NUTRITION AS MODULATOR OF AGING, DISEASE, AND LONGEVITY

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INTRODUCTION

" Let food be your medicine, and let medicine be your food"

Hippocrates, 400 BC

As the world's population grows, so increases the emphasis on the maintenance of good health. This is more evident among the aged, who now represent a greater demographic proportion of the population than at any previous time in history. Of particular challenge to life scientists today is to find ways to deter age-associated declines in physiological function [1,2]. One of the more pertinent propositions for the maintenance of good health is proper nutritional practice [2,3]. This approach makes sense, not only scientifically, but also fits well with the public concern for geriatric health improvement through dietary optimization [1,4]. Nutrition has often been described as a 20th century science, because of the great strides made in the amelioration of nutritional deficiencies and the improvement in the health status [1,2].

Serious gerontological research began in the late 1950s and expanded very rapidly during the 1970s. Within the field, research on the effects of nutrition on longevity was at the forefront of science with the emergence of nutritional gerontology [1,2]. With a renewed impetus in the search for the nutritional basis of the life-prolonging and disease-suppressing effects of dietary restriction [5,6], the role of nutrition in the prevention of aging is a major thrust of nutritional gerontology of today. In stressing that dietary habits influence the aging process, Rowe and Kahn [7] highlight how lifestyle choices –more than heredity– determine a person's health and vitality. Based on a study of 25,000 genetically identical Swedish twins, these researchers make strong arguments for the modifying effects of extrinsic factors such as nutrition and exercise. The study concludes that only 30% of their subjects' age-associated deteriorations are genetically related; the remaining 70% are due to environmental factors. Within this context, preventive nutrition is the most practical intervention to slow aging and to suppress age- related diseases [7].

Traditionally, primary emphasis has been placed on the nutritional requirements and deficiencies during infancy and maturation, neglecting the senescent period [1,2]. A good example of this

assertion is evidenced, even today, by the lack of recommended dietary allowances (RDA) in vitamin intake for persons older than 51 years. Since information on metabolic requirements during aging is only fragmentary, considerably less is known about specific nutritional needs of the aged [6,]. Available information on nutritional status for the senescent phase of life has indicated clearly that the optimum dietary requirements for the aged are quite different from those of the young adult [2,8].

My presentation covers nutrition as a modulator of aging, highlighting the nutritional status of the aged and the putative intervention of preventive nutrition during aging. This report focuses on selected areas, and is not intended to be a broad review of the subject. Interested readers should refer to original articles listed in the references for additional information.

Change in body composition and nutritional status in the aged

A growing body of literature demonstrates that the prevalence of undernutrition increases with age, reaching relatively high levels for the elderly in nursing homes as well as for those who are home-bound and hospitalized [4,8,9]. Thus, inadequate nutrition is a widespread problem of the aged today. However, because the nutrient needs of adults are based mainly on studies of young adults, many of the dietary allowances for the aged are largely estimated [4].

Two main difficulties involved in the accurate determination of nutritional requirements for the aged are: 1) the age-related changes in body composition occurring throughout the senescent period, and 2) the altered nutritional status due to the confounding diseases that aggravate the aging process (see figure 1). A number of metabolic changes may significantly influence the nutritional requirements of the aged. For example, during senescence, the amounts of body protein and fat are in continual flux with fat mass increasing while metabolically active muscle tissues slowly reduce, causing for a fall in basal energy metabolism. This situation is worsened by a reduction in physical activity of the aged.

The energy needs and intake of adults at various ages were examined most extensively in a cross-sectional study in the U.S. The study shows that energy intake declines linearly from 2700 k cal/day at age 30 to 2100 k cal/day at age 80 [1,2,10]. This reduction partly accounts for the decline in basal metabolism (200 kcal), which parallels the reduction in lean body mass, and decreased physical activity (400 kcal) [10]. The lean body mass of healthy elderly declines at a rate of approximately 0.3 kg/year beginning in the third decade [1,2]. Much of this decline is due to the decreased skeletal muscle mass, loss of bone mass, and decreased organ size associated with aging. This signifies that even maintaining the same body weight throughout life does not necessarily mean maintaining the same body composition because decreased lean body mass tends to be offset by an increase in body

fat, which continues until age 65-70. In addition, fat distribution in the body also changes with age, thinning the skin and being more centralized in abdominal area.

Although there is general agreement that physical activity, metabolism, and many physiological processes change with increasing age, there is considerable disagreement among researchers in this field concerning the nutritional requirements for macronutrients and specific micronutrients for the aged. Because of decreased protein synthesis and the decline of body protein mass, dietary protein needs is estimated to decline by almost 30% between 20 and 75 years of age [11]. The controversial question on the optimum protein intake for the aged has finally been settled at 0.8 g/kg, BW/day following a long dispute. What we need now is evidence that populations living on 0.8 g/kg (or lower) of dietary protein show accelerated losses in lean body mass and tissue function, information that appears to be lacking.

Although vitamin and mineral deficiencies are presumed to be common in the aged, little experimental data is available with which to assess exact daily dietary requirements [6]. Increased needs for vitamins and minerals with age may result from an altered metabolism and less efficient absorption and excretion [2,8].

Several factors or reasons contributing to the malnutrition of the elderly have been identified [1,3,12]. The causes of malnutrition in the aged can be categorized into primary and secondary causes. The primary causes include the following: 1) ignorance regarding the need for a balanced diet; 2) affordability, which determines the range of food available; 3) social isolation, which causes loss of interest in eating; 4) physical disability and 5) mental state. The secondary causes of malnutrition includes: a reduction in food intake due diminished taste and smell, as the number of taste buds decreases by 50% with aging; malabsorption due to a variety of gut conditions results in reduced amounts of fat-soluble vitamins as well as folic acid and vitamin B complex. Alcoholism, which causes malnutrition by the substitution of alcohol for energy sources, interferes with nutrient absorption (e.g., folic acid). The use of certain drugs may interfere with nutrient utilization.

Regarding' an inadequate nutrient intake, a special attention should be made about B vitamin complex status in relation to neurocognitive function. A high prevalence of atrophic gastritis, a common disease of the aged, with hypochlorhydria due to a reduced gastric acid secretion (about 20% to 50%) was found to cause a limited bioavailability of vitamin 12 and folate for absorption due to the lack of an acidic condition in the stomach, having a higher pH (the optimum pH for active folate uptake is 6.3). Interestiongly, low folate and B12 levels are inversely correlated with increased plasma homocysteine as occurring in the aged population. Because this inverse relationship is so consistent, homocysteine is used as a functional marker of B vitamin status. A combination of low folate and high homocysteine levels is considered a causative factor for age related brain dysfunction

[13-15]. Several studies show improvement in cognitive performance following supplementation with these vitamins [13]. One interesting study by Snowdon and his team at the University of Kentucky in 1998 [16] supports this interrelationship, finding high levels of folate and low evidence of Alzheimer's disease incidence among 678 very old nuns of a Notre Dame convent. This famous study now known as the Nun Study reinforced another study showing that Alzheimer's patients had low levels of folic acid in their blood [3,16].

Anti-oxidant nutrients as geroprotectors

Antioxidants are defined broadly as compounds that inhibit the oxidation of various cellular components by free radicals. Whether overt or marginal, the aged are at risk for antioxidant deficiency as a result of decreased dietary intake, inefficient absorption, diminished retention or storage capacity, and increased elimination. In terms of actual vitamin intake, aged individuals appear to consume levels far below the RDA. Not surprisingly, smokers consume far less vitamin C than nonsmokers. Garry et al. [4] noted that approximately 40% of elderly individuals consume less than two-thirds the RDA for vitamin E. Ironically, vitamin E absorption is thought not to change with age, and no deficiency has been reported for healthy elderly. However, new information is emerging on a possible link between vitamin E and memory loss, as first revealed by Perkins on this a correlation in an elderly population (n=4,809) [17]. Moreover, the study lends support for the possibility that vitamin E is a potent geroprotector against neurodegenerative processes. To this end, a recent review article further elaborating on the connection between vitamin E and vascular dementia [3,9] should be mentioned.

Similar findings were reported on vitamin C. When blood ascorbic acid levels of the aged were compared with younger subjects, the levels were generally shown to be lower in older individuals. In a study examining whether low levels of ascorbic acid might be a physiological characteristic of aging, researchers were able to raise the levels three to four times by the administration of 100 mg/day, and when the supplement was withdrawn, the levels quickly dropped to baseline values [18]. On the other hand, when studying healthy centenarians, Paolisso, et al. [19] found plasma levels of vitamin E and C were higher than those of 75-99 year-olds, and only slightly lower than those subjects <50 years old.

Nutritional intervention of aging

Humans, in their preoccupation with life extension, have sought the elixir of life throughout time. Our forefathers have not spared their imagination in attempts to prolong life, only to be frustrated by a myriad of false claims [5,20]. We have learned that the prolongation of life without scientific basis

ends merely in wishful thinking. During the last several decades, remarkable advances in aging research using various animal models have produced insightful clues into aging intervention and life extension [21-23].

Among the first aging interventions tried was dietary antioxidant supplementation. Based on free radical data, the use of antioxidants have gained widespread public acceptance for their benefits to good health, and their ability to possibly stave off degenerative diseases such as cancer, heart disease, diabetes, and other age-dependent disorders. The use and effectiveness of antioxidants are entirely based on the rationale that free radical-derived oxidative damages are a major causative factor responsible for aging and the related diseases. Various natural and synthetic antioxidants, including vitamin C, E, acerbate, BHT, b-carotene, cysteine and 2-mercaptoethylamine, have been tested for life extension [20,24]. Results from experiments show–that the mean lifespan of most laboratory organisms, such as nematodes, drosophila, and rodents were extended, but with no change in maximum lifespan. These results were interpreted as the antioxidant action working through the secondary, pathological aging process [see figure 1], rather than through the primary, biological aging process.

The attenuation of pathogenesis by antioxidants seems to be a plausible approach for an intervention strategy. The work of Princen et al. [25] intended to establish the minimal supplementation dose of vitamin E required to protect against LDL peroxidation. Twenty subjects who ingested, consecutively (with a 2-week wash-out period in between), 25, 50, 100, 200, 400, and 800 IU/day during six months showed dose-dependent resistance to LDL oxidation, even after ingestion of only 20 IU/day. Many clinical trials studying the intervention effect of vitamin E on coronary heart disease are known [10,15]. For example, a randomized placebo trial in England evaluated the effect of 400 or 800 IU/day on the risk of myocardial infarction in 2002 patients. Results show that the supplementation significantly reduced the risk of nonfatal myocardial infarction by 46% [9, 26]. Jain et al. [27] investigated the effects of vitamin E (100 IU/day for 3 months) on plasma lipid peroxidation in type 1 diabetic subjects. Their data show that lipid oxidation and triglyceride levels were lowered, indicating a beneficial effect for a reduced risk for diabetes-related cardiovascular disease.

Czernichow and Hercberg [28], stating, "The available data from basic science and observational epidemiological research suggest that antioxidant vitamins represent a promising (although still unproven) means of significantly reducing the risk of cardiovascular diseases." The authors further state, "The accumulation of mechanistic and epidemiological data suggest that antioxidants act not only individually but also cooperatively and in some case synergistically," proposing, rather than a single antioxidant nutrient, the use of a balanced combination of antioxidants for maximal efficacy.
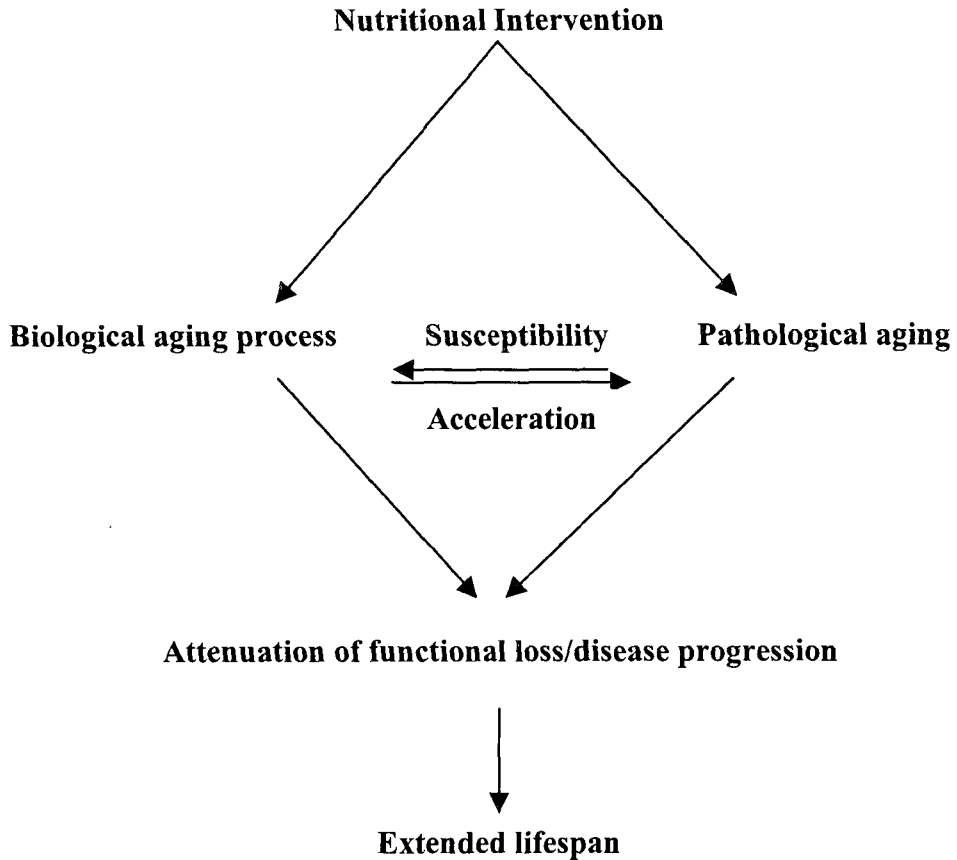
Nutritional Intervention

Biological aging process   Susceptibility   Pathological aging

Acceleration

Attenuation of functional loss/disease progression

Extended lifespan

Figure 1. A scheme illustrating the nutritional intervention of aging processes by modulating two pathways.

By now, for maximum efficacy, it should be clear that among the all the intervention trials tested to date, none comes close to showing the clear-cut, global effects of dietary (calorie) restriction on the anti-aging action. Many consider this unique efficacy is only possible by suppressing both aging pathways as outlined in Figure 1, thereby serving as the reference point by which other intervention results can be compared for effectiveness. Nutritional gerontologists utilize the calorie restriction paradigm as a prototype to obtain clues in other nutritional intervention study.

Several hypotheses have been proposed to explain such remarkable, robust anti-aging actions of low calorie intake [6]. Recent discussions on stress resistance derived from the hormetic response draw attention from nutritionists. Hormesis refers to a normal biological phenomenon in which mild stress becomes a stimulus for an organism's well being. Examples of hormesis are readily observable

in animal and plant kingdoms, such as vaccination for stimulated immune defense activity, response to heat shock, physical exercise for vigor, or even pruning trees for growth.

According to this notion, nutrition-wise, reduced calorie intake (as mild stress) acts as a stimulant for survival by counteracting (i.e., resisting) the destructive force of aging, including the insults of disease-causing oxidative stress. This resistive ability is believed to have been acquired through the evolutionary process by maximizing limited energy for only essential, life-supporting systems or components. A recent study by Lee et al. [22] using a gene expression profiling DNA chip method produced supporting data. The authors found that out of 6,347 genes of gastronomies muscle activated under calorie restricted conditions, 16% were stress responses and 13% were related to energy metabolism, suggesting metabolic shifts occur to maximize the energy utilization. Observed hormetic responses in the biological system are impressive; for instance, turmorigenesis by radiation or carcinogens is significantly suppressed by calorie restriction [see review ref 33]. The lifespan extension (about 20%), rather than shortening, by a mild low dose of gamma irradiation in mice reported by Caratero et al. [29] is another good illustration of a hormetic response.

The significance and relevance of the findings on nutrition manipulation that we discussed in this review are: 1) the findings prove the powerful impact of nutrition on modulating various genes, setting the courses of aging and disease processes, 2) the findings provide a sound rationale for intervention by nutritional means, and 3) the findings provide the impetus for designing an anti-aging strategy.

Future research directions of gerontological nutrition

With emphasis on the nutritional needs for the aged, preventive nutrition should play a larger role in establishing the nutritional requirements to ward off deficiencies in the elderly. An optimal nutritional status through proper dietary habits and adequate nutritional intake is the cornerstone of the body's defense against the ravages of aging. Because aging is the biggest risk factor underlying major chronic diseases, including cancer, cardiovascular disorders, diabetes, and osteoporosis, using preventive nutrition to arrest functional loss seems to be a more effective approach [30].

Current available data raise several important points for future research on the nutritional intervention of aging. As depicted in Figure 1, the best intervention of aging can be achieved only when both processes -- physiological aging and pathological aging -- are slowed. One possibility is to explore an antioxidant's multifunctional action [31], beyond its traditionally defined role as a mere free radical scavenger. Revelations of new properties for antioxidants as bona-fide physiological regulators and therapeutic agents add a new dimension to potential anti-aging applications. Vitamin E,

for instance, is now recognized as immune stimulant, effective in cell proliferation [31] and prostaglandin biosynthesis, and a regulator of various genes. One caveat is to recognize the possible prooxidant effect of vitamins, such as carotenoids and C vitamin in biologic system [32].

We have learned many lessons from dietary restriction studies on how prevention nutrition works: In biological aging, nutrition exerts its preventive actions by activating the genes that are beneficial only for functional improvements. For age-related diseases, nutrition influences both the onset and/or progression of a specific disease. As more becomes known about the genomic factors involved in the pathogenesis of disease, the targeted action of nutrients can be formulated. To understand molecular events underlying the effect of dietary influences on individual genes, and the interaction between nutrients and the disease process requires new approaches like the gene expression profiling using currently available DNA chip and microarray technologies. These approaches are appealing because of the ability to generate tremendous amounts of data that are needed for a better understanding of functional proteomics.

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