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PREVENTING MUSCLE LOSS — SARCOPENIA

The word sarcopenia comes from two components: sarco, meaning muscle, and penia, meaning a deficiency or lack. Sarcopenia is defined as the age-associated decrease in muscle mass, strength and function, and is related to increased frailty, falls, illness, disability and even death in the elderly. For the individual, sarcopenia presents the threat of decreased quality of life and, in particular, a loss of independence. For society, sarcopenia is a problem because it is associated with increased healthcare costs. It is estimated that \$18.5 billion, or approximately 1.5 percent of total healthcare costs in the United States, were attributed to sarcopenia in 2000.

In large epidemiological studies, it has been suggested that, beginning in the fourth decade of life, adults lose strength at the rate of 8 to 10 percent per decade. This decrease in strength appears not only to be associated with a decrease in the total amount of muscle mass, but also a decrease in the quality of muscle. This means that not only do older individuals have less total muscle compared to younger adults, but the muscle they do have does not generate as much strength

per unit muscle area as it did when they were younger. There appears to be a selective reduction in Type II (fast twitch) fibers with aging. The Type II fibers generate more power than the Type I (slow twitch) endurance fibers.

Although the cause of sarcopenia is not known, several possible mechanisms have been suggested. They include loss of the nerve cells (motor neurons) in the spinal column that control muscle function. Such a loss can result in a decrease in Type II fibers. Another possibility is decreases in circulating levels of hormones related to muscle mass such as growth hormone, testosterone and estrogen, or increases in hormones associated with muscle breakdown such as cortisol. Inadequate nutrition, particularly regarding intake of high-quality protein, may also play a role. Finally, reduced physical activity, especially strength-related activities, like weight training, is a common accompaniment of aging.

Let's examine the factors that contribute to sarcopenia in greater detail. With

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Kronos Longevity Research Institute

2390 E. Camelback Rd.
Suite 440
Phoenix, Arizona
85016

Tel: 602.778.7499

www.kronosinstitute.org





DIRECTOR'S MESSAGE

Growth Hormone Revisited

Growth hormone (GH) is a large molecule (protein) messenger produced by the pituitary gland and released into the circulation. GH stimulates growth of bone and is a vital factor required for children to reach full adult height. It also tends to reduce body fat and maintain lean body tissues, especially muscle — effects that continue into adult life. GH production tends to decrease during normal aging and may become very low by the time we are in our 70s and 80s.

In the last 15 years, GH has attained notoriety as an “anti-aging” hormone. Many middle-age and older persons are injecting thousands of dollars worth of this hormone every year in an effort to keep themselves physically younger and prolong life. Injectable human recombinant GH (hGH) is prescribed for them at several anti-aging clinics and medical practices around the country. In addition, a huge industry has grown around hGH, so that hundreds of Internet sites promise eternal youth and longevity to those who purchase products advertised as containing GH or GH-like substances.

I have consistently stated for the last six years or more that treating otherwise healthy older men and women with growth hormone (GH) is unlikely to provide any significant health or longevity benefits and has potential risks, some of which are known and others that are not. My position has been based on my knowledge of the published research data, including a large study performed by my colleague, Dr. Marc Blackman and myself while I was an investigator at the National Institute on Aging. This study, published in the *Journal of the American Medical Association (JAMA)* in 2002, showed that when human recombinant GH (hGH) was given to men and women over the age of 65 for six months, they had significant improvements in body composition. Approximately 10 percent increased lean body mass and 14 percent decreased in fat, as well as modest improvements were demonstrated in their levels of “bad” LDL cholesterol. Men (but not women) also barely had significant increases in muscle strength and fitness.

However, participants in the JAMA study also had problems with joint pains, fluid retention, causing foot and ankle swelling (edema), and, more importantly, increased blood insulin levels and high blood sugar levels, with some even developing diabetes. Other concerns dealt with possible effects of GH to increase risk of cancer or even accelerating the aging process itself. While these two latter risks are more theoretical than proven, they should carefully consider “off-label” use of hGH.

The purveyors of anti-aging hGH have long maintained that, by giving low doses, they can obtain beneficial results in their patients. However, the anti-aging clinic doctors seldom publish results of objective measures of GH response in their patients. Rather, they cite testimonials as to how this patient or that had a wonderful increase in strength and energy and a rejuvenated sex life, etc. In the absence of reliable measurements of strength, body composition, bone density and other objective criteria, it is difficult to know what to make of such claims, and they are best taken with a large “grain of salt.”

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DIRECTOR'S MESSAGE ... *Continued from Page 2*

Nonetheless, it is important to remain open-minded and to pay attention to new scientific data as they appear. Recently, endocrinologists at the university hospital in Göteborg, Sweden, have published a series of observations on the effects of GH treatment of a large group of patients they have been following for many years. These patients are all men and women with diseases of the pituitary gland. That is to say, they all have had damage to their pituitary glands leading to total or near-total loss of GH production. Thus, their GH levels are extremely low and do not respond well to stimuli that normally provoke GH secretion. Although such patients cannot be equated with persons undergoing normal aging, many otherwise healthy elderly persons have GH levels that are similar to these patients.

The most interesting finding from this Swedish research is that their elderly GH-deficient patients, treated for five years or more with low doses of hGH, appear to benefit. Their body fat and LDL-cholesterol levels decrease significantly, and they have modest but meaningful improvements in lean body mass and muscle strength. The best news is that this appears to occur without any notable change in blood sugar or insulin levels. Moreover, long-term follow-up on these patients shows no excess risk of cancers and a lower rate of death from heart disease compared with similar patients not treated with hGH.

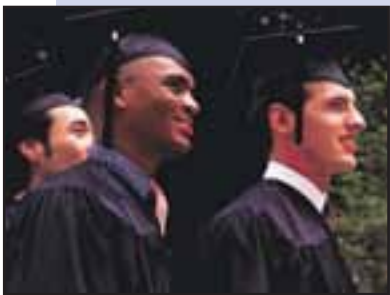
What is the difference between these patients and the research participants we treated? First, the doses used by the Swedish group are only about one-third of those employed in our JAMA study. We gave an average of about 9 micrograms per kilogram of body weight per day, whereas the patients in the Swedish studies were getting only about 3 micrograms per kilogram per day. The other possible difference, as noted above, is that our participants did NOT have pituitary disease, just normally aging pituitary glands.

Is it possible that, as claimed by the anti-aging doctors, their patients are actually benefiting from hGH treatment, while avoiding the ill effects Dr. Blackman and I (and others) have observed? What should we do next to clarify these issues? I suggest, as does the Swedish group, that we need serious studies to examine the effects of low dose hGH in healthy elderly men and women with low GH levels. My colleague, Dr. Fred Sattler at the University of Southern California, is close to completing one such study, but his research participants are being treated for only three months. In order to get a real appreciation of the risks and benefits, it seems to me that we will need at least two and possibly three years of observations. Another strategy with great appeal would be to "convince" the aged pituitary to increase its own GH production back to levels more like those seen in the young. This may be possible. KLRI scientists are currently preparing to do a pilot study examining effects of a drug, which, given at bedtime, has the potential to rejuvenate nighttime GH release by the pituitary gland.

So stay tuned. The GH story has not been entirely told as yet. It now seems likely that some maneuvers for increasing the body's exposure to GH, done carefully and avoiding excess, will prove helpful in at least some elderly persons. However, until we have learned the way to do this safely and effectively, caution should remain the watchword.

S. Mitchell Harman, MD, PhD
Director and President
Kronos Longevity Research Institute

aging there is a predictable alteration in body composition. In most individuals, weight gain and increased body fat occur with a concomitant reduction in fat-free (lean body) mass. Muscle comprises the largest component of fat-free mass so it is not surprising that the loss of fat-free mass is expressed as declining muscle strength and function. This alteration in body composition with aging has important implications for a person's ability to carry out daily activities and impacts quality of life.



The average college-age male carries about 15 percent of his body weight as fat compared with approximately 24 percent body fat in college-age females (the difference between males and females is related to sex-specific

fat deposits, like hips and breasts, which are larger in women). With aging, men and women increase their percent of body fat so that by age 50 these are approximately 25 to 30 percent and 35 to 40 percent of their body weight, respectively. At the same time, there is a decrease in the amount of fat-free mass. Most of this loss is due to shrinking of muscle with less change observed in other components of the fat-free mass (such as total body water and total bone mineral). This reduction in muscle mass does not typically result in weight loss, as the gain in fat tends to offset the loss of muscle. This means the remaining muscle is required to deal with more weight per unit of muscle mass. This loss of muscle is due not only to muscle fibers becoming smaller, but to an actual loss of muscle fibers. It has been estimated that older men have about 20 to 25 percent fewer muscle fibers in their quadriceps (large thigh) muscle compared to younger men.

As you might expect, the reduction in muscle mass is associated with decreased muscle strength. Several studies suggest that, beginning in the fourth decade of life, there is loss of strength at the rate of 8 to 10 percent per decade. In addition to the loss of muscle mass being associated with decreased muscle strength, it has also been suggested that quality of

muscle is affected by aging. In one study, maximal force capability from isolated slow (Type I) and fast (Type II) muscle fibers taken from young (36 years) and older (74 years) men were measured. The results of this study indicated that Type I and Type II fibers in young men exerted greater force (by 44 percent for Type I fibers and 37 percent for Type II fibers). These differences remained even after adjusting for the fact that older men had smaller fibers than younger men.

In addition to the age-related decline in muscle mass and muscle quality, other changes within the muscle may contribute to sarcopenia. As stated previously, there appears to be a specific reduction in fast-twitch fibers with aging. Other changes within the muscle include an increase in the amount of fat and connective tissue as well as an impairment of nerve function.

The consequence of the loss of muscle mass, fibers and quality is a reduction in muscle strength and power. From a functional standpoint, this loss contributes to

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- **Roughly 45% of the U.S. population is sarcopenic**
- **Healthcare costs in U.S. in 2000 related to sarcopenia = \$18.5 billion**
- **Healthcare expenditures due to sarcopenia cost roughly \$900 per person per year**
- **Lifestyle exercise programs cost about \$200 per person per year**
- **No race or ethnicity is protected from sarcopenia**

disability in old age, including problems with walking, stair climbing, rising from a chair and carrying a load such as groceries. Because having adequate strength is important to maintain mobility and balance, loss of strength with aging may contribute to increased risk of falls.



Because the maintenance of muscle mass is a result of the balance between synthesis and breakdown of muscle proteins, the effects of age on protein turnover has been studied extensively. The best studies have controlled for diet, hormone supplementation and physical activity, since these factors affect protein turn-

over. Existing data indicate that aging is associated with a reduction in rates of synthesis of a variety of individual muscle proteins, with the overall rate of protein synthesis decreasing in the elderly by 30 to 40 percent compared with young participants.

Another important contributor to the loss of muscle's ability to generate strength and power with aging may be changes in the mitochondria within muscle cells. The mitochondria are the cell's energy producers. These tiny "generators" use oxygen to "burn" the cell's fuel (sugars and fats), releasing energy that they "trap" in a molecule called ATP. ATP is the immediate energy source the muscle uses for fiber contraction. However, aging is associated with mitochondrial decay. The observed reduction in the rate of mitochondrial protein synthesis (about 40 percent) is associated with an age-related decline in oxygen consumption during maximal exercise (the gold standard measure of cardiovascular fitness).

Finally, the development of sarcopenia has been associated with an age-related decrease in anabolic (tissue building) hormones such as growth hormone (GH) and the male hormone (androgen), testosterone. Many age-related physical alterations resemble

those seen in men with GH-deficiency and/or androgen deficiency, including reduced muscle mass and exercise capacity, increased body fat, especially fat inside the abdominal cavity (visceral fat), unfavorable cholesterol lipoprotein profiles, reduction in bone mineral density, increases in falls and fractures, depression, decreased libido, and cerebrovascular and cardiovascular disease. The uncanny resemblance between normal aging and hormone deficiency has led to the suggestion that hormonal decline may be an important cause for many of the physical and mental declines associated with aging.

GH secretion decreases beginning in young adulthood, with 24-hour GH secretion falling by approximately 50 percent every 7 to 12 years. Because GH affects both muscle mass and fat oxidation, it has been suggested that the decline in GH observed with aging may cause some part of the observed increase in body fat (particularly visceral fat) and the decrease in fat free mass.



Although several male sex hormones are present in the blood, the most important androgen in the circulation is testosterone. Testosterone declines in an age-associated manner beginning in the fourth or fifth decades of life with the availability of testosterone reduced by 35 to 50 percent after the sixth decade. Between the fifth

and ninth decades of life, blood total testosterone is thought to decrease by 1 to 2 percent per year. Testosterone deficiency in men may be associated with depressed mood, decreased libido, erectile dysfunction, decreased energy, decreased strength, sleep disorders, reduced bone quantity and quality (with heightened risk of fractures), decreased red blood counts (hemoglobin and hematocrit), and loss of memory and cognitive function.

One might conclude from the information presented above that aging and the development of sarcopenia

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paint a hopelessly bleak picture. However, prevention and treatment of sarcopenia are areas of great interest for aging research. Exercise, particularly strength training, has been shown to be a very effective prevention and intervention strategy. Because protein synthesis declines with aging, there is also interest in examining the effects of increased dietary protein intake, in combination with strength training, on changes in muscle mass in older adults. Finally, research is being performed to investigate the effectiveness of hormone supplementation as a potential treatment for sarcopenia. However, to date, there are not enough conclusive data to support the use of hormone therapy as an intervention strategy.



Exercise is a powerful tool for the prevention and treatment of sarcopenia. Because increased cardiovascular fitness is associated with decreases in morbidity and mortality as well as a reduction in risk for developing cardiovascular disease, metabolic syndrome and Type 2 diabetes, aerobic exercise is very important for individuals of all ages. However, endurance training does little with respect to increasing the amount of muscle mass. In contrast, a number of studies have shown that strength (also called weight or resistance) training can result in large increases in muscle size and strength, even in elderly people. It is important to understand that such improvement is intensity dependent. When intensity of strength training is low, only modest increases in strength are seen in elderly participants. However, when strength training is performed at an appropriate intensity, which for most people is 80 percent of 1 repetition max (maximal weight that can be lifted 1 time) performed as three sets of 8 to 10 repetitions per set, older men and

women show relative strength gains similar to those seen in younger men and women.

A study using the above approach in healthy older men resulted in a doubling of knee flexion strength and a tripling of knee extension strength in only 12 weeks. The increases in strength averaged 5 percent per training session (about the same as is seen in young men) and total muscle area estimated by CT scan increased by more than 11 percent. Similar increases in size were observed for both Type I and Type II fibers. Half the men in this study received a protein-calorie supplement that provided an extra 560 calories per day. Although strength gains were similar between the supplement and non-supplement groups, the men who received the supplement had greater gains in muscle mass. Furthermore, strength training in

older adults, even without protein supplementation, is associated with decreased protein breakdown and, therefore, lower protein needs.



Similar findings have been reported in frail, institutionalized elderly men and women. After only eight weeks of training, one group of nursing home patients increased strength

by 180 percent and muscle size by 11 percent. Other studies in frail elderly have not only demonstrated increases in muscle size and strength as a result of strength training, but have also shown improvements in walking speed, the ability to climb stairs and in balance. In addition to these benefits, participants who strength trained also increased spontaneous physical activity (e.g. activity of daily living), whereas activity in the non-exercise control group did not change. It has been suggested that since muscle weak-

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ness is a primary cause of loss of function in the elderly, increasing strength may allow people to participate more comfortably in aerobic activities like walking or cycling.

In studies where protein/calorie supplements were administered with and without strength training, several important findings were reported. First, the administration of a protein/calorie supplement in the elderly without strength training did not affect total energy intake in these participants. Instead, these participants reduced the number of calories from their normal diet resulting in a substitution of one source of energy for another. In contrast, older participants who strength trained and received the protein/calorie supplement, gained weight. These findings have important implications for treating the frail elderly, particularly those individuals who have had involuntary weight loss. In normal healthy aging, the co-administration of strength training and increased protein/calories has also resulted in an increase in muscle size compared to strength training alone.

Hormonal approaches to treating sarcopenia include supplementation with GH and/or testosterone. Most of the data in the literature that have examined the effects of GH treatment in adults have come from studies of patients with diagnosed GH deficiency. It is generally agreed that adults with pituitary disease causing severe GH deficiency should be treated. Since normal aging is associated with a reduction in GH, it has also been suggested that GH treatment might be an effective “anti-aging” treatment.

In 1990, a study was published in the *New England Journal of Medicine* that reported that administration of GH to healthy elderly men resulted in an increase in IGF-I (one of the primary mediators of GH action) to levels similar to those seen in young men. This change was accompanied by increases in fat free mass and

loss of body fat. This and other studies have sparked a large interest in the use of GH to restore muscle mass and function in the elderly and has resulted in off-label prescription of GH to combat normal aging. The limited number of well-controlled studies that have examined GH supplementation in healthy elderly agree that GH reduces visceral fat and increases fat free mass. However, there is no consensus regarding the effects of GH treatment on muscle mass and strength.

In one study, one year of GH administration in older men and women had no effect on muscle strength above that seen with strength training alone. In addition, no studies have been performed that have examined enough participants and followed them for long enough periods of time to examine clinically important outcomes such as falls, fractures, quality of life and maintenance of independent living. Although there may be anecdotal reports of GH administration providing significant benefits in some elderly men and women, at present there are not enough safety and efficacy data to warrant the use of GH administration for the treatment of



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definition

sarcopenia (sar.coh.PEE.nee.uh) *n* (from the Greek meaning “poverty of flesh”). The age-related loss of muscle mass and strength. — **sarcopenic** *adj.*

EXERCISE, HYPERTENSION AND AGING

High blood pressure, or hypertension, is a leading cause of cardiovascular disease (CVD), including heart attack, chronic heart failure, kidney disease and stroke, in all ages and in both sexes. About 50 million adults in the United States have systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, which are the levels that define hypertension. However, even lower levels of blood pressure are associated with an increased risk of CVD. In fact, the risk of CVD begins at 115/75 mm Hg, and doubles with each increment of 20/10 mm Hg. Individuals who have normal blood pressure, which is 120/80 mm Hg or lower, have a 90 percent risk of developing hypertension during their lifetime. Individuals who have a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg are considered pre-hypertensive and should adopt health-promoting lifestyle habits, such as exercise or a weight-loss diet to help lower their blood pressure and prevent CVD. African-Americans are more likely than Caucasians to have hypertension, although the specific reasons for this racial difference are unknown. In many individuals, hyper-

tension clusters with other risk factors such as obesity, high cholesterol and glucose intolerance, which together increase the risk of CVD. For example, about 60 percent of individuals with Type 2 diabetes are likely to also have high blood pressure.

An advantage of exercise as a treatment for hypertension is its beneficial effects on multiple cardiac risk factors. There is good evidence that exercise will lower triglycerides, increase HDL cholesterol and reduce body fat, among other benefits.

Causes of hypertension

Essential hypertension is the most common form of hypertension. While there is no single cause of essential hypertension, blood pressure is mainly determined by the product of cardiac output, or how much blood is ejected by the heart and its force, and total peripheral resistance, or how much resistance there is to blood flowing through the arteries. The arteries carry blood to the body tissues and cells at rest and during exercise. Resistance to blood flow

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When Hypertension Strikes

Hypertension: Also known as high blood pressure. Hypertension is a leading cause of cardiovascular disease in men and women.

By the numbers: 50 million adults in the United States have systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, which are the levels that define hypertension.

Pre-hypertension: Individuals who have a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg are considered pre-hypertensive.

Risk factor: Individuals who have normal blood pressure, which is 120/80 mm Hg or lower, have a 90 percent risk for developing hypertension during their lifetime.

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occurs primarily in the smaller arteries. In younger individuals, hypertension is often related to a high cardiac output state. In older individuals, hypertension is often related to an increase in the resistance to blood flow.

In older individuals, besides resistance in the smaller arteries, there also develops stiffening of the larger arteries like the aorta, the main blood vessel coming from the heart. Ordinarily, the larger arteries have elastic-like properties so they expand and absorb some of the force of each heartbeat. However, with aging, as well as diseases like diabetes, the arteries accumulate calcium and fibrous tissue and become stiff and hard. This results in a loss of their capacity to expand, and thereby contributes to an increase in systolic blood pressure, which is the pressure when the heart is contracting and pushing blood to the body. For this reason, older individuals are more likely to have systolic hypertension, which is characterized by an increase in the upper blood pressure number rather than an increase in the lower blood pressure number. The lower number, or diastolic blood pressure, is the pressure in the blood vessels during the phase of the heart cycle when it is filling (diastole) rather than contracting. As the systolic blood pressure rises while the diastolic blood pressure remains the same, the pulse pressure, the difference between systolic and diastolic blood pressure, rises. The pulse pressure is an important marker for predicting future cardiovascular problems.

The primary factors associated with hypertension in both younger and older persons are obesity, high salt intake, low potassium intake, physical inactivity, heavy alcohol consumption and psychosocial stress. Regarding obesity, there is growing research evidence

that the accumulation of fat in the abdominal region of the body is a particularly strong risk factor for developing high blood pressure along with other risk factors for CVD, such as diabetes and abnormal cholesterol levels. For these reasons, lifestyle changes that favorably alter these contributing factors play an important role in preventing and treating hypertension.

Role of exercise for reducing blood pressure

Numerous research studies have shown that exercise can lower blood pressure. In fact, several health organizations including the American College of Sports Medicine, the National Institutes of Health, and the American Heart Association, endorse increased physical activity for hypertension. For many individuals with milder forms of high blood pressure, and without other significant health conditions or multiple risk factors for CVD, it is generally recommended that six months of exercise, diet and weight loss be tried as the initial treatment for lowering blood pressure rather than first starting blood pressure lowering drugs. If these lifestyle modifications fail to bring the blood pressure down to the goal established by a physician, then drug treatment should be started.



Although individual responses will vary and will depend on the initial blood pressure level, among other factors, many studies have shown that increased physical activity has the potential to lower blood pressure by 8 to 10 mm Hg for both systolic and diastolic blood pressure. When combined with a low salt diet and

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weight loss, the potential for lowering blood pressure is even greater.

There are several possible mechanisms by which exercise reduces blood pressure. The lowering of both the heart rate and peripheral vascular resistance at rest and at any given level of work after exercise training is one theory. Another mechanism is the reduction of levels of the stress hormones circulating in the blood.

While overall weight loss appears to contribute to reducing blood pressure, some studies have shown that the loss of fat in the abdominal region with exercise seems to make a greater contribution to blood pressure reduction than total body fat loss.

Medical therapy and implications for exercise

Effective management of hypertension with or without the use of antihypertensive medications can reduce cardiovascular disease mortality for all patients.

Medical management is often complicated by concomitant hyperlipidemia, sedentary lifestyle, hyperinsulinemia, glucose intolerance and obesity found in hypertensive patients. These additional disorders compound the risk of hypertension. Age, race, sex and the presence of other risk factors should be considered in determining treatment strategies. Subtle abnormalities in insulin resistance and hyperinsulinemia, each precursors to developing Type 2 diabetes, may worsen hypertension. For example, insulin has a salt-retaining effect on the kidney, increases levels of stress hormones, and may reduce the effectiveness of some antihypertensive medications. Insulin resistance, like hypertension, can be treated with regular aerobic exercise, weight reduction, high-fiber diet and/or medications. To provide maximal

protection against the cardiovascular complications, hypertension should be managed to reduce total cardiovascular risk burden and not just the blood pressure.

Another consideration is that some antihypertensive medications produce side effects whereas exercise, diet and weight loss improve multiple cardiac risk factors with virtually no side effects. Patient adherence to medications is often a problem, particularly for active older adults or individuals for whom exercise is encouraged. In many cases, exercise training may reduce or eliminate the need for antihypertensive medications in patients with mild or severe hypertension. It is important that each individual discuss the various treatment strategies with their healthcare provider to establish an optimal approach for lowering blood pressure and managing other health conditions and risk factors.

Exercise guidelines: Aerobic exercise

The primary recommended mode of exercise is aerobic exercise like walking, jogging, cycling, stair-stepping or swimming. These large muscle activities, which increase the heart rate and the demand for oxygen, should be performed at least three to five times each week for 45 to 60 minutes per session. The intensity should be moderate. This can be accomplished by maintaining a heart rate during exercise at 65 to 80 percent of the age-predicted maximum. For most

individuals, maximum heart rate is equal to 220 minus age in years. For example, some 65 year olds would



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have an age-predicted maximum heart rate calculated as $220 - 65 = 155$ beats per minute. For individuals with markedly elevated blood pressure, exercise training at somewhat lower intensities (40 to 70 percent) is recommended after starting antihypertensive medical therapy. Some medications such as beta-blockers will blunt the heart rate during exercise. For individuals using these medications, exercise should be done at a level that raises the heart rate 20 to 30 beats above the resting level.

The effectiveness of exercise training as a complement to medical therapy has been demonstrated in persons with blood pressure as high as 180 mm Hg systolic and 110 mm Hg diastolic. After antihypertensive medications were administered in an effort to reduce the blood pressure to lower levels, participants were divided into exercise and sedentary groups. Endurance exercise for three days a week, 45 minutes/day at 75 percent of maximum heart rate for 16 to 32 weeks was the training program. By week 16, the exercise group lowered their blood pressure and partially reversed their enlarged heart. These effects persisted even after a reduction in antihypertensive medications. Thus, moderate aerobic exercise may reduce blood pressure, and the number of antihypertensive medications required to control blood pressure.

Exercise guidelines: Resistance exercise

A resistance exercise workout acutely increases the blood pressure. However, compared with aerobic exercise, there is less of a heart rate increase with resistance exercise. In many instances, the load on the heart, which is directly related to the rate pressure product (heart rate \times blood pressure), may be lower with resistance exercise rather than aerobic exercise.



This response was demonstrated in two studies of hypertensive men performing weight training and walking/jogging. Heart rate during walking/jogging was higher than during weight training, while blood pressure was higher during weight training. The rate pressure product was similar during weight training and walking/jogging. Of note, blood pressure responses to aerobic or resistive exercise are variable, and blood pressure at rest does not provide independent information about exercise responses. Therefore, exercise testing that includes assessment of blood pressure to resistance forms of exercise (e.g., handgrip, weight lifting or isometrics) should be considered for participants with hypertension.

While most research studies have focused on aerobic training, the benefits of resistance training for reducing blood pressure and improving cardiovascular health have been recognized in recent years. The American Heart Association recommends mild-to-moderate resistance exercise for reducing blood pressure and improving muscular strength and endurance, preventing and managing a variety of chronic medical conditions, modifying coronary risk factors, and enhancing psychological well-being. In a study of men with mild hypertension conducted at Johns Hopkins University, the effects of strength training combined with aerobic exercise in patients also randomly assigned to antihypertensive medications or placebo was examined. After 12 weeks of training, resting systolic and diastolic blood pressure fell by 13 to 14 mm Hg in all groups. The most striking finding was that resting blood pressure fell equally between the drug and placebo groups, showing no added benefit of medications if participants exercised regularly.

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In a more recent study conducted at Johns Hopkins, individuals ages 55 to 75 years with mild hypertension underwent six months of combined aerobic and resistance exercise or were assigned to a sedentary control group. After six months, exercisers reduced their systolic blood pressure by 5 mm Hg and their diastolic blood pressure by 3 mm Hg.

While these changes represented a significant and clinically important reduction from their baseline values, surprisingly, the sedentary control group also reduced their blood pressure by 4 mm Hg systolic and 1.5 mm Hg diastolic. After the six-month period, neither group of participants showed an improvement in the stiffness of arteries. Thus, it is possible that six months of exercise was too short a period of time for changing the arteries, which is a likely contributor to hypertension in older persons, and thereby limited their ability to reduce their blood pressure to the extent commonly seen in younger persons. Regardless of the modest reduction in blood pressure, exercisers still attained numerous benefits from exercise, including increased aerobic and muscle fitness, a reduction of body fat, and an increase in lean muscle tissue. Furthermore, there were improvements in several cardiac risk factors, such as increased HDL cholesterol, lower triglycerides, and a reduced prevalence of metabolic syndrome.

Summary

Hypertension is a common and chronic problem and adequate treatment is likely to reduce cardiovascu-

lar morbidity and mortality, particularly as we age. Physical activity plays an important role in the treatment and prevention of hypertension.

Based on numerous research studies, regular physical activity and exercise training appear to lower blood pressure. One caveat is that while exercise will lower blood pressure in older persons, the reductions may be less than what would be attained by younger persons over the same period of time. For this reason, the guidelines for exercise that have been developed based mainly on studies of young adults may not fully apply to older persons. Therefore, it may be prudent for older persons to consider starting antihypertensive medications sooner than what might be the case in younger persons. Exercise also has a beneficial effect on many other risk factors for CVD. Exercise prescription for hypertension, as well as a decision to initiate antihypertensive medications, should

be based on medical history and risk factor status, in consultation with a healthcare provider. For those individuals using antihypertensive medications, the exercise prescription may require modification since the medications may affect the exercise heart rate and blood pressure. Finally, although much of the exercise literature has focused on aerobic exercise for individuals with hypertension, there is ample evidence to recommend that resistance training be combined with aerobic exercise for controlling blood pressure and improving cardiovascular health.

Kerry J. Stewart, EdD, is a scientific advisor for Kronos Longevity Research Institute and is a Professor of Medicine at Johns Hopkins School of Medicine.



Who We Are!

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization that conducts state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. KLRI tests new strategies to detect and prevent chronic diseases associated with aging and investigates the effects of innovative interventions to slow the aging process and improve health outcomes for older persons. In addition, KLRI helps the medical and lay communities understand important aging issues. KLRI research findings support a healthier quality of life and a robust lifestyle in our senior years.

Our Mission

To perform and foster clinical translational research aimed at healthier human longevity and communicate results to the professional and lay communities.

Our Governance

A distinguished board of directors, with a unique mix of scientists, longevity specialists, and community leaders govern KLRI. There is also a scientific advisory board of recognized international experts in medical and scientific fields, including nutrition, exercise, hormones, bone and joint diseases, cancer and heart disease.

What Is Translational Research?

Translational research takes promising findings from the basic research laboratory and carries them forward into the clinical arena. It is the link between basic research (experiments done with animals or cultured cells, genes, etc.) and improved clinical care. It requires controlled studies of living human participants.



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Research Snapshots

Current Research Projects

Testosterone's Effects on the Progression of Atherosclerosis in Aging Men (TEAAM): KLRI is collaborating with Boston University, the University of California at Los Angeles and Drew University School of Medicine on a study designed to determine the effects of testosterone replacement in older men on cardiovascular disease risk. Loss of testosterone with age may lead to decreases in bone and muscle strength and contribute to frailty and poor quality of life.

Kronos Early Estrogen Prevention Study (KEEPS): KEEPS is designed to provide prospective data on the risks and benefits of early menopausal hormone therapy, particularly as it relates to the progression of atherosclerosis (heart disease). KLRI will oversee KEEPS research and the eight study centers that are involved in recruitment.

Kronos Statin Pilot Study: Statins are cholesterol lowering drugs that decrease the risk for cardiovascular disease. However, statins lower coenzyme Q10, a vitamin that is important for aerobic energy production. Energy is critical for normal muscle function. Many patients who take statins complain of muscle aches, cramps, and weakness. KLRI is performing a pilot study on the effects of statins on exercise capacity and skeletal muscle function during mild and moderate exercise.

Diabetes and Oxidative Stress: KLRI supports and assists with a Veteran's Administration study which measures the effects of better glucose control on oxidative stress-related risk factors for heart disease in adult-type diabetics. This study investigates how changes in these risk factors relate to the progression of coronary heart disease.

Completed Research Projects

Cancer Detection with the AMAS Test: Malignin is a protein found on the outer surface of many kinds of cancer cells. Therefore, measuring levels of anti-malignin antibody in serum (AMAS) could help diagnose cancer. KLRI completed a study in women having biopsies for breast cancer. A manuscript reporting the findings has been submitted for publication.

Validation of Oxidative Stress Assessments: Oxidative stress is the ongoing damage to an organism due to oxidation (the reaction of cell components with oxygen). This resembles the rusting of metal components in a car, and leads to loss of function. Oxidative stress is considered an important factor in the aging process. KLRI completed a study to characterize and validate laboratory methods needed to measure the effects of therapies designed to slow or reduce oxidative stress.

Omega-3 Fatty Acids and Endocrine/Immune Dysfunction in Humans: Omega-3 fatty acids are polyunsaturated fatty acids found in certain natural foods, especially fish, like salmon and tuna. They are known to help protect against heart disease. Omega-3 fatty acids may help hormone signals get into cells whose outer layer (cell membrane) has been stiffened by age. KLRI examined whether a diet high in omega-3 fatty acids may help restore normal hormone balance.



sarcopenia. Until appropriate studies are conducted and consensus is reached, treatment of the elderly with GH should be confined to properly controlled research programs.

Similarly, it has been suggested that sarcopenia of aging may be related to diminished levels of testosterone. Although it has been suggested that a decrease in testosterone production may play a role in the clinical changes that occur with aging, the clinical relevancy of this decline in testosterone with aging has not been completely established. Few well-controlled studies that have examined the risks and benefits of testosterone administration to elderly men have been conducted, and most of these have had durations of one year or less.

Although doses of testosterone that produce levels higher than normal for young men can result in favorable alterations in body composition and muscle strength in both young and older men, the side effects associated with these doses preclude their long-term use. Most studies have reported that testosterone administration in older men has a favorable effect on body composition; less convincing findings have been reported for muscle strength and function. While some studies report strength benefits, the majority of available studies did not find an improvement in strength (in particular leg strength) with testosterone administration. Furthermore, to date, there is no convincing evidence of clinical benefits such as improved mobility, reduced risk of falls, or maintenance of independent living with testosterone supplementation.

Finally, the risks of prolonged androgen treatment of older men have not been well defined. The potential risks include prostate cancer, adverse changes in cholesterol leading to heart disease, increased red blood cell counts that can cause strokes, and other

problems. As was suggested for GH, until appropriate studies are conducted and consensus is obtained regarding risks and benefits, treatment of elderly men with testosterone should be confined to properly controlled research programs.

In summary, aging is associated with sarcopenia, a lifelong process of loss of muscle mass and quality that likely begins in young adulthood. This process is associated with increased body fat, decreased metabolic rate and daily energy needs, loss of bone, reduced strength and impaired function. Although a number of different prevention and treatment strategies have been suggested, it appears that regular strength training at an appropriate intensity is the most effective, and certainly the safest strategy for the prevention and treatment of sarcopenia.



Strength training has been shown to lower dietary protein needs of older individuals, increase muscle strength and size, and increase spontaneous physical activity. The addition of a protein/calorie supplement to a strength training program may result in a further increase in muscle size. Strength training in combination with protein/calorie supplements can help to prevent involuntary weight loss in the elderly. There is compelling evidence that anyone, regardless of age, will benefit tremendously from regular exercise and, in particular, from muscle strength training. While both aerobic and strength training are highly recommended, only strength training can stop or reverse sarcopenia.

Arthur Weltman, PhD, is a scientific advisor for Kronos Longevity Research Institute and is a Professor of the Department of Human Services and Department of Medicine at the University of Virginia. He is also Director of the GCRC Exercise Physiology Laboratory and of the Exercise Physiology Graduate Program at the University.

KLRI Staff

Director and President
S. Mitchell Harman, MD, PhD

Clinical Director

Panayiotis D. Tsitouras, MD

Senior Clinical Research Associate

Tinna Traustadóttir, PhD, ATC, CSCS

Medical Assistant

Erika Adame, BS

Director of Operations

Michael H. Gibbons, CPA, MBA

Administrator

M. Carol Jackson, BA

Marketing Coordinator

Diana Vuong

Clinical Study Coordinator

Frank Gucciardo, PA-C, BS, MPA

KEEPS Principal Clinical Study Coordinator

Mary F. Barksdale, BSN, CNM, MPH

Clinical Research Associate

Anthony Stock, MS

Vice President, Education and Public Affairs

Patricia A. Crenshaw

Administrative Associate

Jane Heilman

To contact us,
please call

(602) 778-7499 or

visit our Web site at

www.kronosinstitute.org

or write to

2390 E. Camelback Road

Suite 440

Phoenix, AZ 85016

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