**Nutrition Therapy in Aging: Emerging Approaches to Support the Mind and Muscle**

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Running Head: Nutritional Therapies for the Aging Mind and Muscle

**Abstract**

This narrative review highlights recent advances and ongoing trials using nutrition approaches for healthy aging. Focus will be placed on nutrition therapies that target cognition (“the mind”) and mobility (“the muscle”), both critical components to quality of life in older adults. For the mind, two seemingly incongruent therapies are being investigated to improve cognition – the MIND diet (high in carbohydrates and anti-oxidant fruits and vegetables) and the ketogenic diet (low in carbohydrates, high in fats). For the muscle, a focus on protein and energy intake has dominated the literature, yet a recent clinical trial supports the use of whole-grains as a tool to improve whole-body protein turnover – a primary regulator of lean body mass and muscle. Finally, emerging data and clinical trials on caloric restriction have solidified this strategy as the only nutritional approach to slow intrinsic factors of whole-body aging, which may positively impact both the mind and the muscle.

**Keywords:** Medical nutrition therapy, ~~aging~~, ketogenic, ~~MIND~~

**INTRODUCTION**

The world population is rapidly approaching a new era, where older adults (age 65+ years) outnumber children. This unprecedented global demographic shift is anticipated to occur by 2034 (1). With an ever-growing aging population, the health needs of older adults are at the forefront of research interest. Aging is an inevitable and multifactorial process that culminates in a progressive loss of physiological function (2). Aging presents with impairments of two critical functions that contribute to the loss of independence, reduction of quality of life (3) and increased mortality risk (4): cognition (“the mind”) and physical function (“the muscle”). Loss of cognition ranges from short-term memory deficits to advanced dementia, processes which may be accelerated by sub-optimal nutrition intake (5). Similarly, muscle mass declines at about 8% per decade after age 40 years and accelerates to ~15% per decade after age 70 years resulting in profound loss of both muscle mass and strength (6), again accelerated by sub-optimal nutrition intake (7). This mini-review will focus on the emerging nutritional approaches that have potential to prevent or reverse the decline in cognitive (“the mind”) and physical function (“the muscle”) with aging.

**THE MIND**

Cognitive function plays a critical role in normal daily function and is imperative to maintain healthy aging. Components of cognitive function include attention, memory, verbal fluency, abstract reasoning and visuospatial skills (8). Loss of cognitive function is not only associated with reduced quality of life, but also increases the risk for development of Alzheimer’s disease (9) or other dementias (10). Therefore, maintaining cognitive function throughout aging is of utmost importance for the health and wellness of older adults. Emerging evidence suggests two distinct nutrition therapies may support cognitive function: the MIND diet and the ketogenic diet.

*The MIND Diet*

The MIND Diet was developed by Dr. Martha Clare Morris and colleagues out of Rush University Medical Center in Chicago, IL (11). It incorporates neuroprotective dietary components from two diets associated with better cognitive function in older adults (12): the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets (13). Thus, the MIND diet acronym stands for **M**editerranean-DASH Diet **I**ntervention for **N**eurodegenerative **D**elay. The diet was developed from the data of a unique longitudinal population study, the Chicago Health and Aging Project (14). The MIND diet places a focus on plant-based foods, fish and poultry, while minimizing saturated fats and added sugars. Similar to other healthy dietary patterns, it is high in carbohydrates and moderate in proteins and fats. A typical MIND diet would include daily green leafy vegetables and whole-grains along with protein foods such as fish and poultry. Unique to the MIND diet is an additional emphasis on berries, recommending 2 or more servings per week, nuts (5 or more servings per week), and beans (4 or more servings per week). Foods recommended to consume sparingly include high saturated fat or high sugar items such as red meats, butter, cheese, refined grains, and fried foods.

Epidemiological studies have identified that several dietary patterns are associated with protection from cognitive decline or dementia, including the DASH and Mediterranean diets (15, 16). One critical study that followed these large-scale associations was conducted by Morris et al. as part of the Rush Memory and Aging Project, which investigated whether the MIND diet was protective against cognitive decline or dementia. This study recruited over 1,500 volunteers from retirement communities and senior public housing and followed them for 4.5 years on average. Participants underwent annual neurological exams, which included cognitive tests and assessment for Alzheimer’s disease, and reported their diets through food frequency questionnaires. This study showed that adherence to either the DASH, Mediterranean, or MIND diets provides cognitive protection. Importantly, only a *modest* adherence to the MIND diet may provide significant cognitive protection, whereas a *high* adherence was required for either the DASH or Mediterranean diets to confer the same protection (17). Since its development, many trials have been conducted on the MIND diet and its role in cognitive health. A recent systemic review corroborated the benefits of the MIND diet on cognition, reporting that the MIND diet was positively associated with cognition and global cognitive function, specifically in older adults (18). It further reported that the MIND diet outperformed other diets such as the DASH, Mediterranean and other plant-based diets. Taken together, the MIND diet is consistently associated with cognitive health and in older adults may be superior to other similar dietary patterns.

The biological mechanisms underlying cognitive decline and Alzheimer’s disease remain unclear, and therefore effective pharmacologic interventions are lacking (19). While the link between the MIND diet and improved cognitive health is not fully understood, information from pre-clinical studies, epidemiologic associations and our understanding of human physiology have led to hypotheses for nutrition-related mechanisms. Primary nutrition factors include antioxidants, B vitamins and omega-3 fatty acids (reviewed in (20)). Oxidative stress is a pillar of physiologic aging (21) and is implicated in neurodegeneration, such as seen with cognitive impairment and Alzheimer’s Disease (22). Antioxidants neutralize free radicals that cause oxidative stress. Nutrients that are antioxidants include vitamins A, C, and E and phytochemicals such as flavonoids or carotenoids. Foods that have high amounts of A, C, E or related phytochemicals include colorful vegetables and fruits as well as nuts – foods that are consistent with the MIND diet. The B vitamins are not antioxidants, but play unique roles in neurocognitive function. They are critical for neural development (folate, B9, prevents neural tube defects during pregnancy) while deficiency of B12 in adults includes neurological symptoms like peripheral neuropathy and cognitive impairment. B12 deficiency is common in older adults due to either increased food intake or a reduced ability to absorb B12 from foods. Notably, a recent systematic review suggests that B vitamin supplementation may delay cognitive decline in older adults (23). Foods that have high amounts of B vitamins include fish, poultry, green leafy vegetables and legumes– consistent with the MIND diet. Finally, omega-3 fatty acids are polyunsaturated fatty acids that must be obtained from the diet. Omega-3 fatty acids (particularly docosahexanoic acid or DHA) are present in the brain. Omega-3 supplementation in animal models has been shown to aid in neural development and emerging data in humans suggest improved cognitive function in adults (24). Foods that have high amounts of omega-3 fatty acids are fish and nuts – consistent with the MIND diet. Ultimately, the MIND diet shows potential for preserving the aging mind, however, a distinct low-carbohydrate approach is seeing parallel interest for the aging mind.

*The Ketogenic Diet*

The classic ketogenic diet utilizes a low-carbohydrate and high-fat macronutrient profile, which causes elevated production and oxidation of ketones. In contrast to the recently developed MIND diet, the ketogenic diet was first used clinically to treat epilepsy in the 1920s (25). (26). The brain is a highly metabolic organ, accounting for about 20% of the body’s basal metabolic rate (27). The brain relies primarily on glucose to provide its energy needs, except when glucose availability is scarce (as is the case on a low-carbohydrate, ketogenic diet or with prolonged fasting), when ketones become the predominant energy source for the brain (28). Common foods on the ketogenic diet include foods high in fat, such as red meats, cheeses, or full-fat dairy. While many high-fat foods are not consistent with the MIND diet, some foods do overlap well, including nuts and fatty fish, like salmon. Other ketogenic food staples include non-starchy vegetables, like leafy greens. Aside from food staples, restricted nutritional components are just as important to maintaining an effective ketogenic diet. To achieve a low-carbohydrate diet, consumption of carbohydrates typically falls between 20-50 grams per day. This requires an elimination of high-carbohydrate foods such as starchy vegetables like potatoes, legumes, grains, cereals and juices. Finally, in contrast to the MIND diet, ketogenic diets utilize butter for cooking, which is high in saturated fats, whereas the MIND diet would utilize oils with poly- and monounsaturated fats such as olive oil. Despite these distinct differences in dietary profiles, emerging evidence suggests the ketogenic diet, similar to the MIND diet, may improve cognition with aging and prevent age-related neurodegenerative disorders.

The restrictive ketogenic dietary pattern, unlike the MIND diet, is not widely followed and therefore epidemiologic associations between the ketogenic diet and healthy brain aging are limited. However, several short-term clinical trials offer insight into the effect of a ketogenic diet on the mind. Krikorian et al. randomized 23 older adults to either a ketogenic diet or a high carbohydrate control diet for 6 weeks (29). All adults had mild cognitive impairment (a risk factor for Alzheimer’s disease) with an average age of ~70 years and were largely college educated (average education years >15 years). After a 6-week ketogenic diet, participants improved verbal memory performance compared to the high-carbohydrate control diet. The concentrations of blood ketone levels were also positively correlated with memory performance. In a similar study, Brandt et al. randomized older adults with mild cognitive impairment to a 12-week ketogenic or high-carbohydrate control diet (30). Although only 14 participants completed the trial, with modest dietary adherence, individuals adhering to a ketogenic diet improved episodic memory scores and positive mood states. Another small trial showed the ketogenic diet improved a cognitive component of the Alzheimer’s Disease Assessment scale over a 12 week intervention (31). Finally, yet another small trial conducted by Sheffler et al. included 9 older adults who were counseled to consume a ketogenic diet for 6 weeks, after which they observed significant improvement in cognitive performance (32). Taken together, these small clinical trials support the ketogenic diet as a potential therapeutic strategy for mild cognitive impairment with aging. Certainly, larger clinical trials are warranted to better understand this therapeutic potential, while the underlying mechanisms continue to be more fully elucidated.

The biological mechanisms linking a ketogenic diet and cognitive health are primarily thought to be related to nutrient metabolism. The development of cognitive impairment and Alzheimer’s disease are related to impaired glucose metabolism in the brain (33). This glucose hypometabolism in the brain occurs with normal aging, is accelerated in the cognitively impaired, and is postulated to be due to reduced glucose transport (34). Since the landmark findings of Owen et al. in 1967, showing that ketones replace glucose utilization in the brain when glucose availability is lacking (35), interest in the impact of shifting brain fuel utilization has gained interest. Additional information can be gained from studies that experimentally increased circulating ketones using medium chain triglycerides (MCT). Six months of MCT supplementation increased circulating ketones, uptake of ketones into brain white matter and increased processing speed from a neurocognitive battery test (36). A systematic review further shows MCTs increase ketones and may improve cognitive impairment, however, studies remain inconsistent and have additional risk of bias (37). Other mechanisms postulated in the neuroprotection of the ketogenic diet include mitochondrial function (38), protection again neuro-inflammation (39) or structural changes (40).

*The Mind Summary*

Two distinct dietary approaches show promise for preserving cognitive function with aging: the MIND diet and the ketogenic diet. The proposed mechanisms are unique to each approach but need to be fully elucidated. Despite promising human data, clinical trials remain limited by small sample size, inconsistency and risk of bias. Given the growing need to support an ever-aging population, determining nutrition options to support the mind is of prime research and public health interest.

**THE MUSCLE**

In comparison to emerging data on the mind, nutrition to support the muscle has a more established history which has led to more concrete nutritional recommendations. Still, recent findings have implicated novel nutritional components that may affect the muscle and suggests we may have more to learn about the role of nutrition and aging muscle. The muscles play a critical role in locomotion and performing day-to-day activities. Loss of muscle mass and function with aging contributes to immobility, increased mortality, and reduced quality of life (41). Although this loss occurs as a natural part of the aging process (6), excessive loss leads to sarcopenia, a disease that only recently gained a consensus definition (42, 43) and clinical diagnostic coding (44, 45). Therefore, maintaining muscle mass and function with aging remains a critical part of healthy aging. Established recommendations for protein and energy intake effectively support disease-free living in children and adults. However, emerging data suggest novel nutritional approaches beyond these established recommendations may be necessary to optimally maintain muscle mass and function with aging.

*Established Recommendations for Protein & Energy Intake*

Protein and energy intake are essential for the maintenance of lean body mass and muscle, whereby adequate intake is required for both growth and preservation. Total energy intake to maintain body mass is a necessity, but protein intake *per se* is required for the maintenance of a positive nitrogen balance and preservation of lean body mass, including muscle. National guidelines recommend the consumption of 0.8 grams of protein per kilogram body weight for adults regardless of adult age (46). However, a persistently growing body of literature has evidenced higher protein intake as a protective measure to the maintenance of lean body mass and muscle mass throughout aging (47, 48). The traditional recommendations of 0.8 grams of protein per kilogram of body weight may have been low be due to limitations in the original methods (nitrogen balance) used to develop the recommendations (49), the populations used to develop them (50, 51) or new information on reduced protein synthesis responses to protein intake in older adults (52). Regardless of the reason for this discrepancy, an international group of experts have developed new recommendations for older adults of 1.0-1.2 grams of protein per kilogram body weight (53). Greater protein intake is also consistent with epidemiologic association studies, whereby greater protein intake is related to greater lean body mass (54, 55) and physical function (56, 57).

Regarding the impact of aging on skeletal muscle, a potential biological mechanism underlying the loss of muscle mass over time is an impaired protein synthesis response to protein intake. Skeletal muscle mass is regulated by the net effect of protein synthesis (muscle accretion or growth) and protein breakdown (muscle loss). While basal rates of protein synthesis are similar in young and old adults, rates of protein synthesis in response to protein ingestion (i.e. meals) is blunted in older adults (58). Maximal protein synthesis response is achievable in older adults if protein intake is increased (e.g., 20 gram protein bolus versus 40 gram protein bolus)(59). This protein bolus to achieve a maximal protein synthesis response is greater in older adults than in young adults, based upon comparisons with dose-response studies previously conducted in young adults (60). The requirement to ingest greater protein to elicit maximal protein synthesis response in older adults is termed “anabolic resistance (48).” Although optimal total and per-meal protein dose for the preservation of muscle mass with aging remains to be determined, consuming 1.2 grams of protein per kilogram body weight dispersed over 3 or more meals on the backdrop of adequate calorie intake to maintain body weight appears promising.

*Emerging Evidence on Whole-grains*

The predominance of the literature regarding nutritional approaches to preserve muscle mass and function in aging is targeted at protein and energy intake – and rightly so. The evidence is profound and clear that protein and energy intake play a dominant role in the regulation of lean body mass, including muscle. Excitingly, emerging evidence implicates whole-grains as a novel nutritional factor to maintain a positive protein balance and potentially preserve muscle mass and function in aging. Whole-grain consumption is a pillar of national nutrition guidelines (61), while epidemiologic association studies show that whole-grain intake improves body composition (relatively more lean mass compared to fat mass) (62-64). Few interventional trials on whole-grains and lean body mass or the underlying physiology of protein turnover (synthesis and breakdown) have been conducted and the literature remains inconclusive (65-68). However, a recent feeding trial has offered new insight into the potential role of whole-grains in lean body mass. Kirwan et al. designed a cross-over feeding trial comparing eight weeks of a whole-grain versus refined-grain diet in middle-aged adults. Diets were matched for macronutrient content and were isocaloric, differing only in the presence of whole-grains or refined-grains (primary grain components included oats, rice, wheat, and barley) (69). The primary outcomes report did not reveal differences in body composition, although we recently published a secondary outcomes report that included whole-body protein turnover assessed by two stable isotope tracers. This revealed a more positive 24-hour integrated net protein balance on a whole-grain diet, with no difference in net balance when observing the fasted state in isolation (70). These data suggest whole-grain intake may support a more positive protein balance in combination with adequate protein and calorie intake. Although we cannot derive a potential effect on skeletal muscle from whole-body protein turnover, skeletal muscle comprises ~1/3 of whole-body protein turnover and is the body’s largest mobile reservoir of amino acids/nitrogen. In this report, we conducted an *in vitro* investigation in skeletal muscle cells, showing a whole-grain wheat bran extract increases global protein synthesis rates. Finally, to investigate whether whole-grain intake has an appreciable effect on aging, we analyzed the National Health and Nutrition Examination Survey and showed whole-grain intake was positively associated with greater walking speed in older adults, a representative measure of muscle function. Despite our interesting and provocative report, protein and energy intake remains the primary nutritional effectors of muscle mass and strength with aging. Future research will be required to assess the potential therapeutic effect of adding optimal whole-grain intake on the backdrop of these established nutritional approaches.

*The Muscle Summary*

Adequate protein and energy intake persist as the primary nutritional factors that protect skeletal muscle in aging. Although national guidelines have not adjusted, recent work suggests a protein intake above 1.2g/protein/kg bodyweight/day, split among 3-4 meals supports muscle mass and strength with aging. It is important to note that despite established (protein and energy intake) and emerging (whole-grain) nutrition factors, another major factor is not related to diet at all, but rather to physical activity and resistance exercise training (71). The effect of physical activity and exercise is so potent, that it even brings into question whether additional protein intake or energy provision provides benefit beyond exercise in isolation (at least in mobility-limited older adults) (72). Certainly, an integrated approach including both physical activity, resistance exercise training, and optimal nutrition is prudent and supported by the literature. Still, the precise recommendations to effectively preserve muscle mass and function in aging remain to be fully elucidated.

**CALORIE RESTRICTION: A UNIVERSAL TOOL?**

It is noteworthy to mention that muscle strength and cognitive function are consistently linked in observational studies (73) and thus addressing one may be critical to addressing the other. Chronic calorie restriction on the backdrop of optimal nutrition (micro- and macronutrient intake) has recently gained interest as an anti-aging tool with the potential to impact both the mind and the muscle (74). Calorie restriction does not focus on what you eat, but rather how much. Commonly, we focus on obesity, where weight loss is the goal and provides indisputable benefits to human health. However, calorie restriction even in otherwise healthy adults may bestow unique anti-aging properties that impact both the Mind and the Muscle. A plethora of pre-clinical work, including drosophila (75, 76), murine models (77, 78) and non-human primates (79-81) have established calorie restriction as the only non-genetic method that increases lifespan. Logistical limitations prevent long-term human trials of longevity (e.g., maximal human lifespan ~120 years compared to ~2 months for drosophila, ~2 years for murine models or ~40 years for non-human primates). Still, human observational studies in Blue Zones (82), the Biosphere II experiment (83), and the Calorie Restriction Society International (84) suggest a protective effect of moderate calorie restriction of ~12% less than habitual intake improves indicators of longevity and population health. Recently, a randomized clinical trial, CALERIE II showed a similar restriction improved biological measures of aging (DNA damage) (85) without negative effects on cognitive performance (86) or muscle function (87). Of note, both body weight and muscle mass were reduced after calorie restriction and the potential risks of aging with a lower body weight and muscle mass such as sarcopenia, frailty and immobility remain to be empirically determined. Still, calorie restriction in the context of optimal nutrition may be a universal tool to slow the aging process and aid in the preservation of both the mind and muscle.

**CONCLUSION**

In a globally aging population, the prevalence of age-related cognitive and physical health deficits is inevitably increasing. Preserving these health aspects is essential to maintain quality of life during aging. Promising evidence from studies assessing nutritional strategies to combat cognitive and physical decline (i.e. the mind and muscle) have revealed various methods to improve health in older adults. Dietary interventions focused on changing the balance of both micro- and macronutrients (the MIND and ketogenic diets, respectively), have shown improved cognitive health and reduced risk for neurodegenerative conditions such as the development of Alzheimer’s disease. On the other hand, a focus on protein intake specifically may prove beneficial for maintaining physical health by reducing muscle loss over time. However, strategies shown to improve cognitive health may not exhibit the same benefits for physical health, and vice versa. While calorie restriction may have the most universal benefits, the multitude of nutritional modifications available may prove essential for individualized optimization of health during aging. While physical exercise cannot be excluded as a critical factor in maintaining overall health, ensuring that the mind and body are equipped to sustain physical exertion go hand-in-hand, ultimately creating a well-rounded lifestyle amenable to healthy aging.

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