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Investigating the Mechanisms and Treatment of Muscle Loss in Older Adults

Even in healthy adults, there is a steady loss of muscle mass with advancing age. When this muscle loss is pronounced, the condition is termed sarcopenia. While some clinicians define sarcopenia as a height-adjusted appendicular muscle mass greater than two standard deviations below the mean for a standardized population of young adults,[1–3] others use the term less precisely. Regardless of the definition employed, sarcopenia generally is considered a potentially serious problem that affects approximately one quarter of adults older than 65 and almost one third of those older than 80.[3] Although there is no clear gender, racial, or ethnic predisposition, people with below average muscle mass as young adults are likely to be at increased risk for developing sarcopenia when they reach advanced age.

While sarcopenia can develop over many years, relatively rapid loss of muscle mass may occur due to serious illness, injury, or major surgery, particularly when inactivity, anorexia, or ongoing inflammation accompanies the condition. For these reasons, hospitalized, older adults are at particular risk for developing profound sarcopenia. This condition has serious public health implications, particularly for the VA, in which the proportion of patients older than 65 tops 45%.

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Investigators at the Geriatric Research, Education and Clinical Center (GRECC) of the Central Arkansas Veterans Healthcare System (CAVHS) are working to improve the understanding of several mechanisms involved in illness-associated muscle loss, including the impact of nutritional compromise, inactivity, dysregulated inflammation, and specific pharmacologic agents. This research has targeted older adults in hospital and postacute care settings and includes both observational studies and clinical trials that examine the effects of pharmacologic, nutritional, and exercise interventions on muscle mass and physical function. Also, in a series of parallel studies, GRECC investigators are looking into the effects of bed rest on healthy, older subjects.

PINNING DOWN THE CAUSES OF MUSCLE LOSS

Despite the deleterious impact of sarcopenia, the etiology of this disorder is not fully understood.[4,5] The available evidence suggests that sarcopenia is a multifactorial condition. These factors include age-associated changes in hormone secretion (including declines in levels of testosterone and insulin-like growth factor–1), muscle innervation (due to a loss of alpha motor neurons), and muscle metabolism (caused by reductions in muscle protein synthetic capacity).[4,5] Physical inactivity and dietary factors, particularly reduced caloric or protein intake, also are important.[4,5]

In addition, a growing body of evidence implicates the immune system in sarcopenia development. Many older adults have elevated levels of interleukin-6 or other evidence of chronic inflammation.[5] Even when this inflammation is evident only in terms of elevated blood cytokine levels, it appears to have an adverse impact on muscle metabolism and is associated with a higher risk of sarcopenia.[4,5]

Many diseases and their treatments also can increase a person's risk of sarcopenia. High dose glucocorticoids

The VHA's Geriatric Research, Education and Clinical Centers (GRECCs) are designed for the advancement and integration of research, education, and clinical achievements in geriatrics and gerontology throughout the VA health care system. Each GRECC focuses on particular aspects of the care of aging veterans and is at the forefront of geriatric research and clinical care. For more information on the GRECC program, visit the web site (http://www1.va.gov/grecc/). This column, which is contributed monthly by GRECC staff members, is coordinated and edited by Kenneth Shay, DDS, MS, director of geriatric programs for the VA Office of Geriatrics and Extended Care, VA Central Office, Washington, DC.

represent a classic example of a therapeutic intervention that can have a negative impact on muscle mass and function.

THE EFFECTS OF INADEQUATE NUTRITION

Although most clinicians recognize that nutritional intake may suffer during acute hospitalization, the health consequences that can result from such nutritional deprivation are often underappreciated. In 1999, investigators from the CAVHS GRECC reported that more than 20% of older veterans admitted to an acute care hospital maintained an average daily nutrient intake less than 50% of their maintenance energy requirement throughout their hospitalization.[6] Even after adjusting for age, admission diagnoses, and other indicators of illness severity, the risk of in-hospital and 90-day mortality for those in this seriously compromised nutritional intake group was threefold to eightfold higher than that of the remaining geriatric patients. Previous studies of older patient populations conducted by the same investigative group demonstrated a similarly strong association between mortality risk and indicators of nutritional health, including a low body mass index (defined as 20 kg/m^2 or less) and weight loss. These study findings highlight the significance of nutritional status as a determinant of health outcomes in older, hospitalized patients.

THE EFFECTS OF PHARMACOLOGIC APPETITE STIMULATION

Weight loss is recognized as a common problem for older adults in recuperative and long-term care settings. Numerous studies have found that the risk of death and other adverse health outcomes increases in direct proportion to the amount of weight lost. As persistent anorexia often is a significant contributor to the weight loss in these nutritionally compromised older adults, pharmacologic interventions that stimulate appetite and nutrient intake hold great promise for improving clinical outcomes in these patients.

Figure. A staff member of the Central Arkansas Veterans Healthcare System's Geriatric, Research, Education and Clinical Center monitoring a study participant's performance of lower body resistance training.

Of the orixogenic agents (drugs that stimulate eating) that have proven effective in increasing nutrient intake in older adults, megesterol acetate (MA) is one of the more frequently prescribed in long-term care settings. The CAVHS GRECC has conducted several studies on this medication to determine its effects on body composition and muscle.

One study looked at the effects of MA on body composition in older, underweight men when the drug was used alone or in conjunction with testosterone supplementation with or without resistance exercise (RE) training.[7] Participants were assigned randomly to one of four groups for this 12-week study: testosterone injections, placebo injections, testosterone injections plus high-intensity RE, or placebo injections plus high-intensity RE. All participants received MA 800 mg/day orally. The testosterone intervention consisted of a weekly injection of testosterone enanthate 100 mg. Placebo injections, identical in appearance to the testosterone, also were given weekly. The high-intensity RE consisted of upper and lower extremity weight lifting exercises performed at 80% of the patient's one-repetition maximum (1RM).

As noted in previous studies of MA, all participants who received placebo injections had a dramatic decline in their testosterone concentration (total serum and free) to castrate levels, and gained more than 5 kg of fat mass as a result of the MA ingestion (regardless of whether or not they were assigned to RE training). Those who received placebo injections and did not exer-

cise lost almost 2 kg of lean tissue and experienced a substantial decline in thigh muscle area, as determined with computed tomography imaging. In fact, all participants had a loss of lean tissue except for the group assigned to both testosterone supplementation and high-intensity RE training. Regardless of their changes in lean mass, all of the participants performing high-intensity RE significantly increased their lower extremity muscle strength. The group assigned to receive testosterone supplementation with no exercise maintained normal testosterone levels but had no measurable improvement in lower extremity muscle strength and experienced a significant decline in thigh muscle area.[7]

These study findings confirm that MA is a strong appetite stimulant that induces an increase in body weight. This weight gain is primarily due to an increase in body fat, however, and can be associated with a loss of muscle mass if other interventions are not provided simultaneously. Adding high-intensity RE, alone or with testosterone replacement, can minimize the muscle mass loss due to MA while also improving muscle strength.

A later study by the CAVHS GRECC examined the independent effects of exercise intensity and MA on lower extremity muscle function in older patients undergoing recuperative care.[8] Patients were assigned randomly to one of four groups: high-intensity RE plus MA, high-intensity RE plus placebo, low-intensity RE (20% of the patient's 1RM) plus MA, or low-intensity RE plus placebo. The researchers found that patients in the high-intensity RE plus placebo group significantly increased their lower extremity muscle strength, while patients who received MA failed to improve their strength, regardless of the RE intensity.

Both of these studies highlight the significant adverse impact MA has on body composition and muscle mass in older patients. Specifically, MA results in a substantial decline in testosterone levels and can lead to a significant loss of skeletal muscle mass and a blunting of the beneficial effects of exercise. Additional analyses have indicated that both adrenocorticotropic hormone and cortisol are suppressed during MA therapy, which is consistent with the drug's known cortisone agonist properties. Given these results, careful evaluation of the risks and benefits of MA are warranted prior to prescribing it to older, adult patients.

THE EFFECTS OF INACTIVITY

In addition to examining the multiple facets of nutritional compromise in older veterans, CAVHS GRECC investigators recently have completed the first portion of an innovative study, funded by the National Institutes of Health, examining the effect of bed rest on older individuals.[9] This study was designed to evaluate the independent effect of bed rest on skeletal muscle protein synthesis, muscle mass, and lower extremity strength, as well as measures of aerobic capacity and whole body physical performance.[9]

Healthy, older adults remained in bed continuously (except for toileting) for 10 days. Participants were provided with a eucaloric diet containing the recommended dietary allowance (RDA) of protein (0.8 g/kg/day). Mechanical prophylactic measures to prevent deep vein thrombosis were applied and all participants received lower extremity ultrasounds at the completion of bed rest, as well as blood D-dimer assays before and after the bed rest period. No deep vein thromboses were found and no other significant adverse events occurred in any participant.

The effects of inactivity on these healthy participants, however, were dramatic. On average, they lost a greater amount of lower extremity lean tissue after just 10 days than younger participants in a previous study examining 28 days of bed rest (950 versus 350 g, respectively). Significant declines in the rate of skeletal muscle fractional protein synthesis (30%) and knee extensor strength (16%) also occurred. Contrary to the investigators' expectations, all of the participants were in negative nitrogen balance throughout the period of bed rest—despite consuming the RDA of protein.

The initial results of this study highlight the importance of limiting bed rest in older adults in order to prevent potentially serious detrimental effects on skeletal muscle and overall health status. They also suggest that efforts should be made to increase the nutrient intake of older patients confined to bed rest, with a focus on optimizing protein intake. Future investigations with this study will examine the effect of different nutritional and exercise interventions on the adverse effects of bed rest.

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LOOKING AHEAD

Research efforts made by the CAVHS GRECC have expanded our under-

standing of the harmful impact of nutritional compromise and prolonged bed rest in older adults, as well as the potential dangers associated with the use of a commonly prescribed appetite stimulant in this population. Future areas of investigation will address methods of preventing or ameliorating these adverse consequences. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this column.

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