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Our Intestinal Microbes Might be Driving Us Nuts

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Nuts have existed as part of human diets for at least 780,000 years. Consumption of nuts, and in particular almonds, has been associated with improvement of disease risk for various chronic disorders in humans.[1][2][3] Health benefits of almonds include lower blood sugar levels, reduced blood pressure, lower cholesterol levels, as well as reducing hunger and promoting weight loss. Almonds possess a variety of healthy bioactive components that contribute to these beneficial actions, including fermentable fibres, plant sterols, polyphenols, and vegetable proteins. Although these agents have been demonstrated to exert favourable actions on biomarkers for disease, to date, mechanistically, how such actions are exerted has not been fully elucidated.

An emerging possible mechanism for the health benefits of foods and food components is through their actions on the intestinal microbiome, as demonstrated by recent work.[4][5] While some studies have explored the ability of almond consumption to produce shifts in the relative abundance of the various species of the gut microbiome,[6][7][8][9] the actions of nuts—and particularly almonds—on microbiome profiles have not been thoroughly evaluated, nor has the relationship of changes in the microbiome been linked to shifts in disease biomarkers.

Lamuela-Raventos and St Onge, in a review of available literature, suggested that nonbioaccessible material of nuts in general provide substrates for the human gut microbiota that may partly explain the health benefits of nut consumption.[10] Mandalari et al. used a gut-model system to show that dietary fibre from almond skins in particular altered the composition of gut bacteria, suggesting that almond skins resulting from industrial blanching could be used as potential prebiotics.[11] Liu et al. reported that both raw and roasted almonds exhibit potential prebiotic effects, including regulation of intestinal bacteria and improved metabolic activities.[6] Burns et al. demonstrated that moderate intakes of almonds improve diet quality in adults and their children, purportedly by modulating the microbiota composition.[8] Similarly, Ukhanova et al. showed that increasing the consumption of almonds or pistachios appears to be an effective means of modifying the gut microbiome composition in human subjects,[9] while Liu et al. found increases in the populations of *Bifidobacterium* and *Lactobacillus* species in fecal samples as a consequence of almond or almond-skin supplementation.[7]

In terms of blood-lipid level modification, while Phung et al. assert that almond consumption imposes a neutral effect on serum lipid profiles,[12] Musa-Veloso et al., in a systematic review of 18 relevant studies, showed that almonds reduce levels of circulating total cholesterol, LDL-cholesterol, and triglyceride levels.[1]

These provocative initial findings affirm

the health benefits of almonds on gut microbiome patterns and their association with circulating disease risk biomarkers, as well as the key biochemical pathways that control them. Future work will undoubtedly result in a better understanding of how nut—and in particular almond—consumption improves health through their action on gut microfloral patterns.

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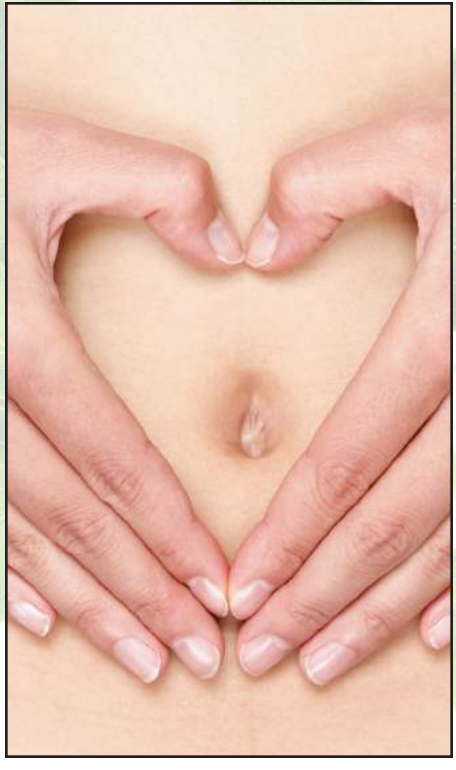

Neuronutrition: From Restoring Vitality in the Elderly to Management of Neurodegenerative Disease

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Neurodegeneration is an umbrella term for the progressive loss of structure or function of neurons, including death of neurons. Dementia, Alzheimer's, Parkinson's, cognitive impairment, Huntington's, ALS, and MS are some common diagnoses sharing a process of neurodegeneration. Certain clear treatment targets emerge when addressing this patient population:

- Address frank malnutrition
- Slow/prevent/reverse sarcopenia—increase/preserve muscle mass
- Engage neuroplasticity
- Improve cerebral blood flow, address secondary factors that compromise blood flow
- Improve mitochondrial function
- Address "type III diabetes," provide

alternate fuel source to glucose for the brain

While the evidence base for applying these intervention strategies to the elderly stems from studies in the various realms of neurodegenerative disease, it is easy to argue that all individuals over the age of 80, most individuals over the age of 70, and some individuals in their 60s likewise benefit from application of these treatment targets.

It is beyond the scope of this review to provide a comprehensive approach for the treatment targets identified. This review will focus on the role of a multivitamin, whey protein, and creatine to address the widespread malnutrition afflicting the elderly in North America and other industrialized nations, as well as prevent/slow sarcopenia and indeed increase muscle mass in the elderly. A list of strategies for consideration will be provided that address other key treatment targets for this important patient population.

Multivitamin

An eloquent two-year intervention trial among institutionalized elderly (mean age 84) was undertaken.[1] A valuable feature of the trial was that participants were assessed at baseline for status of a selection of essential nutrients; 68% were deficient in selenium, 61% deficient in zinc, 75% deficient in vitamin C, 70% deficient in folic acid, and 15% were deficient in β-carotene. Relative to placebo, intervention with a multivitamin reduced the risk of infection over the two-year period by a staggering 200%. Given that infection emerges as the principal cause of death in the elderly, the magnitude of importance of this outcome cannot be overstated. In addition to the impact of simple whey-protein supplementation highlighted below, this outcome provides powerful evidence of widespread malnutrition among the elderly.

Whey Protein

Sarcopenia, or a loss of muscle mass that accompanies aging, predisposes to a wide array of common health concerns among the elderly. Malnutrition and limited mobility are two key contributors to the phenomena. Sarcopenia is then a direct contributor to falls—and thus fracture and associated mortality and morbidity risks, reduced quality of life, further reduced mobility... and the vicious cycle continues.

Healthy older men, mean age 73, were assigned to various doses of whey protein (10 g lowest dose, 35 g highest dose) that included radiolabeled phenylalanine.[2] All doses of whey achieved positive amino-acid balance, in a dose-respondent manner, with the greatest effect occurring with the largest dose used. Stimulation of *de novo* muscle protein synthesis also occurred in all groups, again with maximal effect at the largest dose of whey used.

Healthy elderly (ages 70–85) were recruited into a resistance-training regime and supplemented with whey protein or isocaloric control.[3] Both groups increased muscle strength and stair-climbing performance. Muscle mass increased 1.6% and 0.6% in the whey and control groups, respectively. Muscle cross-sectional area was increased 4.6% and 2.9% in the whey and control groups, respectively.

Patients with ALS supplemented with whey protein achieved the following:[4] weight gain; increased body mass index (BMI); increased arm-muscle area and circumference; higher albumin, white blood cell, and total lymphocyte counts; and reduced creatine-kinase, aspartate aminotransferase, and alanine aminotransferase. Lastly, a 90-day trial (126 participants) compared whey protein plus lactoferrin to control.[5] The total number of colds recorded over the study period was 48 for the treatment group, versus 112 for the placebo group ($p < 0.001$).

Creatine

Tarnopolsky and colleagues have authored dozens of reviews of creatine for a wide array of indications, principally championing its use for various muscular dystrophies, yet reviewing their work clearly showcases that this simple, safe, and inexpensive intervention is grossly underutilized.[6] The most compelling basis for intervention with creatine among the elderly in fact comes from evidence of its use in immobilization injury. When a limb is placed in a cast for several weeks, upon removing the cast, the limb is profoundly atrophied. Several trials have shown that if creatine is supplemented during the immobilization, upon removing the cast, the limb is essentially the same size as it was prior to being immobilized.[7][8][9] This is not an effect of water retention: instead, mechanistically, it relates to the maintenance of preimmobilization levels of Glut-4 activity in the muscle. Creatine provides a hormone-like effect to spare muscle mass and prevent muscle catabolism.

As such, creatine is a mainstay prescription in a wide array of applications, from elderly to immobilization injury to muscular dystrophies to advanced cancer to HIV and

Table 1: *Important intervention strategies in management of the elderly patient and the treatment targets they address.*

Treatment	Target Addressed
Mediterranean dietary pattern	All
Exercise	All
Video games	Neuroplasticity
Multivitamin	Malnutrition, factors that compromise blood flow (homocysteine), mitochondrial function
Whey protein	Malnutrition, muscle mass
Creatine	Muscle mass
Fish oil	Malnutrition, neuroplasticity
CoQ_{10}	Mitochondrial function
Acetyl-L-carnitine	Mitochondrial function
Ginkgo biloba	Cerebral blood flow
Coconut oil	Alternate fuel source
Lion's mane mushroom	Other
Melatonin	Other

beyond. Dosing of creatine as per product instructions is discouraged. Several trials have shown equivalent muscle creatine and performance outcome with much lower dosage regimes,[10][11] relative to the overly aggressive industry standard of 20 g per day for 5 days, followed by 5 g per day thereafter. Our prescription for creatine is typically 2.5 g per day (the product comes with a 5 g scoop).

Summary

The scope of this review does not allow for the comprehensive strategy to be discussed. Table 1 (page 5) provides a summary of key strategies to be considered, and the treatment targets they address. A combined strategy that effectively addresses the identified treatment targets typically provides an important magnitude of benefit for individuals with a diagnosis of neurodegenerative disease, as well as for otherwise healthy free-living or institutionalized elderly.

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Community-Level Effects of Probiotics: Revealing the Mechanisms that Help Maintain Human Health?

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Most of the proposed mechanisms of action of probiotics are based on studying single strains in isolation. Although this information is important, it lags current evidence indicating the entire gut microbiota acts collectively as a complete ecosystem,[1] and/or a distinct endocrine organ,[2] with different species working in unison to perform common functions.

Emerging evidence suggests probiotics also have community-level properties, including supporting homeostasis of the microbiota as a collective and helping perturbed microbiomes return more quickly to their predisturbance state.[3] In other words, probiotics might support resilience* of the microbiome by increasing "the magnitude of maximum displacement the system can absorb and still recover."[4] They may also support the "elasticity" of the human microbiome, "i.e. the rate at which the system returns to its pre-disturbance

* *Resilience in this context is considered as the amount of stress or perturbation that can be tolerated before the gut ecosystem changes towards a different state of equilibrium. In systems biology, it includes the ability to actively adapt successfully in the face of internal and/or external stressors.*

equilibrium, or the time it takes to return (to either its pre-disturbance equilibrium, or some fraction of its maximum displacement)."[4] These novel functions align with current suggestions that "a healthy microbiome,† considered in the context of body habitat or body site, could be described in terms of ecological stability (i.e. ability to resist community structure change under stress or to rapidly return to baseline following a stress-related change)";[5] therefore, when stressed, may manifest dynamic systems-level properties including resistance,‡ resilience, redundancy, as well as possibly dysbiosis.[6]

Probiotics may enhance diversity as well as functional redundancy of the microbiome, leading to a more stable, robust resident microbial community, with increased resistance to developing disease following major perturbations including antibiotics and dramatic dietary changes.[7] Indeed, most studies which examined the composition of fecal microbiota postintervention§ showed increases in bacterial species other than the ones contained within the probiotic,[8] suggesting an increase in overall diversity. Probiotics also may help maintain critical metabolic functions performed by the collective gut microbiota,[9] supporting the suggestion that "it is more important that key functions in the gut are carried out rather than specific microbes be present to carry them out."[10]

Comprehensive genome scale studies on probiotics (termed "probiogenomics") are now underway to help elucidate gene-microenvironment interactions of probiotics in the entire human gastrointestinal tract.[11] This technology and others are proving useful in bridging gaps between understanding function(s) of probiotics in isolation and function(s) of probiotics within the entire microbial community. Systems-level technologies could help identify probiotics with a higher degree of interconnectedness within the entire microbial ecosystem, and therefore, provide the most widespread effect on the targeted anatomical niche.¶ These probiotics could act as important foundation** or

† *Due to extreme intra- and interindividual variability in composition, a consensus definition of a healthy microbiome has not yet been reached (see Bakhed, F., et al.* Cell Host Microbe *2012;12:611–622).*

‡ *Resistance in this context is defined as the property of a given microbiota or gut ecosystem to avoid change after being subjected to a disturbance. It is part of the systems biology definition of robustness, which is the ability of a system to resist change and continue functioning in the face of external and/or internal stressors.*

§ *Although these studies use state-of-the art, next-generation sequencing, they are still limited to the measurement of fecal stool samples. Current evidence suggests "microbial profiling of fecal samples, which is the most common strategy employed in microbiome studies, represents an incomplete and skewed view of even the colon, which has distinct mucosal communities and spatial heterogeneity that is lost upon sample homogenization" (see Donaldson, G.P., S. Melanie Lee, and S.K. Mazmania.* Nat Rev Microbiol *2016;14(1):20-32).*

¶ *It is evident that the microbial communities in different human body parts are unique. Indeed, "the key groups of the digestive and genital tracts are totally different" (see Jordan, F., et al.* Sci Rep *2015;5:15920), suggesting that different keystone or foundation probiotics would need to be developed for different anatomical regions.*

** *A foundation species is defined as "a single species that defines much of the structure of a community by creating locally stable conditions for other species, and by modulating and stabilizing fundamental ecosystem processes." (e.g.* Bacteroides thetaiotaomicron, Bacteroides fragilis*).*

keystone†† species, and therefore, function as "important ecosystem stabilizers because of their potential to cascade through the community with major effects on the structure and function."[12] This property helps support non–strain-specific claims in Canada, including "contribute to healthy gut flora," as well as general structure/function health claims in the USA, including "improving gut health, maintenance of health, and stimulating immune function." Other probiotics could be used in more specific indications, pending demonstration of clinical efficacy.[13] The potential for probiotics to have more widespread effects on human health, by maintaining essential metabolic functions performed by a healthy microbiota community, support their regular inclusion into lifestyle and dietary strategies implemented to maintain optimal health, and improve wellness.

†† *A keystone species is similar to a foundation species, because they are critical for maintaining the organization and diversity of their ecological communities via their multiple interdependent biotic interactions with other community members. However, in contrast to foundation species, keystone species are found in relatively rare numbers, and therefore, represent a point of vulnerability for the overall ecosystem. (e.g.* Fecalibacterium prausnitzii, Akkermansia muciniphila*).*

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