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Challenges and New Opportunities for Clinical Nutrition Interventions in the Aged[1–3]

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Abstract

Nutritional status plays a critical role in the prevention and management of many chronic health conditions that are common in the elderly and are likely to become more prevalent as the population ages. This paper highlights several aspects of nutrition that require additional basic science and clinical application research to improve the health and well-being of older adults. Topics addressed are selected demographic and health indices, the uncertain benefits of energy restriction in aged humans compared with other species, the impact of food insecurity on health, the relationship between dietary protein and sarcopenia, the prevention and management of obesity while maintaining muscle mass and functional status, and controversy regarding high intakes of folic acid. Research needs regarding the safety, efficacy, and application of clinical interventions related to these topics also are discussed. J. Nutr. 141: 535–541, 2011.

Introduction

The Aging 2010 symposium of the ASN at the Experimental Biology meeting in Anaheim, California, in April 2010 brought together experts to discuss research on this topic. This paper summarizes the research findings discussed and recommendations offered for future basic science and clinical application research.

Aging and nutrition in the U.S. population

Between 2010 and 2050, the number of people aged 65 y and older in the United States will more than double from 40 million to 88 million (1) and older Americans will become more ethnically and racially diverse. In 2010, 2.8 million Hispanics and 3.3 million blacks were older than 65 y of age, and in 2050, experts estimate that 17.5 million Hispanics and 9.9 million blacks will be older than 65 y (1).

Overall, 39.1% of older adults described their health as excellent or very good in 2008, but fewer blacks (25.1%) and Hispanics (28.0%) reported excellent or very good health than whites (41.8%) or Asians (35.2%) (2). In 2005–2006, >70% of adults aged 65 y and older had diagnosed diabetes, undiagnosed diabetes, or prediabetes (3) and in 2007–2008 the prevalence of obesity (BMI ≥ 30) in those aged 60 y and older was 37.1% in men and 33.6% in women; obesity was even more common in non-Hispanic black women (50.5%) and Hispanic women (46.7%) (4).

In 2008, 38% of older adults reported some type of disability, such as difficulty in hearing or cognition (2). Obesity, loss of strength and lean body mass, osteoporosis, and bone fractures contribute to disability in older adults and all of these factors are sensitive to nutritional status and physical activity (5). Older adults typically consume adequate amounts of protein (6), but protein intake appears to be inversely associated with loss of lean body mass in older adults (7).

In 2005–2006, ~26% percent of people aged 65–74 y but only 9% of those aged 85 y and over reported engaging in regular leisure-time physical activity (8). Older blacks (13.5%) and Hispanics (22.7%) were much less likely to be physically active than whites (22.7%) (8). About 13% of older adults participate in strengthening exercises that help maintain muscle and bone mass (8).

Adults over 65 y of age are frequently dietary supplement users, although the benefits and risks of some of them are uncertain, especially when intakes are very high, which increases the risk of exceeding the tolerable upper intake level for certain

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nutrients (9). In 2005, the dietary quality score, as measured by the Healthy Eating Index, was 68 of 100 points in those aged 65 y and over, suggesting that there was a good deal of room for improvement in eating habits (9). However, dietary quality in the older population may be deteriorating, because the prevalence of food insecurity markedly increased in 2008 across all age groups, including older adults (10).

Together, these demographic, health, and nutrition-related trends show a growing need for evidence-based nutrition interventions to prevent and manage chronic health conditions in older Americans.

Can energy restriction increase the human lifespan?

In the 1930s, researchers discovered that restricting caloric intake [generally called energy restriction (ER) or dietary restriction] while maintaining adequate micronutrient intake extended rats' lifespan (11). Since then, others have found that restricting calories by up to ~60% has a linear effect on maximum lifespan (12,13). More severe ER increases the lifespan of mice by 50%.

Researchers began investigating the possibility that ER could extend the lifespan of humans in the 1970s, and books began to be published in the 1980s and 1990s that promoted ER as a potential longevity therapeutic (14,15). Perhaps the greatest early advocate of ER for humans was Roy Walford, who studied immune system aging in the late 1960s and started to use ER himself in the late 1970s (R. Weindruch, personal communication, University of Wisconsin, Madison, WI) at about age 55 y. Walford died at age 79 in 2004 after 25 y of restricting his diet. ER's lack of success in its foremost proponent has not dented enthusiasm for it; in fact, several groups, such as the Caloric Restriction Society and the CRONies (caloric restriction with optimal nutrition), engage in voluntary ER.

The most widely cited reason why ER might extend the human lifespan is that it apparently extends the lifespan of a very wide variety of species, including *Caenorhabditis elegans*, *Drosophila melanogaster*, water striders, rotifers, spiders, mice, rats, dogs, and cows (14). Furthermore, ER retards age-related mortality in nonhuman primates (16). However, although ER's effects are widespread, they are not universal. In water striders and rotifers, for example, the effect depends on the species, and some species respond to ER by increasing their reproductive effort and consequently die sooner. Moreover, ER has no impact on the lifespan of houseflies (17). A recent study showed that lifespan increased as a result of ER in only ~40% of separate recombinant inbred mouse lines (18). This study has been criticized, because the animals were group housed (19), which may affect their individual experience of ER (18).

The "disposable soma" theory offers an explanation for this diversity of response to ER (20–22). According to this theory, ER extends the lifespan in some animals by causing them to "switch off" their reproductive functions and divert the saved energy to survival and somatic protection. Supporters of the disposable soma theory argue that ER is unlikely to have a substantial effect in primates, because their investment in reproduction is smaller than that of rodents (23). Indeed, the recently reported effect in nonhuman primates was only significant when the researchers considered age-related mortality. Furthermore, total mortality did not differ between ER and control animals (16).

Studies of ER in rodents have typically initiated ER at weaning; this could not be replicated in humans for ethical reasons. Researchers therefore wondered whether ER would have any benefit if it started later in life. Early studies of ER initiated later in life in mice and other species were promising, because both transcriptional profiles and instantaneous mortality estimates showed rapid onset (24–27). This finding prompted the suggestion that it is never too late to start an ER program (28). However, a review of rodent studies showed that ER's benefits decline with commencement age (13). Rather than it being never too late to start, it is the case that it is never too early to start and if the effect in rodents were translated to humans, starting ER at age 55 y would theoretically extend a person's lifespan by <1 y (13).

Persistent hunger is probably the most challenging aspect of sustaining ER for protracted periods. Studies of brain neuropeptides linked to feeding behavior strongly suggest that mice undergoing ER are perpetually hungry and this hunger does not abate with time (29). Indeed, persistent hunger is one of the biggest downsides of ER listed on the Calorie Restriction Society's Web site, along with loss of libido and feeling cold (people undergoing ER have a reduced body temperature) (30). Research has not determined whether people undergoing ER could reduce their hunger by taking appetite-suppressing drugs. Specifically, researchers have not determined whether centrally acting appetite suppressors, such as sibutramine (including Meridia and Reductil), would stifle the neuropeptide profile that develops under ER and might play a key role in initiating a response. Without the experience of hunger, longevity might not increase.

Studies of the molecular mechanisms underpinning ER point to a common mechanism across widely divergent species (31). For example, physiological and behavioral responses (e.g. in physical activity and resting metabolism changes) are remarkably similar between mice and humans (30,32), providing hope that ER might produce similar molecular responses in humans and other species.

However, although the pathways that are activated and the behavioral and physiological responses are similar in humans and other species, certain aspects of the responses are different. A key question therefore is whether the most important features are those that are common or those that differ in different species. At present, the answer to this question remains uncertain. Therefore, whether ER extends life in humans and the magnitude of this potential effect also remain unclear, and clinicians should bear this in mind in providing advice to patients who ask about it. For many individuals, the hardships of maintaining a ER lifestyle are too great to justify the potential life-extension benefits, although the improved health profile that ER can create may be an even more important driver. Nevertheless, the discovery of drugs that may mimic the ER response in people who do not reduce their dietary intake, so-called ER mimetics (33–35), may prove far more attractive than ER. Recent progress in this context is encouraging (36–40).

Key questions for future investigation of ER include: Is the response to ER dependent on the pathogen-free environment in which many laboratory animals are maintained? Will the same responses be expected in free-living humans continually exposed to pathogen challenges? What is the basis of the genetic differences between recombinant inbred lines that lead to the diversity in ER responses? Will ER be advantageous in some human individuals with a favorable profile, but actually be disadvantageous in others? To what extent is the continued experience of hunger an integral part of the ER program initiation and maintenance? If humans take drugs that will suppress hunger, will they also lose the ER benefits?

Food insecurity in older adults

Food insecurity is defined as "the limited or uncertain availability of nutritionally adequate and safe foods or limited or uncertain ability to acquire acceptable foods in socially acceptable ways" (41). In 2008, food insecurity levels were the highest they

had been in 14 y; ~4 million adults aged 60 y and older and >8% of households with older adults had experienced food insecurity (10).

Nationally, the prevalence of food insecurity is markedly higher in specific subgroups of the older population such as in older blacks compared with whites (16.66 vs. 4.40%), older Hispanic compared with non-Hispanic (13.26 vs. 5.19%), older food stamp recipients compared with nonrecipients (40.14 vs. 4.51%), and older adults with grandchildren in the house compared with no grandchildren in the house (15.39 vs. 5.19%) (42).

The prevalence of food insecurity is also likely to be very high among older adults receiving or requesting congregate meals, home-delivered meals, and other community-based services (43). For example, in Georgia in 2007–2008, the prevalence of food insecurity among those receiving congregate meals was 19% (44), but it was 59% among those who were waitlisted for home-delivered meals (45). Also in Georgia, weight-related disability and abdominal obesity were each independently associated with an ~1-fold increase in the prevalence of food insecurity, suggesting that a food insecurity-obesity paradox exists in that food insecurity occurs even among obese older persons (44).

Research is needed to explain why food insecurity has been associated with both obesity (44) and poor quality diets that were reported to be low in energy, protein, vitamin C, and calcium (46) and other nutrients (47). Food insecurity in middle-aged and older adults is associated with increased health care use, including more clinical and phone contacts with physicians (48) and a higher number of comorbidities among those admitted to the emergency room (49). Among respondents aged 18–65 y in NHANES 1994–2004, the prevalence of hypertension was 21% higher, diabetes was 51% higher, and poor management of diabetes was 39% higher among those with food insecurity than those without food insecurity when the investigators controlled for age, sex, and race or ethnicity (50). Among Puerto Ricans aged 45–75 y, food insecurity was associated with a higher prevalence of depression and of poor cognition (51). Among older adults receiving or on waiting lists for congregate and/or home-delivered meals in Georgia, those who were food insecure were 3 times more likely to have poor medication management practices (52).

The 2006 amendments to the Older Americans Act emphasized that food and nutrition assistance programs, such as the congregate and home-delivered meals programs, should reduce food insecurity (53). Thus, food insecurity should be assessed, preferably using validated measures such as the Household Food Security Survey Module (10,43,44,54), and monitored along with other nutritional, clinical, physical, and mental health outcomes.

Food insecurity in older adults is a relatively new research area. Evidence to date strongly suggests that food insecurity is a clinically relevant nutritional problem because of its association with obesity, physical and mental health problems, healthcare use, chronic disease management, medication management, and poor food and nutrition intake. Key questions that warrant further investigation include (43): What is the best way to measure food insecurity in older adult subgroups in various community and clinical settings? How can food insecurity best be used as a measure of the need for and impact of food and nutrition assistance programs? Do adults have unique risk factors for food insecurity, such as functional and mobility limitations, obesity, and specific physical and mental health problems? What is the cost of food insecurity related to adverse health outcomes, poor disease and medication management, and medical expenditures? Could additional and better approaches improve healthy food choices among those with limited income and other resources such as access to food and transportation? How can the availability, accessibility, and affordability of healthful foods be improved in the diverse social, economic, and geographic settings across the country where older adults live? And finally, how can healthcare providers and the aging services network improve their advocacy efforts to make eradication of food insecurity and hunger a priority?

Obesity in older adults

The prevalence of obesity is growing among older persons in the United States and expenditures for outpatient services and pharmaceuticals in 2008 for each obese Medicare beneficiary totaled more than $600/y more than for nonobese beneficiaries (55). Disability and costs associated with obesity will likely increase in the future, because of the high prevalence of obesity in upcoming cohorts of adults in their 50s (56).

A recent review of research related to interventions for obesity in older adults found that the comorbidities associated with obesity contribute to functional decline and the pathogenesis of disability. However, these outcomes could also be associated with an obesity-associated bodily inflammatory milieu, sarcopenia (loss of lean body mass), and impairment of muscle function and strength (57).

Sarcopenic obesity is defined as muscle loss in the setting of obesity and is common among obese persons who are older or have severe disease burden or injury (57). Critical factors in the development of sarcopenic obesity likely include inflammation-mediated muscle mass mobilization and a vicious cycle of progressive physical inactivity with increased adiposity and an accumulating disease burden (57). Sarcopenic obesity has adverse effects not only on health but also on muscle quality, thus reducing strength and function, making sarcopenic obesity clinically relevant and raising important opportunities for new therapeutic interventions (57).

Recommendations for volitional weight reduction interventions for obese older persons are controversial (57), because, among other reasons, nonvolitional weight loss is associated with adverse outcomes in aging populations (58) and with underlying disease or inflammatory conditions. However, these factors might not be associated with deliberate (volitional) weight loss. Also, overweight and mild obesity status (BMI 25.0–34.9), but not severe obesity (BMI $\geq$ 35) may be associated with reduced mortality risk among older persons (59). In addition, healthcare providers are concerned about the potential for undesirable losses of muscle and bone mineral during weight reduction interventions (57). However, exercise and supplementation interventions have the potential to attenuate these losses (57).

The ASN and North American Association for the Study of Obesity (now the Obesity Society) (60) position statement and the NIH guidelines (61) recommend that healthcare providers consider weight reduction in obese older people but in a manner that minimizes muscle and bone losses and only after careful evaluation of potential risks and benefits for each patient. Some obese patients may achieve positive metabolic and functional outcomes through a combination of a prudent diet, behavior modification, and exercise. However, for the very frail and obese older person, a better approach might consist of interventions that preserve strength and flexibility rather than reduce weight. Among the priorities for screening older populations and for planning, implementing, and evaluating services for homebound older persons, obesity and its associated concerns must be considered.

Research is needed on obesity's impact on function in older adults to inform the development and implementation of appropriate prevention and treatment strategies. In the past 2 decades, important research advances have been made, but the following key questions continue to warrant further investiga-

tion (57): Which obese older persons should try to lose weight? Which prudent diet, behavior modification, and exercise programs are appropriate for which older patients? What degree of weight loss is appropriate for which older patients? Could we improve existing approaches to preserving muscle and bone mineral levels during weight reduction? For which patients is an emphasis on strength and flexibility rather than weight loss the best option? Could some antiinflammatory, resistance-training, hormonal, or other interventions help prevent or treat sarcopenic obesity? Can aging persons maintain the benefits of weight reduction and avoid its adverse effects?

Interventions for sarcopenia: targeting protein intake and nutritive flow

Sarcopenia is a major contributor to physical frailty in older adults, with a prevalence of between 5 and 50% in adults aged 60 y and older, depending upon age and the methodology used to define sarcopenia (62,63).

Sarcopenia is a complex condition that is probably caused by a variety of biological and lifestyle factors, including nutrition (64–66). A recent report from the Health ABC study stated that muscle loss in older adults is negatively associated with protein intake after the authors adjusted for many other variables, including energy intake (7). The study showed that as protein intake declined, muscle loss increased (7). Interestingly, this correlation occurs in older adults eating, on average, more than the RDA who are thus not protein malnourished. Protein requirements could therefore be higher for older adults than for younger people.

Studies in animals and humans have demonstrated that aging induces anabolic resistance in muscle proteins to feeding (67,68). Although younger people respond to mixed feeding with a robust increase in muscle protein synthesis and net anabolism, the response to feeding in older participants is blunted.

One reason for this finding is that older adults appear to be resistant to the anabolic effect of amino acids at low doses (69). This may lead to the inefficient use of amino acids following meals that contain moderate amounts of protein. As a result, older persons may never use some of their daily protein for anabolic processes, thereby triggering an increase in total protein requirements. However, adding leucine, an important regulator of muscle protein synthesis, to low-amino acid doses restores an adequate muscle protein synthetic response (70). Overall, an adequate protein dose (e.g. in a meal) for older adults includes ~3 g of leucine (70), which corresponds to 30 g of a high-quality protein (71).

Another reason why muscle protein synthesis and net anabolism does not increase in response to feeding in older people is that insulin's anabolic effect on skeletal muscle proteins is significantly blunted in this population (72,73). Recent data indicate that the insulin resistance of muscle proteins that increases with aging is mechanistically associated with endothelial dysfunction and reduced anabolic signaling (74,75). In fact, this insulin resistance can be recreated in young healthy adults by blocking the insulin-induced physiological vasodilation with N(G)-monomethyl-*l*-arginine, an NO synthase inhibitor (74). Blocking the insulin-induced physiological vasodilation with N(G)-monomethyl-*l*-arginine, in turn, reduces muscle perfusion and nutritive flow and these effects are accompanied by blunted anabolic signaling and protein synthesis. Conversely, interventions that improve endothelial function and nutritive flow, such as aerobic exercise (75), and pharmacological vasodilation can restore the normal muscle protein anabolic response to insulin and to mixed feeding in older adults.

In conclusion, sarcopenia is a highly prevalent condition in older populations and a significant contributor to frailty, disability, and morbidity. Nutritional interventions involving amino acid or protein supplementation, possibly combined with a pulsed, balanced distribution of daily protein requirements, can help prevent and treat sarcopenia. In addition, interventions that enhance insulin sensitivity and muscle perfusion may benefit older adults with or at risk of sarcopenia, because these interventions improve the muscles' ability to maximally use nutrients and respond to anabolic stimulation. Clinical trials are necessary to test the effectiveness of these interventions in reducing the loss of muscle mass and function in older adults.

Does folic acid impair vitamin B-12 status in older adults?

The U.S. and Canadian governments began requiring manufacturers to fortify cereals and grains with folic acid in 1998 to reduce the incidence of neural tube defects. Folic acid fortification has been highly successful in reducing neural tube defects, the incidence of which has decreased by 19–40% in the United States (76–78) and to an even greater extent in certain Canadian provinces (79). In addition, the prevalence of folate deficiency (as measured by low plasma or RBC folate levels) has decreased from >20% to ~1% in the general U.S. population (80), and the prevalence of hyperhomocysteinemia has decreased by ~50% (79). More than 50 countries and territories, but not the countries of the European Union, have now instituted folic acid fortification programs.

Despite the success of folic acid fortification, questions have arisen about its safety (81). Research shows, e.g., that excess folic acid intake may promote the proliferation of neoplasias (82); interfere with antifolate medications used to treat cancer, epilepsy, malaria, psoriasis, and rheumatoid arthritis (83); and inhibit NK cell activity, an important component of immune defenses (84). In addition, excess folic acid may exacerbate vitamin B-12 deficiency, which is of particular concern to older adults, because the condition is more common among them than in other population groups.

Since the 1940s and 1950s, experts have known that folic acid therapy reverses macrocytic anemia due to vitamin B-12 deficiency. However, folic acid does not protect against, and in fact may exacerbate, the neurological manifestations of vitamin B-12 deficiency (85). Moreover, the effect of folic acid on macrocytic anemia is often suboptimal and only temporary.

Post-folic acid fortification epidemiological data support these clinical observations. For example, Morris et al. (86) found in a cross-sectional analysis of NHANES (1999–2002) data that older adults (aged 60 y or older) with low serum vitamin B-12 levels (<148 pmol/L) and high serum folate levels (>59 nmol/L) had higher OR for both anemia [3.1 (95% CI = 1.5, 6.6)] and cognitive impairment [2.6 (95% CI = 1.1, 6.1)] than those with low vitamin B-12 and low folate levels. A follow-up study by Selhub et al. (87) found that the combination of low vitamin B-12 and high folate levels was also associated with the highest circulating homocysteine and methylmalonic acid concentrations. Miller et al. confirmed this observation in a cohort of Hispanic elderly people (88) and this study also showed that low vitamin B-12 and high folate levels were associated with the lowest concentrations of holotranscobalamin, an emerging sensitive indicator of vitamin B-12 status. According to a report from India, in utero exposure to low vitamin B-12 and high folate levels is associated with an increased risk of glucose intolerance and excess adiposity in childhood (89).

Importantly, researchers have not identified the mechanism by which folic acid exacerbates vitamin B-12 deficiency. One hypothesis is that folic acid causes the oxidation and consequent

inactivation of intracellular vitamin B-12 (87), although no experimental evidence supports this possibility. However, research has documented a similar occurrence: the anesthetic gas, nitrous oxide, irreversibly oxidizes vitamin B-12, precipitating vitamin B-12 deficiency (90). Alternatively, Berry et al. (91) have proposed that when population cohorts are divided into groups based on low and high vitamin B-12 and folate levels, cohorts with the most severe vitamin B-12 deficiency are in the low vitamin B-12/high folate group. Thus, the apparent association between clinical and metabolic manifestations of vitamin B-12 deficiency and low vitamin B-12 and high folate levels may be coincidental.

These observations point to an ethical quandary: how should clinicians and public health professionals weigh the clear benefit of folic acid fortification in protecting against neural tube defects against the possible negative effects on cancer progression, antifolate drug efficacy, immune function, and vitamin B-12 deficiency? These professionals should take into consideration the fact that the data supporting these negative effects come from association studies that cannot prove causality. Therefore, a high priority for research is to rigorously test the hypotheses generated by the epidemiological studies to determine whether excess folic acid intake does indeed have negative effects, particularly in older adults.

In the meantime, 1 author (J.W.M.) thinks that prudence and caution should spur government agencies that have instituted or are considering folic acid fortification to carry out cost-benefit analyses within their own populations to determine whether the potential benefits outweigh the risks throughout life, including older adults.

Summary and conclusions

ER, food insecurity, obesity management in older adults, the relationship between protein levels and sarcopenia, and questions about folic acid supplementation in older adults are all related to nutrition and healthy aging.

Recent research suggests that the health and life expectancy benefits of ER in older adults are uncertain, so continued investigations are needed to clarify these issues. Food insecurity is a growing concern among older adults; is associated with numerous nutritional, physical, and mental health problems; and apparently cannot be prevented by current national food and nutrition assistance programs. Thus, research is needed to identify the predictors, consequences, and interventions that will reduce food insecurity in older adults.

Obesity is common in older adults and often presents in this population as sarcopenic obesity, which is often accompanied by functional limitations. Research is needed to determine the profile of obese older adults most likely to benefit from weight reduction; the characteristics of the most effective weight-loss interventions in older adults; and the role of antiinflammatory, resistance training, hormonal, dietary, and other interventions in the prevention or treatment of sarcopenic obesity. Sarcopenia is a major contributor to frailty in older adults and may be related to low protein intake, physical inactivity, and age-related anabolic resistance of muscle proteins to feeding. Thus, more research is critical to more clearly define the types and quantities of proteins and amino acids that could reduce sarcopenia in older adults

Although folic acid is known to prevent neural tube defects and other birth defects during early development, the benefits and risks of high folic acid intakes in older adults remain uncertain, so continued research is needed to further evaluate the risks and benefits throughout the lifecycle. Research is needed to balance public health and individual clinical approaches to preventing and managing obesity-related disorders and micronutrient status across the lifespan in our aging society.

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