thus, it may be that supraphysiologic dosing might change the reported results, but there is very little evidence with the data available that hGH offers any significant ergogenic advantage.

ANTIOXIDANTS

Oxidation is a chemical process that is naturally occurring in cells. These reactions can produce free radicals, which start chain reactions that can damage cells. Chemicals with

Table 2. Effects of human growth hormone replacement therapy[51,52,73]

Outcome of Interest[a]	Effect	Comment
Weight	↑ 0.06 kg	Not significant
Fat mass ↑	↓ 2.08 kg	
Lean body mass ↓	↑ 2.1 kg	May be nonmuscle
VO_2 max (exercise capacity) ↓	↑ 0.32 mL/min	Not significant
Bone mass ↓	No effect	Not significant
Skin thickness ↓	↑ 0.7 mm	Not significant
LDL ↑	↓ 0.12 mmol/L	Not significant
HDL ↓	↓ 0.01 mmol/L	Not significant
Muscle strength ↓	↓ 0.2 kg	Not significant
Tissue edema	↑ 42%	
Carpal tunnel syndrome	↑ 18%	
Arthralgia ↑	↑ 16%	
New onset diabetes ↑	↑ 4%	

LDL, low-density lipoprotein; HDL, high-density lipoprotein; VO_2 max, volume of oxygen consumed in one minute.
[a]Arrow shows effect of normal aging.

antioxidant properties can reduce these chain reactions and prevent cell damage.[48,50] Many diseases, such as Alzheimer disease, diabetes, and heart disease, are thought to be associated with oxidative stress; thus, there is tremendous interest in compounds that can oppose this mechanism. Traditional antioxidants include vitamins C and E, glutathione, melatonin, and carotenes. Supplementation with these compounds has been extensively purported to treat chronic diseases, such as cancer and heart disease,[80] but have not yet been proven effective. In fact, meta-analyses on the use of high-dose antioxidant therapy for the prevention of cardiovascular disease have actually shown that treatment with these antioxidants increases mortality.[58,86] Supraphysiologic supplementation at this time, however, cannot be recommended. It should be understood that the mechanisms of these disease processes are quite complex and multifactorial, and antioxidant treatment may yet prove to be an effective approach in disease prevention and treatment.

Polyphenols are natural, plant-derived compounds present in many foods in the human diet, ranging from fruits and vegetables to tea and cocoa. There have been more than 8000 polyphenolic compounds identified, with flavonoids being the most abundant.[17,32,64,69] Dietary polyphenols have many beneficial properties, but most attention has been devoted to the antioxidant activity of flavonoids. Selected flavonoids can directly scavenge superoxides. By scavenging radicals, flavonoids can inhibit LDL oxidation in vitro.[46,78] This action protects the LDL particles, and, theoretically, flavonoids may have preventive action against atherosclerosis.

Flavonoids have the potential to improve cognitive disorders and cholinergic dysfunction related to oxidative stress. In several studies, administration of the flavonoid quercetin in aged mice improved mental function, memory, and attenuation of oxidative damage in the nervous system.[5,87] In addition to their antioxidant properties, some flavonoids may promote osteoblast differentiation and inhibit osteoclast genesis, demonstrating a positive effect on bone metabolism.[75]

Despite encouraging reports, studying flavonoids is complex, and measuring objective endpoints remains difficult. A major problem in assessing the future implications of flavonoids is the limited number of flavonoids that can be measured in biological samples. Quercetin is the largest contributor to the estimated intake of flavonoids, mainly found in apples and onions.[23] Data on the absorption, metabolism, and excretion of flavonoids in humans are also lacking, in addition to contradictory studies regarding absorption of glycosylated and aglycone forms.[47,74]

Another plant-based compound with anti-inflammatory and antioxidant properties is curcumin, which has been used for centuries in traditional Chinese and Ayurvedic medicine for its anti-inflammatory properties.[33] Curcumin is yellow and commonly used as a spice and food-coloring agent. It is isolated from tumeric, or curry powder, derived from the plant *Curcuma longa*.[29,54] Strong molecular evidence has

been published to support its potency for targeting multiple inflammatory diseases.[8,56] However, naturally occurring curcumin cannot achieve its optimum therapeutic outcomes in vivo because of its low solubility and poor gastrointestinal absorption and systemic bioavailability.[8,11,13]

One of the more promising recent additions to the antioxidant market is resveratrol, a phytochemical found in plants such as grape skins, berries, and Japanese knotweed. One of the aspects that sets this compound apart is that it has been well studied in vitro, and its basic science has been confirmed to have potentially promising applications. It gained scientific attention after a 2003 study showed the compound to significantly extend the life span in yeast.[35] Subsequent studies confirmed this life extension property in worms and fish, noting up to a 59% increase in life span.[85,91] One study in mice demonstrated a 30% lower risk of death with the addition of resveratrol in a high-fat diet model,[2] though resveratrol given to healthy lean mice does not appear to increase longevity.[67] While the mechanism of action of resveratrol is still being elucidated, it appears to act similarly to severe calorie restriction, a well-studied path to prolongation, through the Sirtuin 1 gene, improving mitochondrial function and working through an antioxidative pathway. This mechanism gives resveratrol the potential for applications in the treatment of diseases such as cancer,[14] neurodegenerative diseases,[43] and diabetes.[63] There are little data on human volunteers, but one study noted that it can be safely tolerated in doses that mimic those found to be effective in animal models[6] (1-2 g), though in higher doses it may be toxic.[67] Further study is necessary to clearly define whether the longevity and health effects of resveratrol can be transferred from in vitro to human subjects, but the compound appears to have tremendous potential in disease modification and longevity.

CONCLUSION

The scientific study of aging has greatly advanced over the past few decades. The basic science of aging is much more clearly understood, and this has produced rational strategies to combat the direct and indirect effects of aging on health and longevity. Unfortunately, the marketing of products to accomplish these goals has greatly outpaced its scientific support. Clinicians who treat aging patients should balance an open mind for potential antiaging applications with a healthy skepticism for quackery.

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