Review Article

Emerging Therapies to Treat Frailty Syndrome in the Elderly

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Abstract

Frailty syndrome (FS) has become increasingly recognized as a major predictor of co-morbidities and mortality in older individuals. Interventions with the potential to benefit frail elders include nutritional supplementation (vitamins D, carotenoids, creatine, dehydroepiandrosterone (DHEA), and beta-hydroxy-beta-methylbutyrate) and exercise modalities (tai chi and cobblestone walking). While these have not been explicitly tested for their impact on FS, vitamin D supplementation appears to offer significant promise in enhancing long-term health of the elderly. Exercise modalities such as tai chi and cobblestone walking, because of probable low risk and ease of participation, may also confer benefit. Additional studies are needed to investigate interventions that directly prevent, delay, and/or ameliorate frailty. Successful therapies may well involve multi-component approaches utilizing a combination of medication, nutritional supplementation, and exercise. *(Altern Med Rev* 2007;12(3):246-258)

Introduction

Frailty syndrome (FS) has become increasingly recognized as a major concern for older individuals. While definitions of FS vary, most experts agree this syndrome is characterized by a reduced functional reserve and impaired adaptive capacity resulting from cumulative decline of multiple subsystems, and causes increased vulnerability leading to adverse outcomes. The most widely accepted criteria are those of Fried et al, who define FS as including three or more of the following: weakness, slow walking speed, self-reported exhaustion, low physical activity, and unintentional weight loss (Table 1).[1] A large survey of over 5,000 community-dwelling elderly, the Cardiovascular Health Study, determined that seven percent of those over age 65 and 30 percent of those ≥80 years demonstrate diagnostic criteria compatible with FS. The presence of FS is a predictor for hospitalization, disability, decreasing mobility, falls, and even death. Women are frailer than men, and the risk of death from frailty is independent of the presence of chronic disease.[2]

Pathophysiology and Risk Factors for FS

FS is believed to be the result of multiple pathological processes common among the elderly.[3] Aging induces changes in hormone cascades (menopause, andropause, somatopause, and adrenopause) and the immune system, modulating their efficiency and effectiveness in determining a response to stressors.

Nutritional Risk Factors

Several large epidemiological trials have elucidated potential nutritional risk factors. The Women's Health and Aging Studies I and II (WHAS) utilized the definition by Fried et al in identifying risk factors for FS in a cohort of 1,002 women in the Baltimore area in 1992.[4,5] Women with serum carotenoids (representative of intake of fruits and vegetables) in the lowest quartile (adjusted for age, smoking status, and chronic pulmonary disease) were at a slightly greater risk for frailty than

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Table 1. Criteria for Diagnosis of Frailty Syndrome: Three or More of the Following Symptoms[1]

Weakness
Slow walking speed
Self-reported exhaustion
Low level of physical activity
Unintentional weight loss

those in the higher quartiles (odds ratio (OR) 1.39; 95% confidence interval (CI) 1.1-1.92). The total number of nutritional deficiencies was also associated with frailty (OR 1.54; 95% CI 1.11-2.13). In addition to lower serum total carotenoid levels (p=0.006), frail women also demonstrated lower serum levels of alpha-tocopherol (p=0.06), 25-hydroxyvitamin D (p<0.0001), selenium (p<0.0001), and zinc (p=0.001). This study found no significant differences in folate or vitamins A, B6 or B12 between frail and nonfrail women.[4]

In a cross-sectional analysis of a subset of 754 women from WHAS I and II, risk of being frail was significantly greater in women in the lowest quartile for total carotenoids, alpha-tocopherol, 25-hydroxyvitamin D, and vitamin B6. The strongest association between nutrient deficiencies and frailty was demonstrated for total carotenoids, as well as the specific carotenoids beta-carotene and lutein/zeaxanthin (because the latter two occur together in nature, they were measured as a unit).[5]

The InCHIANTI study, which obtained data from 1,299 community-dwelling individuals ages 65 or older from two municipalities near Florence, Italy, observed that low energy intake (<21 kcal/kg, OR 1.24; 95% CI 1.02-1.5) as well as decreased intake of protein, vitamin D (OR 2.35; 95% CI 1.48-3.73), vitamin E (OR 2.15; 95% CI 1.34-1.45), vitamin C (OR 2.15; 95% CI 1.34-3.45), and folate (OR 1.84; 95% CI 1.14-2.98), and poor intake of three or more nutrients in general predicted frailty.[6] The InCHIANTI study did not include weight loss as a criterion for frailty and accepted the presence of only two of the other criteria (Table 1) to consider a subject "frail."

Pathophysiological Factors of FS: Inflammation, Anemia

Sarcopenia and inflammation are believed to be important in the pathophysiology of FS.[3,7,8] The InCHIANTI study noted more physical activity was associated with lower levels of biomarkers of inflammation including the cytokine interleukin-6 (IL-6).[9] The Health ABC study, a cohort study of the health and body composition of 3,075 older men and women, ages 70-79, also showed an inverse correlation between IL-6 and muscle mass and strength.[10]

WHAS identified anemia as a risk factor for frailty.[11] Frailty was observed in 14 percent of subjects, and hemoglobin below 13.5 g/dL was predictive of frailty (OR 1.9; 95% CI 1.1-3.4). These observations may be related to increased IL-6 levels,[12,13] as well as low folate levels and/or suppression of erythropoesis.[10,14]

While researchers are attempting to more precisely define FS and the contributing mechanisms, interventions to alleviate FS are being explored. Various complementary therapies may theoretically offer benefit to the elderly with FS. This article reviews the published medical literature on complementary therapies for FS and associated co-morbidities.

Nutritional Supplementation in the Treatment of FS

Vitamin D

Supplementation with vitamin D is a promising means to alleviate components of FS. Although the body manufactures vitamin D from the skin in the presence of sunlight, in order to synthesize adequate amounts an area of skin equal to that in the thorax or legs has to be exposed each day, until mild erythema results. This is probably difficult for most elderly individuals and virtually impossible at certain times of the year in high latitudes where sunlight is limited.[15] Darker skinned individuals require longer exposure to ultraviolet (UV) radiation, but will still produce similar amounts of vitamin D if mild sunburn is achieved. Given the lack of vitamin D provided by foods, oral supplements are necessary for most elderly individuals. Perhaps as much as 90 percent of all elderly have insufficient vitamin D levels, even those who dwell in parts of the world with greater sunlight exposure,[16-21] and blacks have a higher incidence than whites.[22]

The range of manifestations of bone disease caused by vitamin D insufficiency has been labeled hypovitaminosis D (HVD) osteopathy,[23,24] and is characterized by calcium malabsorption, bone remodeling, osteoporosis, and, in the most extreme cases, cessation of bone remodeling and the symptoms of rickets.[23] In a large epidemiological study of 1,271 independent, community-dwelling individuals in The Netherlands ages 65 or older, low vitamin D levels were associated with the presence of frailty (OR 2.04; 95% CI 1.01-4.13).[25] Frail elderly women in WHAS had a significantly lower mean serum 25-hydroxyvitamin D concentration (43.85 nmol/L) compared to nonfrail women (50.9 nmol/L).[5] Hypovitaminosis D was also identified as a strong predictor of frailty in the InCHIANTI study (OR 2.27; 95% CI 1.45-3.53).[6]

Vitamin D plus calcium improves balance, reduces falls, and lowers the risk of fractures,[26-28] which may lower the risk for reduced walking speed and inactivity. A single intramuscular dose of 600,000 IU ergocalciferol (vitamin D2) reduced postural sway in ambulatory subjects ages 65 and older with inadequate vitamin D levels (≤12 mcg/L).[26] Daily administration of 800 IU cholecalciferol (vitamin D3) and 1,000 mg calcium improved postural sway and quadriceps strength in 242 healthy elderly Germans.[29] An epidemiological study of 4,100 ambulatory persons ages 60 and older revealed those subjects who had vitamin D levels below 60 nmol/L needed more time to stand from a seated position and walked at a slower speed.[30] Higher levels of vitamin D predicted better performance on several neuromuscular performance tasks in a study of 1,300 older subjects.[31]

Some investigations have failed to identify a relationship between vitamin D and physical performance. When ambulatory elderly men were given a trial of 1,000 IU vitamin D daily, no change was observed in upper and lower extremity power and strength.[32] A review of multiple trials of different doses and preparations found no increase in muscle strength when vitamin D was supplemented.[33] It is possible the dose of vitamin D was inadequate to achieve gains in muscle strength or normalize serum vitamin D levels, the testing of muscle strength was not performed in muscle groups that respond to vitamin D supplementation, or the primary effect of vitamin D on physical performance improves balance rather than strength.

Vitamin D decreases the risk of falls even in individuals with sufficient dietary calcium.[27,28] The results of a meta-analysis revealed vitamin D supplementation resulted in a 22-percent lower risk of falls with a number needed to treat of 15.[27] Although supplementation with a vitamin D dose as low as 400 IU did not reduce falls, older individuals supplemented with either 700-800 IU[28] or 1,000 IU[34] exhibited a significantly lower risk of falling.

Many studies have also shown vitamin D protects against fractures. Supplementation with vitamin D in older, independently-living individuals resulted in a lowering of non-vertebral fracture risk by 10-30 percent.[35,36] Daily administration of 800 IU cholecalciferol to 583 institutionalized but ambulatory older women lowered the rate of hip fractures by 40 percent over two years.[37] Three thousand elderly individuals (mean age 84) treated with 800 IU vitamin D daily for 1.5 years demonstrated a 32-percent decrease in non-vertebral fractures and a 43-percent decrease in hip fracture rate.[38] Supplementation with 700 IU vitamin D daily over three years decreased vertebral fractures by 68 percent.[35] A meta-analysis of the effect of vitamin D indicated that 800 IU, but not 400 IU, lowered fracture risk.[39]

Not all studies have confirmed a reduced fracture risk with vitamin D supplementation. A total of 8,000 elderly individuals in two studies were supplemented with 800 IU vitamin D and 1,000 mg calcium daily or an informational leaflet on dietary calcium (control group),[40] or in a double-blind, placebo-controlled fashion were assigned to one of four treatment groups: (1) 1,000 mg calcium, (2) 800 IU vitamin D, (3) both, or (4) double placebo.[41] In the first study, after 18-42 months the fracture rate was not significantly lower in the treatment group, although both groups demonstrated a lower than expected fracture rate.[40] In the second study, after 24-62 months there were no significant differences in fracture rates among the four groups.[41] It should be noted, however, that compliance rates were rather low – approximately 55 percent in both studies – and vitamin D levels were not tested in the majority of subjects. Therefore, supplementation too low to normalize serum vitamin D levels might account for the different findings.

Vitamin D is involved in the pathology of multiple processes in addition to those involving musculature and bone. Epidemiological studies suggest a number of cancer types are more prevalent at high latitudes that afford less sunlight exposure and subsequently less vitamin D production.[42-45] Low vitamin D levels have been correlated with increased incidence of cancer of the breast, colon, rectum, bladder, esophagus, prostate, ovary, gall bladder, uterus, mouth, larynx, and hematopoietic system.[42-45]

Vitamin D has also been implicated in the development of inflammation, sarcopenia, low HDL cholesterol, hypertension, diabetes, and cardiovascular disease.[46,47] Furthermore, serum 25-hydroxyvitamin D levels are positively correlated with improved insulin sensitivity,[46] and increased insulin resistance has been correlated with low serum vitamin D levels.[48]

Improving patient physical activity and strength will likely reduce falls and fractures. Further prospective studies are needed to demonstrate that supplementation with vitamin D directly prevents frailty. To achieve many of the potential health benefits, individuals need to consume more vitamin D than is currently recommended. The U.S. Food and Drug Administration advises 400 IU daily for those ages 51-70, and 600 IU for those over age 70, while the National Osteoporosis Foundation suggests 800-1,000 IU daily. Numerous investigations, however, indicate an optimal protective effect is achieved with serum concentration of 25-hydroxyvitamin D greater than 75 nmol/L.[49] Heaney calculated that ingestion of 2,900 IU daily would achieve this level in 97 percent of the population, but more may be necessary for the elderly.[50] Investigations using doses up to 5,000 IU daily were found to be safe in a population of vulnerable elderly persons.[51,52] Except in persons with primary hyperparathyroidism, individuals can consume as much as 10,000 IU without experiencing toxicity.[53]

Carotenoids

Carotenoids, pigmented organic compounds found in fruits and vegetables, are believed to act as antioxidants.[54] The WHAS study demonstrated significantly lower mean serum carotenoid concentrations in frail (1.376 µmol/L) versus non-frail (1.842 µmol/L) ($p<.001$) older women.[5] Subjects in the highest quartile of plasma carotenoid levels were at lower risk of diminished grip strength (OR 0.34; 95% CI 0.2-0.59), hip flexion (OR 0.28; 95% CI 0.16-0.48), and knee extension (OR 0.45; 95% CI 0.27-0.45).[54] In addition, carotenoids and IL-6 levels exhibited an inverse relationship in the WHAS trial.[55] Low levels of carotenoids were also associated with decreased walking speed and decreased hip, knee, and grip strength in the InCHIANTI study.[56] However, prospective trials using carotenoids to improve physical performance have yet to be performed.

Creatine

Creatine is an amino acid that is a substrate of the enzyme creatine kinase, which helps re-phosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP), and is found primarily in skeletal muscle.[57] Although it is produced endogenously, it can also be taken as a nutritional supplement. U.S. sales approached $200 million in 2003, accounting for 14 percent of all supplement sales that year.[58] Creatine has been evaluated in a number of studies for improvement of muscle strength in the elderly.

Twenty healthy men, ages 59-72 (mean age 65), were given 0.3 mg/kg creatine or placebo for seven days. Creatine supplementation increased fat-free mass by 2.22 kg, statistically significantly improved dynamic and isometric strength, increased lower-body mean power (the mean power of all muscle groups in the lower body) by 5-10 percent, and improved gait and balance.[59]

A group of 42 individuals (14 in each of three groups) comprised of young (mean age 26.0 ± 1.6 years) sedentary subjects, elderly (mean age 70.7 ± 1.7 years) sedentary subjects, or elderly (mean age 66.4 ± 1.9 years) trained cyclists were given either 5 g creatine or placebo for three days. Sedentary subjects who received creatine significantly improved maximal power and work as measured by cycle ergometry, while trained individuals did not experience such improvement.[60]

Several longer studies of creatine supplementation to healthy elderly individuals have shown improvements in muscle function that suggest potential for benefit in frail individuals. In one study, 20 healthy elderly men, ages 60-82 (mean age 67), took 20 g creatine daily for 10 days followed by 4 g daily for 20 days,

or a placebo.[61] Those who ingested creatine generated eight percent less peak torque during knee extensions ($p<0.05$), which means less rotational force is needed to perform the exercises. The benefits were maintained 10 days after discontinuing supplementation. In a second investigation, 28 men (mean age 67.8 ± 4.0 years) and women (mean age 69.3 ± 6.3 years) ingested 5 g creatine daily or a placebo for 14 weeks.[62] Subjects who took creatine had a significantly greater fat-free mass at the end of the trial, and the men in the creatine group exhibited greater dorsiflexor strength. Thirty healthy men (mean age 70) took creatine (0.3g/kg body weight loading dose for five days followed by 0.07g/kg) or placebo for four weeks in addition to a thrice-weekly exercise regimen of resistance training. Those who ingested creatine had a 3.3-kg increase in lean muscle mass compared to a 1.3-kg increase in the placebo group.[63] The average power in an isokinetic knee flexion/extension exercise of the individuals in the creatine group was one-third higher than placebo.

Not all studies of creatine have shown benefit. When 17 healthy men, ages 60-78 (mean age 65), were given 5 g creatine or placebo for five days, creatine supplementation did not enhance performance in knee extension exercises.[64] Limitations of the study include relatively low exercise efforts and the short duration of the trial. In another study of 32 men and women (ages 67-80), subjects were divided into four groups: creatine (20 g for five days followed by 3 g for the remainder of eight weeks), exercise, both, or neither (control).[65] Creatine supplementation, exercise, or both together resulted in no improvement in body mass, strength, or exercise endurance compared to control.

No increased adverse events from creatine were reported in any of the studies. Further studies need to be conducted to determine long-term safety, especially in the case of renal insufficiency and tolerability by frail individuals. Current studies by the National Cancer Institute and the National Center for Complementary and Alternative Medicine are examining a potential role for creatine in correcting weight loss and reduction of muscle strength associated with cancer, Huntington's disease, and amyotrophic lateral sclerosis.[66]

Dehydroepiandrosterone (DHEA)

DHEA is an endogenous steroid precursor to testosterone and estrogen. Its exact function is unknown, but trials of oral supplements have been conducted as a treatment for cardiovascular and neuropsychiatric disorders, diabetes, adrenal insufficiency, cancer, and systemic lupus erythematosis.[67] DHEA deficiency is also suspected to be involved in the development of sarcopenia in FS.[3] DHEA levels decline with age, and epidemiological data have shown a correlation between DHEA levels and muscle strength and mass in men ages 60-79.[68] In an epidemiological study of 684 men ages 55-85, DHEA levels correlated with physical performance on a seven-item test.[69] DHEA may be a marker for health status.[70]

DHEA may be beneficial for conditions associated with aging. In one randomized, double-blind, placebo-controlled trial, 36 subjects (ages 40-70) took 50 mg DHEA daily or placebo for six months. Those in the DHEA group reported significant improvements on psychological scales of well-being compared to those receiving placebo.[71] In a subsequent randomized, double-blinded, placebo-controlled investigation, 19 subjects (ages 50-65) took 100 mg DHEA or placebo for six months. Men who received DHEA experienced a 6.1-percent increase in knee strength ($p=0.02$) and a 13.9-percent increase in lumbar back strength without an increase in muscle mass ($p=0.01$), while women demonstrated an average 1.4-kg increase in total body mass without an increase in muscle strength.[72]

Several subsequent trials, however, failed to demonstrate benefits in the elderly. A nine-month, double-blind, placebo-controlled trial of 100 mg DHEA or placebo daily in 40 healthy elderly men (ages 60-84) and a three-month, double-blind, crossover trial of 50 mg DHEA or placebo daily in 12 men (mean age 59) found no changes in blood chemistries, lipids, insulin, body fat, or self-reported indices of well-being.[73,74] During a one-year trial, supplementation with 50 mg DHEA in older men and women (ages 60-80) did not alter muscle strength, fat, or body mass.[75] Supplementation with DHEA to 87 men and 57 women (ages 65-74) with low levels of DHEA resulted in no improvement in muscle strength, oxygen consumption, insulin sensitivity, or quality of life in either group. In this study, supplementation with DHEA slightly but statistically significantly increased bone mineral density in women.[76] The

Women's Health and Aging Study found an association between both low and high DHEAS levels and mortality – with higher mortality rates from cardiovascular disease noted in the lowest quartile (representing those with the lowest levels of DHEA) and higher cancer mortality rates in the highest quartile (each compared to the third quartile).[77]

Other Supplements – Organic Acids and Amino Acids

Other supplements are popularly used by athletes to attempt to build muscle mass and strength. Potentially, these might reverse the sarcopenia and weakness that occur in FS.

Beta-hydroxy-beta-methylbutyrate, a metabolite of the amino acid leucine, was supplemented at a dose of 3 g daily in a placebo-controlled trial of 30 elderly individuals (mean age 70) for eight weeks.[78] Individuals receiving the supplement lost more body fat (0.63%; p=0.05) than those who received a placebo of rice flour.[78] All subjects participated in an exercise program including weight training, walking, and stretching.

Fifty older adults (mean age 76.7) were supplemented with a combination of beta-hydroxy-beta-methylbutyrate and the amino acids arginine and lysine or placebo for 12 weeks. Those who took the supplement demonstrated increased handgrip and leg strength, limb circumference, and improvement in a "get-up-and-go test" (time to get up from a chair, walk 10 feet, turn around, and sit down again).[79] A randomized, controlled trial of a mixture of beta-hydroxy-beta-methylbutyrate and the amino acids glutamine and arginine failed to reverse cachexia in patients with rheumatoid arthritis.[80]

In a study of amino acid supplementation, elderly men over age 65 undergoing a 12-week resistance muscle-training program demonstrated no additional increase in isokinetic muscle strength beyond that observed with placebo, with the addition of a nutritional supplement containing 12 g daily of eight amino acids (L-lysine, L-leucine, L-valine, L-phenylalanine, L-threonine, L-histidine, L-isoleucine, and L-methionine) and 72 g fructose and dextrose.[81]

Physical Activity for FS

Tai chi

Tai chi exercise has been used in China for hundreds of years and consists of a number of stylized movements in which practitioners continuously change posture; sessions last from 10 minutes to an hour. There are several different forms of tai chi – movements may be long or short, fast or slow, etc.

Tai chi might directly or indirectly address three components of FS – weakness, slow walking speed, and low physical activity. By improving strength and balance, it provides potential benefit for those with reduced ambulatory capacity or a tendency to fall.

While a growing body of literature has suggested tai chi confers many health benefits, including greater balance and reduced falls, there are serious limitations to the studies, including small numbers of subjects, differing outcome measures, and lack of blinding, appropriate controls, standardization of tai chi exercise, and measurements of compliance.

Tai chi has been utilized as part of a more comprehensive exercise program in older individuals to maintain strength and balance and prevent falls.[82-84] In these studies, tai chi intervention preserved improved postural sway[85] and balance,[84] but did not prevent falls.[82]

In several studies, balance was tested by comparing experienced elderly tai chi practitioners recruited from tai chi clubs to individuals who did not perform tai chi. The mean ages of the tai chi practitioners were 67-71 (exercise experience ranged from 1-35 years) and the mean ages of the sedentary elderly control subjects were 66-69. In each of these studies, tai chi practitioners demonstrated improved balance measured by posturography (subjects stand on a computerized forceplate that changes position and records changes in balance) or by unmechanized balance tests (e.g., subjects' time standing on one foot or ability to walk heel-to-toe).[86-91]

Hain et al examined 22 subjects who attended a balance clinic for self-reported "mild balance disorders" (diagnoses not specified).[92] Subjects, divided by age, participated for eight weeks in one-hour tai chi sessions of eight movements culled from several different tai chi schools. The nine subjects who were older than 76 (and those younger than 60) demonstrated improved posturography scores, but not improved symptom scale scores.

Other investigations have examined the potential of tai chi to augment strength and flexibility. Lan et al trained 38 healthy younger elderly individuals (ages 58-70) in one-hour tai chi sessions five times weekly for one year; the activity of the control group was undefined.[93] Tai chi practitioners demonstrated improved flexibility and knee extensor and flexor strength by 10 percent and oxygen consumption by approximately 20 percent compared to no change in the control group. Twenty-six healthy elderly individuals (mean age 71.9) engaged in 20 weeks of tai chi training or no exercise. Those who engaged in tai chi experienced a significant increase in maximum knee isometric extensor contraction.[94]

A population of community-dwelling elderly subjects (n=180) was randomized into three groups for 12 months: tai chi three times weekly, resistance training exercise consisting of 30 repetitions of several exercises three times weekly, or no intervention.[95] There was no benefit in muscle strength or balance in any group.

In another study, 213 older individuals (mean age 78) who had difficulty standing on one foot or walking in tandem participated in tai chi (one-hour sessions, three times weekly for 10 weeks) or a conventional balance and step-training program.[96] The conventional program yielded statistically significantly greater improvements in a timed get-up-and-go-test, maximal step length, and a rapid step test.

Wolf et al compared tai chi to computerized balance training in 200 independently living ambulatory individuals (≥70; mean age 75).[97] These subjects were part of a large National Institute of Aging study of interventions to reduce falls and frailty in the elderly (FICSIT). The tai chi used was a "synthesis of 108 forms into 10" taught in 15-week sessions lasting 45 minutes per week. Although subjects were asked to practice at least 15 minutes twice weekly, compliance was not verified. Tai chi reduced the relative risk of falls (RR=0.632; 95% CI=0.45-0.89) over four months and reduced fear of falling as measured by a survey instrument. Computerized balance training did not significantly affect falls in this group. However, when another group of subjects from the FICSIT trial who lived in a single assisted-living facility was given similar training, only those who received balance training noted improvement from baseline as measured by posturography.[98]

Sedentary but healthy elderly individuals (n=256; mean age 78) participated in a six-month intervention of either 30-minute tai chi sessions three times weekly or stretching exercises; a single traditional style of tai chi was practiced.[99,100] The individuals in the tai chi group experienced a 50-percent reduction in falls, fewer injuries, and significantly improved performance on several non-computerized tests of gait and balance (e.g., 50-foot walking speed, time-to-stand on one foot).

Wolf et al prescribed 48 weeks of tai chi or wellness education (one hour per week sessions of instruction about nutrition, fall prevention, mental health, and legal issues in aging) to 291 elderly subjects (ages 70-97; 90% women) who were "transitioning to frailty."[101,102] Transitioning to frailty was defined as three deficits in: vision, gait, balance, lower extremity strength, ability to walk or exercise, or presence of depression or lower extremity disability. Tai chi intervention significantly reduced subjects' fear of falling. Although there was no statistically significant difference in the rate of falls between the tai chi group and the wellness education group, there was a trend toward improvement in the tai chi group – 47.6 percent of individuals fell at least once compared to 60.3 percent in the education group.

Tai chi has also been used to treat aspects of specific disorders that might have relevance for FS. Fifteen patients with congestive heart failure (mean age 66) participated in an exercise program for one hour twice weekly for 12 weeks, using five maneuvers from a single tai chi style.[103] A control group received "usual care" without any formal exercise. Only tai chi practitioners demonstrated improved functional status rated by a questionnaire and improved six-minute walking distance.

Tai chi may benefit osteoarthritis, thus improving mobility in the elderly. In one trial, 72 individuals with osteoarthritis participated in a 12-week tai chi exercise program or placebo; the drop-out rate was 41 percent.[104] Those who completed the tai chi program exhibited statistically significant improvements in balance and scores on subjective indices of pain, stiffness, and physical function. Forty-one elderly subjects (mean age 70) with osteoarthritis completed either a tai-chi program of three 40-minute sessions weekly for six weeks followed by six weeks of home practice or six weeks of

Table 2. A Summary of the Most Promising Treatments for Frailty Syndrome

Treatment	Potential Uses to Treat Frailty	Studies in Elderly	RCTs* Showing Benefit in Elderly
Vitamin D	Improve Balance Increase Strength	✓	✓
Cartenoids	Improve walking speed Increase strength	✓	
Creatine	Increase strength		✓
DHEA	Increase strength	✓	
Beta-hydroxy-beta-methylbutyrate	Increase strength	✓	✓
Tai-chi	Improve balance Increase endurance	✓	✓
Cobblestone walking	Improve balance Increase activity	✓	✓
Other exercise	Improve balance Increase strength	✓	✓

*randomized, double-blinded, placebo-controlled clinical trials

health lectures.[85] The tai-chi participants reported statistically significant improvements in scores of pain, stiffness, and physical function, while the control group experienced no improvement.

Several studies have examined possible mechanisms for tai chi's effectiveness, demonstrating that it improves balance by altering the center of pressure of stance,[105] increasing strength, and decreasing body sway.[106]

Cobblestone Walking

Walking on cobblestone paths is a recreational activity in China. In one small, eight-week study, 40 elderly individuals in an intervention group walked on plastic mats that simulated cobblestones for three 45-minute sessions weekly; a control group attended four meetings of social interaction, discussions on health, and visits to a Chinese garden.[107] The intervention group demonstrated improvement in self-perception of mental and physical well-being and instrumental activities of daily living assessed by questionnaire.

In a larger study, 108 individuals (mean age 72) were randomized to one-hour sessions of walking on the plastic mats or ordinary walking (control group) three times weekly for four months. Those who engaged in cobblestone-walking simulation demonstrated a statistically significant improvement in ability to stand from a seated position compared to the control group.[108] The National Institute of Aging has funded research that explores the health benefits of cobblestone walking in the elderly.[66]

Additional Forms of Exercise

In sedentary older adults ages 70-80 and at risk for disability, Pahor et al recently demonstrated that comprehensive physical activity intervention improved performance in the Short Physical Performance Battery (SPPB) and the 400-meter walking speed test.[109] The intervention consisted of a combination of aerobic, strength, balance, and flexibility exercises that focused on walking and complemented the program with lower extremity strengthening exercises, followed by lower extremity stretching exercises. Perceived exertion assessed by the Borg scale[110] was used to regulate the intensity of the exercise, and the strengthening exercises were performed at a perceived exertion of 15-16. An intervention that improves the SPPB and walking speed offers the potential to reduce frailty and disability.

Progressive resistance training may also prove therapeutic for FS. A three-month trial of progressive resistance training three times weekly, plus exercises to improve flexibility, balance, and speed, enhanced knee extension strength more than a low intensity home exercise program in frail men and women ages 78 and older.[111] Total body fat-free mass increased in the intervention group, but not in the control group. In another study, progressive resistance training twice weekly for four months enhanced performance in both a timed get-up-and-go test and a timed 10-meter walk in subjects with a mean age of 77.[112] However, these improvements did not lead to better functional capacity.

Conclusion and Future Considerations

Several nutrients and exercise modalities hold promise for prevention or treatment of frailty syndrome (Table 2). Given its ability to reduce falls and fractures, vitamin D appears to offer potential in the prevention and treatment of frailty, particularly with regard to frailty components such as physical activity and walking speed. Vitamin D, however, has not yet been shown to increase muscle strength. While the actions of vitamin D on calcium regulation and bone are well-known, the exact mechanism by which vitamin D acts on muscle or the neuromuscular junction has yet to be established. The exact dosage needed in elderly individuals to achieve benefit also needs to be clarified. Elderly individuals probably need a dose of at least 2,000 IU daily, but some may need higher doses. In a study of 46 elderly men ages 70 and older, a dose of 2,000 IU daily for six months reduced the incidence of hypovitaminosis D (25-hydroxyvitamin D level <30 nmol/L) from 47 to 18 percent (Cherniack et al, unpublished data). While the majority responded to 2,000 IU daily, it is clear some individuals will require more in order to achieve serum levels of 25-hydroxyvitamin D ≥30 nmol/L. Two preliminary reports confirm that supplementation with 1,500 IU[51] and 5,000 IU[52] of cholecalciferol daily, while significantly raising 25-hydroxyvitamin D levels in the majority of subjects, still left 35 percent and 10 percent of subjects, respectively, with levels below 30 nmol/L. This may be due to a lower baseline serum vitamin D level and/or the presence of significant co-morbidities and/or frailty. The time of year studies are conducted also needs to be taken into account. An attempt to raise serum vitamin D levels throughout the winter will typically require higher dosages than supplementation commencing in spring or early summer. Additional studies are needed to more completely identify those requiring larger doses. These studies reinforce the need to assess 25-hydroxyvitamin D levels prior to supplementation and to reassess levels 2-3 months after initiating supplementation.

The potential utility of other nutritional supplements awaits larger, more complete trials in healthy and frail elderly individuals. Although creatine shows promise, it has only been studied in healthy subjects.

Exercise modalities (tai chi and cobblestone walking), because of probable low risk and ease of use, may confer benefit in the treatment of FS. Most have not been tested for FS and before this can be done appropriate control procedures need to be designed. Tai chi has been the most well-studied unconventional treatment to improve strength and flexibility, which might ultimately reduce physical inactivity and increase walking speed.

In order to confirm whether tai chi is an appropriate option, some important questions need to be answered. Is tai chi more effective for reducing fall risk and more easily learned by the elderly than conventional balance and strength training? Since elderly individuals with FS might have physical, cognitive, or sensory disabilities, would simplified tai chi exercises be more appropriate than complete tai chi training in classically practiced forms? Is tai chi more effective in reducing morbidity in elderly individuals who already have FS or better utilized to prevent frailty in healthy elderly? Thus far, the latter appears to be the case, but there is a paucity of studies in the frail elderly. Many of the same questions might be asked about the effect of other exercise modalities on endurance and balance in the elderly.

The pathogenesis of FS is complex and may be linked to alterations in cytokines, hormones, vitamins, free radical production, and genetics. While future interventions may be able to target specific genes, cytokines, and cell receptors, this review has focused on presently available interventions that show promise in ameliorating aspects of frailty syndrome. Given the wide range of unanswered questions regarding pathophysiology and treatment, and the looming increase in frail elders due to aging demographics, there is an increasing need for additional large-scale trials to augment care for elderly frail patients.

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