



NUTRITION AND AGING

ABSTRACT

The rate of elderly is growing with time in the developed as well as in the developing societies in a rate of about 5% a year. This population has higher morbidity than the general population. Elderly are characterized by changes in different physiological activities as well as multiple pathologies. Cellular function is based on hormones, cytokines and neurotransmitters acting through cell's receptors. Dietary structure is considered as one of the components of health and well-being. Having high morbidity with slower rate of cure, elderly are major consumer of nutrition support.

It is important to differentiate between the role of nutrition as part of lifestyle, in aging and the role of nutrition in treatment of the sick elderly. Nutrition has important role in the process of healthy aging, nevertheless aging has impact on the nutrition of the person secondary to its physiological changes.

The recent developments in the technology of nutrition support give us the tools to supply every person with all nutrients compounds in different manners. We can modulate the dietary structure in any way that we think that can benefit the person. There are enriched solutions with different substances, that either bypass the swallowing mechanism in different ways supplying enteral nutrition or going parenterally directly to the circulation through different ports. Despite these various opportunities there are many questions about the efficacy of the nutrition support in the elderly in certain opportunities and ethical debate about the indication with different opinions is running now, questioning the medical indications, the techniques and the timing for the implementation of support.

Sarcopenia, the decline in muscle mass is part of the aging process, the differentiation between low muscular mass resulting from starvation secondary to disease and that derived as a consequence of different responses to disease with the background effect of aging is has been recently determined.

The role of the feeding process as part of the needs of the old person, reflecting empathy and psychosocial support, is becoming more prominent part of elderly care.

The main challenge of clinical nutrition in the aged now, are in the determination of the optimal faster timing for intervention.

Key words: Aging, Nutrition deficiencies, Nutrition support, Elderly nutrition, Elderly care.



DERLEME

YAŞLILIK VE BESLENME

Öz

Yaşlı nüfus hem gelişmiş hem de gelişmekte olan ülkelerde yılda yaklaşık %5'lik bir artış göstermektedir. Bu grubun morbidite oranı genel nüfustan daha yüksektir. Yaşlanma, farklı fizik aktivitelerde değişiklik ve çeşitli patolojilerle karakterizedir. Hücre fonksiyon, hücre reseptörleri üzerinden etki eden hormonlar, sitokinler ve nörotransmitterler tarafından sağlanır. Sağlıklı olmanın en önemli bileşenlerinden birisi de diyetdir. Daha yavaş iyileşme ve yüksek morbidite nedeniyle yaşlılar beslenme desteği için en önemli adaylardır.

Yaşlanma sürecinde bir yaşam biçimi olarak beslenme ile yaşlı hastanın beslenme destek tedavisinin karıştırılmaması önemlidir. Her ne kadar yaşlılık oluşan fizyolojik değişikliklere bağlı olarak bireyin beslenmesini olumsuz etkilerse de beslenme, sağlıklı yaşlanma sürecinde önemli bir role sahiptir.

Beslenme desteğinde son yıllarda kat edilen yol bize farklı gereksinimleri olan her hastaya destek tedavisi verebilme olanağı sağlamıştır. Diyetin içeriğini hastaya yararlı olacağını düşündüğümüz yönde değiştirebiliriz. Çeşitli maddelerle zenginleştirilmiş enteral ya da parenteral yolla verilebilen çok çeşitli beslenme ürünleri mevcuttur. Böylesine zengin ürün yelpazesi ve uygulama olanaklarına karşın halen, endikasyonlar, teknik ve zamanlama hakkında farklı görüşler mevcuttur.

Sarkopeni, yaşlanma sürecine bağlı olarak kas kitlesinde oluşan azalmadır ve hastalıklara sekonder açıklı sonucu oluşan tablodan ayrılmalıdır.

Yaşlı bireyin gereksinimlerinin bir parçası olarak beslenme desteği, aynı zamanda empati ve psikososyal desteği de yansıttığından yaşlı bakımının ayrılmaz bir parçası olmuştur.

Şimdilerde yaşlılarda klinik beslenmenin yaptığı en önemli katkı, girişimler için optimal zamanlama ya olanak vermesidir.

Anahtar sözcükler: Yaşlılık, Beslenme yetersizliği, Beslenme Desteği, Yaşlı bakımı

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INTRODUCTION

Life expectancy is rapidly increasing in the Western civilization. Throughout the history people have been looking for the well-being of the youthful and for being able to have prolonged good life. Nutrition has a significant impact on physiological function, thereby on health and well-being. Since the work of McCay in 1935, demonstrating the effect of energy restricted diet by about 30% of the “ad libitum” eating on median and maximal life span in a cohort of rats [1], many works have confirmed these findings in different species: rat, mice, hamsters, fish, flies, protozoa, worms, water fleas and partially in several mammals. Certain works have demonstrated minor effect of lower protein intake, but the major effect was of restricted energy intake starting in young adult life or even in early middle age. [2].

Several possible mechanisms may explain energy restriction effects on the lifespan extension in animals, including altered glucose utilization [3], decreased oxygen radical damage [4], reduced glycation or oxidation of macromolecules [5], changes in gene expression [6] and increase in stress hormones [7].

There are numerous important intracellular and intercellular factors, which decrease with aging, the decreases of which, have been shown to be attenuated by energy restriction, some of them with increase in the expression of several genes of metabolic response.

Decreased energy intake, in most of the studies, was associated with a decline in cellular and tissue metabolism. These metabolic changes could be explained with intracellular changes in the release of calcium from the endoplasmic and sarcoplasmic reticulum stimulated by inositol-triphosphate, the mitogen-activated protein kinase activities. Decrease sensitivity of receptors as the effect on beta-adrenergic receptors. The expression of several genes of metabolic response as: including the heat shock protein - hsp 70, superoxide dismutase - SOD, catalase, calnexin, IL-2 in rat spleen T-cells and p53. Change in the hormone secretion regulation (including gonadotropins, neuropeptide-Y, TSH, GH, steroids like dehydroepiandrosterone - DHEA, dehydroepiandrosterone sulphate - DHEAS, insulin, prolactin, but not proopiomelanocortin). Oxidative damage manifested in increase exhalation of aldehydes, increased lipid peroxidation, and elevated glutathione concentration and scavenger enzyme activity.

Definitive conclusions regarding the effect of energy restriction to be deduced from studies in non human primates will not be forthcoming for at least another 20 years [3]. But there is one epidemiological observation from Okinawa in Japan, showing that the inhabitants of this island are living lon-

ger, the rate of centenarians being there about 40 times higher than in the rest of Japan with the people being shorter by about 4.1 cm. The average energy intake in the island was shown to be about 83% of the average consumption in Japan [8]. Recently, it was found in a human aging cohort, in the Baltimore Longitudinal Study of Aging, that men with lower temperature and insulin and those maintaining higher DHEAS levels have greater survival than their respective counterparts with lower levels of these biomarkers, consistent with the effects of energy restriction on aging and lifespan observed in monkeys [9].

The mammalian aging is associated with a reduced ability to activate prosurvival signaling pathways in response to oxidative stress, leading to cell oxidative damage [10]. The purpose of this article is to show the impact of energy restriction on the changes in cell metabolism and impulse transduction, observed in aging.

The Impact of Energy Restriction

Many theories try to explain the process of aging. These theories may be divided into several groups including stochastic and genetic theories, environmental theories and intra- and intercellular theories [11]. Two of the theories of the aging process may provide some explanation for the effect of energy restriction on the lifespan extension and the reduction of age-related degenerative diseases: 1. The Free Radical Theory of Aging [12]; 2. The Neuroendocrine Theory of Aging [11].

Determination of Nutritional Deficiencies in the Elderly

Only recently has the American Food and Nutrition Board issued nutritional recommendations, the DRI (Dietary Reference Intakes), which also include allowances for the elderly aged 70 years and older (13-16). Despite the different determinations of nutritional deficiency, nutrient deficiencies do not consist only of the classical Protein Energy Malnutrition (PEM), but also of marginal, borderline or subclinical micronutrient deficiencies caused by inadequate micronutrient intake.

There is some confusion about the terminology used to express nutritional status. Nutritional status studies do not always discriminate between ‘malnutrition’ and ‘the risk of being undernourished’ or ‘being at nutritional risk’. For some, being at risk of malnutrition is different from actually being malnourished: being malnourished certainly sounds worse than being at risk of it. Others think that these two terms are one and the same. The terminology of nutritional risk can also cause difficulties in certain research situations, especially

**Table 1—** Stages of Micronutrient Deficiencies

Stage	Pathophysiologic Meaning	Detection Methods
I Prelatent: Preliminary, biochemical	Decrease in micronutrient concentrations in different tissues	Dietary intake inquiry and chemical studies of different tissues
II Latent: Subclinical, physiological	Decrease in metabolite and enzyme activities	Biochemical and physiological studies
III Overt: Clinical	Morphological and functional disorders	Clinical signs and symptoms Functional evaluation

when nutritionists collaborate with clinical investigators from other disciplines. That a particular demographic or physiologic factor might increase or decrease the risk of being at nutritional risk can be a difficult concept to convey, and the selection of statistical methods can be hampered by the seemingly circular logic (17).

The sequence of events which leads from the healthy state to nutritional morbidity and mortality consists of a preliminary latent phase, through subclinical physiological to marginal clinical and clinical stages (Table 1). The two first stages represent the concept of 'borderline nutritional deficiency' which is of great importance in the fields of health promotion and prevention, especially in the elderly.

Prevalence of Deficiencies in Different Populations

Stanga and Allison have recently stated that PEM, either accompanied or not by micronutrient deficiencies, is prevalent in up to 38% of elderly patients; 12% of the homebound, up to 65% of hospitalized patients and up to 85% of institutionalized elderly (18). Inadequate intakes have been observed in many countries: in free-living old pensioners with additional anthropometric and biochemical findings (19) and in institutionalized elderly (20) in Perugia, Italy; in the SENECA all European study (21,22); in distinct populations in France (23); in the USA (24); and in Israel (25,26).

According to the USDA Survey of Food and Nutrient Intakes by Individuals in the United States (27), approximately one third of men and women over 60 year of age eat less than 0.8 g/kg of protein per day, and approximately 15% eat less than 75% of the RDA. Recent meta-analysis on protein consumption (28) confirms that the RDA for protein for the elderly is set more or less at the optimal level. There is

some data supporting the benefit of higher protein intake for increasing bone strength. However, with higher protein consumption certain risk to the kidney is quite evident.

Age Related Physiological Changes Leading to Nutritional Deficiencies

Weight loss may reflect changes in appetite, dentition, taste, depression, comorbidity, poverty, isolation, constipation and other factors. According to data collected for healthy non-smoking subjects aged 18 to 100 years, between the age of 30 to 70 there is a continuous decline of about 0.1% to 1% (on average about 0.5%) per year in the function of many tissues and organs (29), which is manifested in the shape, needs and metabolism of the older person. However, regardless of cause, loss of lean body mass is an inevitable consequence of this age-related weight loss. Physical activity declines with age, especially in developed societies, depriving muscles of what is probably their most important environmental stimulus to maintaining their mass and function, as was previously discussed. All of the above mentioned changes in the elderly affect their food intake and thereby their nutritional status. The decline in food intake occurs to a greater extent in men than in women (30).

Gastrointestinal Changes and Nutrition with Aging

Changes in the gastrointestinal system also affect nutritional status in the older man. The dental status deteriorates, i.e., there is loss of teeth, the remaining teeth are unsteady and artificial dentures may be ill fitting and disturbing. Only one study of the elderly describes the impact of dentures on nutritional intake. Out of 247 well educated Bostonian elderly of high socioeconomic status, those with artificial dentures consumed more refined carbohydrates and sucrose. With a decrease in the number of teeth, vitamin A, crude fiber and calcium intake decreased (31). The swallowing process is less synchronized due to changes in the pharyngeal structure and deterioration in its neural control because of a decrease in neural conductivity which affects neural response.

Another factor affecting swallowing is atrophy of the salivary glands resulting in dryness of the mouth (xerostomia), which is aggravated by some drugs. Changes in taste and smell reduce appetite and food intake. In addition, there are alterations in brain food-intake control. Because of atrophic changes there is a decrease in normal stomach acid secretion, which in turn reduces the extent of initial protein degradation as well as iron, calcium and vitamin B₁₂ absorption. There are changes in peristalsis which adversely influence gastric emptying and cause early sensation of satiety. The intestinal surface area decreases and blood supply to the intes-



tine is reduced, affecting absorption and nutrient transport. Changes occurring in mucosal secretion have a detrimental effect primarily on disaccharide digestion (32,33).

Changes in Other Systems Affecting Nutrition with Aging

Older men suffer from many disorders in the skeletal and muscular systems. These disorders make it difficult for them to purchase, prepare and serve food and often also to eat it. Changes in the central neural system, peripheral lesions, paralysis and changes in vision also make it difficult to eat. Many studies have tried to prove a cause and effect relationship between low intake of different vitamins and normal brain function (34). One recent prospective study showed no correlation between a decrease in folate consumption and further cognitive deterioration (35). A German study demonstrates that cognitive impairment leads to a decrease in micronutrient intake (36) which may then contribute to further cognitive and functional impairments but does not cause them.

Mood is an important component of well being. Bereavement is a life event which affects the individual's well being for a long time. Two studies have demonstrated the influence of recent bereavement on nutritional status (37) and food consumption (38). The latter provides some explanation to the first. Both studies demonstrate how life events affect the nutritional status of many subjects and how this condition might be reversible with only a little effort by the health care professionals.

The Role of Illness and Comorbidity

Increased consumption of some nutrients during illness may lead to low levels of other nutrients. Low zinc, vitamin A, carotene and vitamin E concentrations were found in elderly subjects with leg ulcers (39). Forty Scandinavians with hip fractures had lower plasma vitamin C concentrations than 102 age-matched controls (40). This nutrient deficiency may affect the immune response in the elderly, as was previously demonstrated by Chandra (41). Recently, a significant decline with aging in Delayed Cutaneous Hypersensitivity (DCH) response to seven antigens was found in a population of elderly subjects with a high prevalence of low and deficient serum values of vitamin C, vitamin E, riboflavin, pyridoxine, iron and zinc. Vitamin supplementation for a period of 10 weeks significantly improved the biochemical parameters for those vitamins and the age related decline in the DCH test was no longer statistically significant (42).

Drugs may reduce appetite and use of medication may change the consumption of a variety of foods and reduce in-

take. Moreover, drugs may affect the nutritional status by altering the patterns of absorption and/or nutrient utilization and excretion, e.g.:

1. diuretics cause excess potassium and magnesium excretion;
2. antacids decrease phosphorus absorption;
3. H₂ blockers reduce vitamin B₁₂ and iron absorption;
4. laxatives affect intestinal nutrient transport and absorption;
5. antibiotics have an influence on the gut microflora that indirectly affect some

nutrient absorption.

Alternatively, drug metabolism may be changed by diet (43). In a recent study on 149 hospitalized elderly subjects, low thiamin plasma concentration was the most prevalent vitamin deficiency and it correlated with consumption of diuretics (mainly Furosemide) which increase the urinary excretion of thiamin (44). In four studies, mild thiamin supplementation was found to improve mood in the elderly, i.e., thiamin has a beneficial effect on the highly prevalent problem of deteriorated mood in the elderly (45).

Multivitamins and Diets

'Multivitamin' supplementation in Western societies widely prevails in some population groups and hardly exists in others. The fact that adequate nutrition requires a minimum caloric intake is often overlooked. Meals eaten by the elderly are hardly capable of supplying adequate amounts of nutrients because their nutrient densities are typically low. The elderly should be informed as early as possible of the importance of switching to foods with high nutrient density. Increased consumption of meat, dairy products, fish, eggs, and soy products should be recommended (46).

"MEALS ON WHEELS"

One of the ways to remember the pathophysiology of weight loss in the elderly is by using the mnemonic "MEALS ON WHEELS" aimed at reminding the clinician of the multiple causes of weight loss in the elderly, either medical and psychological or social and iatrogenic (Table 2). "MEALS ON WHEELS" is actually a common method to improve the elderly nutrition as suggested (47).

Clinical Symptoms of Malnutrition

All early symptoms of nutritional deficiencies are nonspecific and progress slowly (Table 3). Malnutrition is often considered as a normal age-associated phenomenon and is regarded as a "sign of aging." Thus, an early diagnosis of malnutrition

**Table 2— MEALS-ON-WHEELS**

CAUSE	
M	Medications: iatrogenesis
E	Emotional problems: depression .
A	Anorexia: anorexia tardive or abuse of elderly
L	Late life paranoia
S	Swallowing disorder: dysphagia
O	Oral factors: dentition , tongue
N	No money: poverty- social factors
W	Wandering: memory loss due to dementia
H	Hypothyroidism, hypoparathyroidism, hypoadrenalism: endocrine
E	Enteric problems: malabsorption
E	Eating problems: inability for self feed
L	Low salt, low cholesterol: restriction diets
S	Stones: fecal impaction, constipation

is difficult. The most typical early signs observed at the onset of malnutrition are diminished appetite and dislike of meat (48).

Magnitude of the Problem of Nutritional Deficiencies The Aging Population and its Special Health Problems

An increase of about 2.5 years per decade has been observed in the life span of Israelis during the second half of the 20th century. A similar trend has been found in other Western societies (e.g., 1.8 years per decade in the United States). Consequently, the elderly population (65 years and ol-

Table 3— Clinical Symptoms of Malnutrition in the Elderly

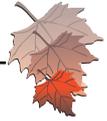
Early symptoms	Diminished appetite
	Dislike for meat
	Reduced nutrition intake by 1/3 of the daily needs
	General restlessness
	Permanent fatigue
	Reduced mobility
Late clinical symptoms	Loss of appetite
	Avoidance of meat consumption
	Reduced nutrition intake by 2/3 of the daily needs
	Muscle wasting and weakness
	Permanent severe fatigue
	Significant weight loss
	Dry, thin, and cracked skin
	Immobility
Dependence	

der) is constantly growing, with elderly people over 85 years old representing the fastest growing segment. Morbidity prevalence in this specific age group is of greater magnitude. Nutritional status derived from the intake of different nutrients is one of the components determining the physiological, medical and functional states of the elderly. Nutritional status is assessed as part of the CGA – Comprehensive Geriatric Assessment (49). Most clinical professionals would agree that in the care of sick or frail elderly patients, nutritional and hydration concerns often rank far too low on the list of evaluation and treatment priorities. In hospitals and nursing homes (50,51), and in the community, elderly patients often receive a variety of costly and complex medical treatments, e.g., extensive drug therapy (52) and mechanical ventilatory support (53), while routine provision of adequate food and fluids is neglected. Compared with the many serious maladies already established and diagnosed in elderly patients, being at risk of malnutrition sometimes seems less than urgent. The need for nutritional assessment and intervention is particularly crucial in this age group because of a higher incidence of chronic diseases and a myriad of socioeconomic factors that increase the likelihood of malnutrition (54). Though this age group has particular needs, only relatively minor-scale research has been conducted.

Common Deficiencies in the Elderly Protein and Energy Deficiencies

The elderly eat considerably smaller amounts of food and eat less often than younger adults. Especially at times of acute or chronic illness, this lower intake leads to energy deficit and general malnutrition accompanied by deteriorated mood, a condition often defined as Failure To Thrive (FTT) (55). Forty percent of elderly hospital admissions in the United Kingdom are undernourished, half severely so. In a recent study Allison et al. (56). showed that elderly patients consume less than 70% of their energy (recommended intake, 30 to 35 kcal/kg/d) and protein (recommended intake, 1 g/kg/d) requirements.

Hypoalbuminemia is found in more than 60% of malnourished geriatric patients and albumin remains one of the most sensitive markers of malnutrition. Hypoalbuminemia arises because diseases and multiple morbidity are frequent in the elderly and they regularly result in the release of cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). The cytokines initiate catabolic phase characterized by breakdown of muscle cells as well as rapid loss of appetite. The aversion to meat consumption of diseased elderly people is well known. Illness and lack of appetite preserve the catabolic state. This is a common phe-



nomenon in geriatric patients. Lack of appetite and the specific cytokine pattern (57), lead to significantly decreased food consumption. Because the albumin deficit is hardly noticed at its early stage or if noticed, is not attributed to preexisting malnutrition (58), malnutrition persists and might even get worse after the patient's admission to the hospital (56). Without prompt diagnosis and appropriate countermeasures, the patient's nutrition parameters will continue to deteriorate from day to day. In such a situation, refeeding to restore normal nutrition parameters can take days or weeks (48).

Protein Energy Malnutrition and Sarcopenia of Aging Definition of Sarcopenia in the Elderly

Sarcopenia is a common phenomenon in elderly subjects. Its pathophysiology is not yet well understood. Because it is prevalent in the elderly, it is most important to differentiate it from PEM. Loss of body weight in older adults may be caused by many factors, of which some may be part of biological aging but others are definitely related to disease. The quantitative definition of sarcopenia is very difficult, and therefore the measurement of its prevalence is quite hard. However, if one defines it according to a boundary condition, such as 2 *SD* below the mean appendicular muscle mass of young healthy adults, one can determine its prevalence according to this level of severity (59). Data are available from the New Mexico Elder Health Survey by Baumgartner et al. (60), who measured appendicular muscle mass in 883 randomly selected elderly Hispanic and white men and women by dual energy x-ray absorptiometry. Sarcopenia was defined as a muscle mass ≥ 2 *SD* below the mean for young healthy participants in the Rosetta Study (61), a large cross-sectional study of body composition in New York. The prevalence of sarcopenia according to this definition increased from 13-24% in subjects aged 65 to 70 years to over 50% in those older than 80. The prevalence increases in both men and women, though it is actually higher in men above 75 years old (58%) than in women (45%) of the same age. The higher prevalence of sarcopenia in men noted is consistent with the greater change in the quality of lean mass that occurs in men, as stated earlier (62). However, the results of Baumgartner et al. (60) as well as of Ellis (62) imply that the biological process of sarcopenia occurs in both sexes, although perhaps to a greater extent in men (59).

The Causes of Sarcopenia in the Elderly

Although the causes of sarcopenia are not yet clearly understood, there are many possible mechanisms. The role of protein deficiency in the development of sarcopenia is problematic. Castaneda et al. (63) showed that eating half the recom-

mended dietary allowance (RDA) for protein of 0.8 g/kg/d, led to a significant decline in strength, body cell mass and insulin-like growth factor-1 (IGF-1) levels in postmenopausal women, but it is not clear whether moderate reductions in protein consumption also contribute to sarcopenia (59). Overall, aging can be considered as the withdrawal of or resistance to several anabolic stimuli to muscle-central nervous system (CNS) input, growth hormone, estrogen, testosterone, dietary protein, physical activity, insulin action and possibly the development of several catabolic ones-subclinical inflammation and production of catabolic cytokines, e.g. TNF- α , IL-6 and possibly IL-1 β . That is, in addition to the decline in anabolic stimuli that occurs with age there is some evidence of an increase in catabolic stimuli. Roubenoff et al. (64) found that production of IL-6 and IL-1Ra (IL-1 receptor antagonist) by peripheral blood mononuclear cells (PBMC) of ambulatory elderly participants (72-92 years old) in the Framingham Heart Study was significantly higher than that of younger controls (40 years old).

Whether the anabolic or catabolic stimulants are more important, or even paramount, remains to be examined (59). If there is a single most important cause of sarcopenia, it is probably the loss of motor neuron input to muscle that occurs with age (65). Because innervation is crucial to the maintenance of muscle mass as well as muscle strength, it is possible that this decline is at the heart of sarcopenia. It is still unknown what role physical activity, hormone levels or genetic factors have in preserving motor unit numbers in older subjects (59).

1. Endocrine and Metabolic Causes of Sarcopenia

Of the hormonal anabolic inputs that decline with age, the sex hormones are probably the most important. Between the ages of 25 and 75 years, mean serum testosterone levels decline by about 30% and free testosterone levels decline by up to 50% and continue to decline with advancing age (66,67). The action of insulin, one of the major anabolic hormones related to muscle, also appears to decline with aging. In the pre-insulin era, diabetes mellitus was associated with severe muscle wasting. Insulin increases body cell mass and body nitrogen in diabetics (68,69). Its main action on muscle tissue appears to be in inhibiting protein breakdown, though it has been difficult to show its sustained effect in increasing muscle protein synthesis (70,71). Insulin resistance could also play a role in the development of sarcopenia. This resistance increases with age due to fat mass (especially visceral fat mass) accumulation and physical inactivity (72-76). The diminution in insulin action that occurs in many older adults may well ha-



ve a procatabolic effect on muscles (59). Growth hormone (GH) begins to decline in the fourth decade and declines progressively thereafter. However, it is not clear at all whether GH deficiency is an important contributor to sarcopenia. Roubenoff et al, (77) found that among postmenopausal women 24-hour GH secretion was highest in those with the lowest body cell mass, which is the opposite of what is predicted by a straightforward GH-deficiency hypothesis.

2. Physical Activity and Sarcopenia

Physical activity is considered an anabolic activity and it is used as the main means of body building. Baumgartner et al. (78), using the New Mexico data, recently performed a cross-sectional analysis which evaluated the relative contributions of physical activity, dietary energy and protein, health status, serum testosterone, estrone, sex hormone-binding globulin and IGF-1 to sarcopenia in 121 men and 180 women aged 65 to 97 years. The authors found that muscle mass in men was significantly associated with free testosterone, physical activity, heart disease and IGF-1. In women, muscle mass was only associated with total fat mass and physical activity. The most convincing evidence of the importance of physical activity probably comes from the demonstrated capacity of exercise to reverse sarcopenia (59).

Micronutrient Deficiency and Borderline Deficiency

Elderly people are at particular risk for marginal deficiencies in vitamins and trace elements. Early detection of deficiencies and appropriate treatment are an important challenge. We can prevent deficiency by adequate micronutrient recommendations, thereby promoting health, increasing longevity and improving quality of life. Concerning micronutrients, the previously discussed concept of 'borderline micronutrient deficiency' is of utmost importance for the elderly. Food intake decreases with aging, resulting in lower micronutrient consumption⁵³⁻⁵⁶. Inadequate intake of microelements and vitamins of varying degrees in the elderly has been described in many studies summarized by us (79). In many of the studies there is no data for many micronutrients, in particular for pantothenic acid, biotin, vitamin K, manganese, copper and iodine. For most of the micronutrients except for vitamin B₁₂ (where one extreme value substantially increased the average value), median values are close to the average ones (79).

Zinc Deficiency

Mild zinc deficiency is common in the elderly, but frequently cannot be confirmed because there are no conclusive criteria for the definition of zinc status. In order to evaluate such criteria, 15 elderly were put on moderately zinc deficient diet

and then on a zinc repletion diet, for 15 days each. Alkaline phosphatase, red blood cells methallothionein, Cu and Zn did not change in response to dietary alterations as expected. Only 5'-nucleotidase significantly decreased after depletion and increased after 6 days of repletion (80). Low plasma zinc levels are more prevalent in the elderly ill (81,82) and they are detected early in the course of malnutrition. Lymphopenia and thymic atrophy, which are early markers of zinc deficiency, are known to be caused by high losses of precursor T and B cells in the bone marrow (83). Because of this, zinc deficiency is considered a causative factor of immune impairment in the elderly.

Iron deficiency

Iron deficiency is prevalent in geriatric patients (84), but less common in 'apparently' healthy elderly subjects. Low iron intake in the elderly was observed in only 2 out of 38 studies (79). Recent evaluation of 1016 subjects from the Framingham study aged 67 to 96 (85), found a prevalence of only 2.7% of iron deficiency while 12.9% had elevated iron stores, of which only 1% could be explained by chronic disease. In a study of 163 hospitalized elderly no correlation was found between iron stores and iron consumption (86). Anemia is one of the most fascinating problems in geriatrics medicine, but recent data suggests a more complicated etiology than just iron intake and loss. Discriminant analysis of iron deficiency in 51 women in their seventies could not clearly differentiate between iron deficiency anemia and anemia of chronic disease (87). In another study, anemia was prevalent in 25% of the subjects with elevated CRP (C-reactive protein) (88). In a study of 1268 British elderly with low iron status, interactions with other nutrients were found. Alcohol, vitamin C, protein and fiber consumptions were positively associated with iron status while calcium, dairy products and tea consumptions were nearly all negatively associated with iron status (89).

Vitamin B₁₂ and Folate Deficiencies

Folic acid and vitamin B₁₂ deficiencies, prevalent in about 10% and 14% respectively of the US population, may explain 25% of the genetic mutations occurring in the US (90). However, low consumption of vitamin B₁₂ was not found in any of 38 studies performed on the elderly, though in 15 of these studies low folate intake was observed (79). Folate depletion was associated with increased DNA methylation in elderly women (91). It has been recently shown that the prevalence of low plasma concentrations of vitamin B₁₂ and antioxidants is lower with better intake of the vitamins (92).



The prevalence of vitamin B₁₂ deficiency is about 40% in hospitalized ill elderly subjects in subacute care (93). However, there is mounting evidence that vitamin B₁₂ malabsorption increases with age, probably as a result of autoimmune atrophic gastritis (94,95). The primary manifestations of vitamin B₁₂ deficiency in the elderly are peripheral neuropathy and reduced nerve-conduction velocity (96), reversible psychiatric illnesses, particularly delirium and cognitive disturbances including dementia (97,98). Slight macrocytosis is often present, but macrocytic anemia is relatively uncommon.

Pyridoxine

Low pyridoxine (vitamin B₆) intake was observed in 18 out of 38 studies (79). According to a recent evaluation of 546 elderly subjects in Europe as part of the SENECA study, 27% of the males and 40% of the females had low vitamin B₆ intake as well as lower plasma concentrations of PLP (Pyridoxal Phosphate), a vitamin B₆ derivative (99).

Riboflavin Deficiency

Riboflavin deficiency has no specific clinical signs. Eight out of the 38 studies reviewed in Table 3 demonstrate low consumption of riboflavin, which is usually associated with lower consumption of other vitamins (79). In a recent study, it was found that in 75% of rural elderly Malays (100), riboflavin deficiency was associated with other deficiency states.

Fat Soluble Vitamins

The densities of vitamins E and D were markedly lower in 13 and 10 studies, respectively, and far below the calculated RDA density values (79). The lower vitamin E value may be partly due to the fact that the database used in the study takes into account a 50% loss of vitamin E during cooking (79,101). Vitamin D density is lower because milk and milk products contain only traces of vitamin D and as in an Austrian study (79,102), the elderly did not consume marine fish. Thus the main sources of vitamin D were eggs and meat, which contain only small amounts of this micronutrient. Vitamin A density in most of the studies exceeded the calculated RDA density value.

Nutrient density appears to better reflect inadequate intake. It is a powerful tool for evaluating adequacy of micronutrient consumption because it is almost unaffected by individual under- or over-estimation of food intake. This is particularly true with the densities of vitamins D and E (fat soluble) as well as biotin, folic acid and vitamin B₆ (water soluble) (79).

Antioxidant Vitamins

In one of the recent surveys on the elderly nutritional status (103), which compared antioxidant vitamin status in elderly

cachectic (n=21) and non cachectic (n=106) subjects, the authors could not demonstrate differences in routine clinical laboratory tests but could show significant differences in plasma concentrations of ascorbic acid and carotenoids. This study demonstrates the significance of clinical evaluation of PEM in further identifying nutritional deficiencies in the elderly. In another study, 10% of 416 hospitalized elderly subjects suffered from atrophic glossitis, which correlated with lower plasma albumin as well as serum cholesterol, ascorbic acid, cholcacidiol and vitamin B₁₂ concentrations (104).

Conclusions

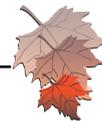
Balanced nutrition is an important and controllable factor in reaching and maintaining healthy old age. The elderly are widely considered to be at higher risk for nutritional problems. Inadequate food intake in old age can lead to marginal or suboptimal intakes of macro- and micronutrients, thereby contributing to the development of many degenerative diseases as well as further promoting various age-related changes in body composition and physiological function. There are many factors contributing to nutritional deficiencies in the elderly: physiological, psychological and social. Diseases, with their direct and indirect consequences, further deteriorate the nutritional status. There are also many physiological processes, like sarcopenia of aging, that are not yet well understood. Nevertheless, in many cases nutritional deficiency can be detected early and treated, thereby minimizing the detrimental effects of malnutrition on the function and general well-being of the elderly.

REFERENCES

1. McCay CM, Crolwell M, Maynard L. The effect of retarded growth upon the length of the life span and ultimate body size. *J Nutr* 1935;10:63-79.
2. Yu BP. Aging and oxidative stress: modulation by dietary restriction. *Free Radic Biol Med* 1996;21:651-68.
3. Masoro EJ. Caloric restriction and aging: an update. *Exp Gerontol* 2000;35:299-305.
4. Sohal RS, Ku HH, Agarwal S, Forster MJ, Lal H. Oxidative damage, mitochondrial oxidant generation and antioxidant defenses during aging and in response to food restriction in the mouse. *Mech Ageing Dev* 1994;74:121-33.
5. Cefalu WT, Bell-Farrow AD, Wang ZQ, Sonntag WE, Fu MX, Baynes JW, Thorpe SR. Caloric restriction decreases age-dependent accumulation of the glycoxidation products, N epsilon-(carboxymethyl)lysine and pentosidine, in rat skin collagen. *J Gerontol A Biol Sci Med Sci* 1995; 50:B337-41.
6. Van Remmen H, Ward WF, Sabia RV, Richardson A. Gene expression and protein degradation. In: Masoro EJ, ed. *Handbook of Physiology*. New York: Oxford University Press, 1995:171-234.



7. Sabatino F, Masoro EJ, McMahan CA, Kuhn RW. Assessment of the role of the Glucocorticoid system in aging processes and in the action of food restriction. *J Gerontol Biol Sci* 1991;46:B171-9.
8. Kagawa Y. Impact of Westernization on the nutrition of Japanese: changes in physique, cancer, longevity and centenarians. *Prev Med* 1978; 7:205-17.
9. Roth GS, Lane MA, Donald K, Ingram DK, Mattison JA, Elahi D, Tobin JD, Denis Muller D, Metter EJ. Biomarkers of caloric restriction may predict longevity in humans. *Science* 2002;297:811.
10. Ikeyama S, Kokkonen G, Shack S, Wang, Xian T, Holbrook NJ. Loss in oxidative stress tolerance with aging linked to reduced extracellular signal-regulated kinase and Akt kinase activities. *FASEB J* 2002; 16: 114-6.
11. Morley JE, Armbrrecht HJ, Coe RM, Vellas B, eds. *The Science of Geriatrics*. Paris: Serdi Publisher, 2000.
12. Harman D. Free radical theory of aging: role of free radicals in the origination of life, ageing and disease processes. In: Johnson JE Jr, Walford R, Harman D, Miquel J, eds. *Free Radicals, Aging, and Degenerative Diseases*. New York: Liss, 1986:3-49.
13. Food and Nutrition Board, Institute of Medicine. DRI for thiamin, riboflavin, niacin, vitamin B₆, folate, vitamin B₁₂, pantothenic acid, biotin and choline, 1998. DRI for calcium, phosphorus, magnesium, vitamin D, and fluoride, 1999. DRI for vitamin C, vitamin E, selenium, and carotenoids, 2000. Washington, DC: National Academy Press.
14. Nutrition Reviews. Dietary reference intakes. *Nutr Rev* 1997;55:319-51.
15. Yates AA, Schlicker SA, Suitor CW. Dietary reference intakes: the new basis for recommendations for calcium and related nutrients, B vitamins, and choline. *Am J Diet Assoc* 1998;98:699-706.
16. Monsen ER. Dietary reference intakes for the antioxidant nutrients: vitamin C, vitamin E, selenium, and carotenoids. *J Am Diet Assoc* 2000;100:637-40.
17. Bales CW. What does it mean to be "at nutritional risk"? Seeking clarity on behalf of the elderly. *Am J Clin Nutr* 2001;74:155-6.
18. Stanga Z, Allison S. Nutrition in the elderly. In: Sobotka L, ed. *Basics in Clinical Nutrition*. 2nd ed. Prague: ESPEN & Galen, 2000:215-34.
19. Fidanza F, Simonetti MS, Cucchia M, Giulioni-Balucca G, Losito G. Nutritional status of the elderly. II) Anthropometry, dietary and biochemical data of old pensioners in Perugia at the fifth year follow-up. *Int J Vit Nutr Res* 1984;54:75-90.
20. Fidanza F, Coli R, Coli AM, et al. Nutritional status of a group of self-sufficient institutionalized elderly people in Perugia (Italy). *Int J Vit Nutr Res* 1992;62:273-80.
21. Cruz JA, Moreiras-Varela O, Van Staveren WA, Trichopoulou A, Roszkowski W, Euronut SENECA investigators. Intake of vitamins and minerals. *Eur J Clin Nutr* 1991;45(Suppl 3):121-38.
22. De Groot LCPGM, Hautvast JGAJ, Van Staveren WA, Euronut SENECA investigators. Nutrition and health of elderly people in Europe. *Nutr Rev* 1992;50:185-94.
23. Hercberg S, Preziosi P, Galan P, et al. Vitamin status of a healthy French population: dietary intakes and biochemical markers. *Int J Vit Nutr Res* 1994;64:220-32.
24. Morley JE. Anorexia of aging: physiologic and pathologic. *Am J Clin Nutr* 1997;66:760-8.
25. Noskovski H, Havivi E, Habor B, Reshef A. Nutritional status of the institutionalized elderly. *Israel J Med Sci* 1985;21:260-3.
26. Dror Y, Stern F, Nemes L, Hart J, Grinblat J. Estimation of vitamin needs - riboflavin, vitamin B₆ and ascorbic acid, according to some blood parameters and functional-cognitive and emotional indices in a selected well-established group of elderly in a home for the aged in Israel. *J Am Coll Nutr* 1996;15:481-8.
27. U.S. Department of Agriculture, Agricultural Research Service. Food and nutrient intakes by individuals in the United States by sex and age, 1994-96. USDA Nationwide Food Surveys Report No 96-2. Betsville: Agricultural Research Service, 1998.
28. Millward DJ. Optimal intake of protein in the human diet. *Proc Nutr Soc* 1999;58:403-13.
29. Sehl ME, Yates FE. Kinetics of human aging: I. Rates of senescence between ages 30 and 70 years in healthy people. *J Gerontol* 2001;56A:B198-208.
30. Morley JE. Anorexia, sarcopenia, and aging. *Nutrition* 2001;17:660-3.
31. Papas AS, Joshi A, Giunta JL, Palmer CA. Relationship among education, dentate status and diet in adults. *Spec Care Dentist* 1998;18:26-32.
32. Roberts SB, Fuss P, Young VR. Control of food intake in older men. *J Am Med Assoc* 1994;272:1601-6.
33. Rolls B, Dimeo K, Shide D. Age related impairments in the regulation of food intake. *Am J Clin Nutr* 1995;62:923-31.
34. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine and neurocognitive function in the elderly. *Am J Clin Nutr* 2000;71:614S-20S.
35. Essama-Tijani JC, Guillard JC, Potier de-Curcy G, Fuchs F, Richard D. Folate status worsen in recently institutionalized elderly people without evidence of functional deterioration. *J Am Coll Nutr* 2000;19:392-404.
36. Stahlin HB. Malnutrition and mental function. *Z Gerontol Geriatr* 1999;32(Suppl):127-30.
37. Rosenbloom CA, Whittington FJ. The effect of bereavement on eating behavior and nutrient in elderly widowed persons. *J Gerontol* 1993;48:S223-9.
38. Shahar DR, Schultz R, Shahar A, Wing RR. The effect of widowhood on weight changes, dietary intake, and eating behavior in the elderly population. *J Aging Health* 2001;13:186-99.
39. Rojas AI, Phillips TJ. Patients with chronic leg ulcers show diminished levels of vitamins A and E, carotenes, and zinc. *Dermatol Surg* 1999;25:601-4.
40. Falch JA, Mowe M, Bohmer T. Low levels of serum ascorbic acid in elderly patients with hip fracture. *Scan J Clin Lab Invest* 1998;58:225-8.
41. Chandra RK. Effect of vitamin and trace element supplementation on immune response and infection in elderly subjects. *Lancet* 1992;340:1124-7.
42. Buzina-Suboticanec K, Buzina R, Stavljenic A, et al. Ageing, nutritional status and immune response. *Int J Vitam Nutr Res* 1998;68:133-41.
43. Schlenker ED. *Nutrition in Aging*. 3rd ed. Boston, Massachusetts: McGraw-Hill Companies, Inc., 1998.



44. Suter PM, Haller J, Hany A, Vetter W. Diuretic use: a risk of subclinical thiamin deficiency in elderly patients. *J Nutr Health Aging* 2000;4:69-71.
45. Benton D, Donohoe RT. The effect of nutrition on mood. *Public Health Nutr* 1999;2:403-9.
46. Sullivan D, Lipschitz D. Evaluating and treating nutritional problems in older patients. *Clin Geriatr Med* 1997;13:753-65.
47. Morley JE. Anorexia of aging and protein energy undernutrition. In: Morley JE, Glick Z, Rubenstein LZ, eds. *Geriatric Nutrition: a Comprehensive Review*. New York: Raven Press, 1995:75-8.
48. Seiler WO. Clinical pictures of malnutrition in ill elderly subjects. *Nutrition* 2001;17:496-8.
49. Feldman J, Peleg L, Yaretsky A. Clinical, social and economic aspects of comprehensive geriatric assessment. *Harefuia* 1999;136:933-5.
50. McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital. *BMJ* 1994;308:945-8.
51. Morley JE, Silver AJ. Nutritional issues in nursing home care. *Ann Intern Med* 1995;123:850-9.
52. Flaherty JH, Perry HM 3rd, Lynchard GS, Morley JE. Polypharmacy and hospitalization among older home care patients. *J Gerontol A Biol Sci Med Sci* 2000;55:M554-9.
53. Montuclard L, Garruste-Orgeas M, Timsit JF, Misset B, De Jonghe B, Carlet J. Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. *Crit Care Med* 2000;28:3389-95.
54. Barrocas A, Belcher D, Champagne C, Jastram C. Nutrition assessment: practical approaches. *Clin Geriatr Med* 1995;11:675-713.
55. Palmar RM. Failure to thrive in the elderly: diagnosis and management. *Geriatrics* 1990;45:47-55.
56. Allison SP, Rawlings J, Field J, Bean N, Stephen AD. Nutrition in the elderly hospital patient Nottingham studies. *J Nutr Health Aging* 2000;4:54-7.
57. Bonnefoy M, Coulon L, Bienvu J, Boisson RC, Rys L. Implication of cytokines in the aggravation of malnutrition and hypercatabolism in elderly patients with severe pressure sores. *Age Ageing* 1995;24:37-42.
58. Pokrywka HS, Koffler KH, Remsburg R, et al. Accuracy of patient care staff in estimating and documenting meal intake of nursing home residents. *J Am Geriatr Soc* 1997;45:1223-9.
59. Roubenoff R, Hughes VA. Sarcopenia: current concepts. *J Gerontol* 2000;55A:M716-24.
60. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol*. 1998;147:755-63.
61. Wang J, Heymsfield S, Aulet M, Thornton J, Pierson R. Body fat from body density: underwater weighing vs. dual-photon absorptiometry. *Am J Physiol* 1989;256:E829-34.
62. Ellis KJ. Reference man and woman more fully characterized: variations on the basis of body size, age, sex, and race. *Biol Trace Elem Res* 990;26-27:385-400.
63. Castaneda C, Gordon P L, Fielding RA, Evans WJ, Crim MC. Marginal protein intake results in reduced plasma IGF-I levels and skeletal muscle fiber atrophy in elderly women. *J Nutr Health Aging* 2000;4:85-90.
64. Roubenoff R, Harris TB, Abad LW, Wilson PWF, Dallal GE, Dinarello CA. Monocyte cytokine production in an elderly population: effect of age and inflammation. *J Gerontol Med Sci* 1998;53A:M20-6.
65. Brown WF. A method for estimating the number of motor units in thenar muscles and the changes in motor unit count with aging. *J Neurol Neurosurg Psych* 1972;35:845-2.
66. Kaufman JM, Vermeulen A. Declining gonadal function in elderly men. *Bailleres Clin Endocrinol Metab* 1997;11:289-309.
67. Morley JE, Keiser FE, Perry HM, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism* 1997;46:410-3.
68. Geyelin HR, Harrop G, Murray MF, Corwin E. The use of insulin in juvenile diabetes. *J Metab Res* 1922;11:767-91.
69. Walsh CH, Soler NG, James H, et al. Studies in whole body potassium and whole body nitrogen in newly diagnosed diabetics. *Q J Med* 1976;45:295-301.
70. Charlton MR, Balagopal P, Nair KS. Skeletal muscle myosin heavy chain synthesis in type 1 diabetes. *Diabetes* 1997;46:1336-40.
71. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J. Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients. *J Clin Invest* 1995;95:2926-37.
72. Hughes VA, Fiatarone MA, Fielding RA, et al. Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. *Am J Physiol* 1993;264(6 pt 1):E855-62.
73. Colberg SR, Simoneau JA, Thaete FL, Kelley DE. Skeletal muscle utilization of free fatty acids in women with visceral obesity. *J Clin Invest* 1995;95:1846-53.
74. Barzilai N, She L, Liu BQ, et al. Surgical removal of visceral fat reverses hepatic insulin resistance. *Diabetes* 1999;48:94-8.
75. Shepherd PR, Kahn BB. Glucose transporters and insulin action. *N Engl J Med* 1999;341:248-57.
76. Cox JH, Cortright RN, Dohm GL, Houmard JA. Effect of aging on response to exercise training in humans: skeletal muscle GLUT-4 and insulin sensitivity. *J Appl Physiol* 1999;86:2019-25.
77. Roubenoff R, Rall LC, Veldhuis JD, et al. The relationship between growth hormone kinetics and sarcopenia in postmenopausal women: the role of fat mass and leptin. *J Clin Endocrinol Metab* 1998;83:1502-6.
78. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Age Dev* 1999;107:123-36.
79. Berner YN, Stern F, Polyak Z, Dror Y. Dietary intake analysis in institutionalized elderly: A focus on nutrient density. *J Nutr Health Aging* 2002; 6: 237-242
80. Bales CW, Di Silvestro RA, Currie KL, et al. Marginal zinc deficiency in older adults: responsiveness of zinc status indicators. *J Am Coll Nutr* 1994;13:455-62.
81. Henderson CT, Trumbore LS, Mobarhan S, Benya R, Miles TP. Prolonged tube feeding in long-term care: nutritional status and clinical outcomes. *J Am Coll Nutr* 1992;11:309-16.
82. Lewis BK. Nutrient intake and the risk of pressure sore development in older patients. *J Wound Care* 1998;7:31-9.
83. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. *J Nutr* 2000;130:1399S-406.



84. Jolobe OM. Prevalence of hypochromia (without microcytosis) vs. microcytosis (without hypochromia) in iron deficiency. *Clin Lab Haematol* 2000;22:79-80.
85. Fleming DJ, Jacque PF, Tucker KL, et al. Iron status of the free living elderly Framingham Heart Study cohort: an iron replete population with high prevalence of elevated iron stores. *Am J Clin Nutr* 2001;73:638-46.
86. Joosten E, Vanderelst B, Kerkhofs P, De Boeck S. Does dietary iron intake influence iron status in hospitalized elderly patients? *J Nutr Health Aging* 1999;3:8-10.
87. Ahluwalia N, Lammi-Keefe CJ, Bendel RB, Morse EE, Beard JL, Haley NR. Iron deficiency and anemia of chronic disease in elderly women: a discriminant- analysis approach for differentiation. *Am J Clin Nutr* 1995;61:590-6.
88. Olivares M, Hertamf E, Capurro MT, Wenger D. Prevalence of anemia in elderly subjects living at home: role of micronutrients deficiency and inflammation. *Eur J Clin Nutr* 2000;54:834-9.
89. Doyle W, Crawley H, Robert H, Bates CJ. Iron deficiency in older people: interaction between food and nutrient intake with biochemical measures of iron; further analysis of the National Survey of people aged 65 years and over. *Eur J Clin Nutr* 1999;53:552-9.
90. Ames BN. DNA damage from micronutrient deficiency is likely to be a major cause of cancer. *Muta Res* 2001;475:7-20.
91. Rampersaud GC, Kauwell GP, Hutson AD, Cerda JJ, Bailey LB. Genomic DNA methylation decrease in response to moderate folate depletion in elderly women. *Am J Clin Nutr* 2000;72:992-1003.
92. Haller J, Weggemans RM, Lammi-Keefe CJ, Ferry M. Changes in vitamin status of elderly Europeans: plasma vitamins A, E, B₆, B₁₂, folic acid, and carotenoids. SENECA Investigators. *Eur J Clin Nutr* 1996;50(Suppl 2):S32-46.
93. Mahamid M, Berner Y. Low plasma vitamin B₁₂ levels in hospitalized elderly population. Tel-Aviv: 10th Israel Congress in Gerontology, 1992.
94. Aimone-Gastin I, Pierson H, Jeandel C, et al. Prospective evaluation of protein bound vitamin B₁₂ (cobalamin) malabsorption in the elderly using trout flesh labeled in vivo with ⁵⁷Co-cobalamin. *Gut* 1997;41:475-9.
95. Nilsson-Ehle H. Age-related changes in cobalamin (vitamin B₁₂) handling. Implications for therapy. *Drugs Aging* 1998;12:277-82.
96. Oishi M, Mochizuki Y. Improvement of P300 latency by treatment of vitamin B₁₂ deficiency. *J Clin Neurophysiol* 1998;15:173-8.
97. Assantachai P, Yamwong P, Chongsuphajaisiddhi T. Relationships of vitamin B₁, B₁₂, folate and the cognitive ability of the Thai rural elderly. *J Med Assoc Thai* 1997;80:700-5.
98. Rabins P. Pernicious anemia and reversible dementia: Strachan and Henderson 30 years later. *Int J Geriatr Psychiatry* 1998;13:139-45.
99. Van der Wielen RP, Lowik MR, Haller J, Van den Berg H, Ferry M, Van Staveren WA. Vitamin B₆ malnutrition among elderly Europeans: the SENECA study. *J Gerontol A Biol Med Sci* 1996;51:B417-24.
100. Shahar S, Earland J, Powers HJ, Rahman SA. Nutritional status of rural elderly Malays: dietary and biochemical findings. *Int J Vitam Nutr Res* 1999;69:277-84.
101. Friedrich W. Vitamins. New York: Walter de Gruyter, 1988:16.
102. Koenig J, Elmadfa I. Status of calcium and vitamin D of different population groups in Austria. *Int J Vit Nutr Res* 2000;70:214-20.
103. Da-Cunha DF, De-Carvalho SF, Del-Lama Unamuno MD, Vannucchi H. Serum levels assessment of vitamins A, E, C, B and carotenoids in malnourished and non malnourished hospitalized elderly patients. *Clin Nutr* 2001;20:167-70.
104. Bohmer T, Mowe M. The association between atrophic gastritis and protein calorie malnutrition in old age. *Age Ageing* 2000;29:47-50.
105. Tucker K. Micronutrient status and aging. *Nutr Rev* 1995;53:S9-15.