Nutritional Reversion of Cognitive Impairment in the Elderly

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Neurocognitive function is a major determinant of life quality for elderly persons. As such, neurocognitive impairment is one of the most feared problems associated with aging. It hinders the capacity of elders to live independent and productive lives, and thus precipitates further disability, both physical and mental. Many people assume that aging is naturally associated with memory loss and cognitive function decline. However, that old hypothesis is increasingly challenged by newer studies which show that, whereas some loss of memory or of cognitive function does occur as a consequence of aging, much of the clinically significant decline in function can be averted or slowed [1]. In that context, dietary, lifestyle and pharmacological interventions have been evaluated to estimate their relative contribution to protecting mental function in people as they age. The purpose of this paper is to review the evidence that various potentially modifiable nutritional or dietary factors are protective.

The role of nonmodifiable factors, such as genetics and life history, in contributing to the heterogeneity of cognitive function in genetics is not trivial. For example, a study done in the Netherlands suggests that mental function decline is a function of genotype [2]. In particular, those who carry the Apo4E gene associated with Alzheimer’s are at greater risk of cognitive function decline than people who did not carry this allele. The challenge, therefore, is to identify and characterize those dietary and lifestyle factors which are modifiable and which may contribute to ‘positive deviation’ or the maintenance of cognitive abilities in aging populations.

Dementia is defined as a syndrome characterized by multiple cognitive deficits severe enough to impair occupational or social functioning, that represents a decline from a higher level of functioning. Dementia is mainly
related to two discrete illnesses, namely Alzheimer’s disease and vascular dementia [3]. The former has been classically considered responsible for over 70% of dementia cases and vascular disease, causing lacunar infarctions or white matter vascular changes in 5–20% of cases, while other causes are hydrocephalus, severe depression, metabolic disorders and mass occupying lesions. However, recent pathological evidence is changing this concept. A study done in Canada showed that 80 of 412 patients with dementia had vascular cognitive impairment and neuroimaging showed that 30% had multiple infarcts, 40% had white matter changes and 14% had a single strategic stroke [4]. Other studies have shown that more than 30% of patients with Alzheimer’s disease show cardiovascular pathology [5]. Taking this into account, preventive approaches to dementia should consider the pathophysiology and conditions associated with both diseases.

Vascular dementia is directly related to classical cardiovascular risk factors [6] and their dietary and pharmacological management will probably reduce the incidence of overt or silent brain infarctions and prevent or reverse at least some of the associated dementia. The incidence of stroke can be reduced by 35–40% for every 5–6 mm Hg reduction in diastolic blood pressure achieved by reducing salt intake and/or by pharmacological means [7]. The HOT study went further and showed that there are optimal ranges of blood pressure in which the best reduction in coronary events and stroke is achieved, demonstrating that the association between stroke and blood pressure describes a J curve [8]. Likewise, stroke incidence is reduced when blood lipid levels are managed using diet or drugs [9]. Therefore, there is no doubt that an adequate management of the classical cardiovascular risk factors, particularly by altering high serum lipid levels and blood pressure through the dietary and pharmacological means which have been well reviewed in consensus conferences and which are well known in the medical community, will contribute to a reduction in the incidence of lacunar infarctions and thus to age-related cognitive impairment secondary to vascular dementia.

As mentioned above, the other cause of dementia is Alzheimer’s disease in which amyloid and tau protein metabolism is altered, and inflammation, oxidative stress and hormonal changes occur [10]. The disease is neuropathologically characterized by the accumulation in the extracellular space of neuritic plaques composed primarily of a fibrillar peptide termed amyloid β. This peptide is derived from the proteolytic cleavage of amyloid precursor protein by a β-secretase. Additionally, some missense mutations may produce a longer amyloid β peptide (Aβ42) that is more fibrillogenic [11]. Abnormal phosphorylation of tau proteins also contribute to the neuronal damage in Alzheimer’s disease. The mechanism by which amyloid β causes neuronal damage is not clear but there are several explanations that have received experimental support. It is possible that this peptide may act through cell membrane receptors, for example causing abnormal phosphorylation of tau proteins or increasing intracellular oxidative stress after binding to receptors for advanced glycation end-products (RAGE).
The peptide could also cause DNA damage or signal apoptotic pathways. Another putative mechanism is that amyloid β increases intracellular calcium levels or potentiates the toxicity of excitatory amino acids (the so-called excitotoxicity mechanism). Other theories propose that the deposition of amyloid β causes physical trauma to surrounding axons and triggers an axonal reaction or an inflammatory reaction [12]. In fact, amyloid β can cause a glial inflammatory reaction. The glial cells are the main mediators of brain immunity and produce an assortment of immune signaling and effector molecules, including proinflammatory and anti-inflammatory cytokines. The latter can further promote the aggregation of amyloid. Inflammation may potentiate NO-mediated neuronal damage or promote NMDA (N-methyl-D-aspartate) excitotoxicity. Brain inflammation can be selectively toxic to cholinergic neurons and explain the selective decrease in acetylcholine release from cholinergic neurons, mainly projecting to the basal forebrain and hippocampus [13]. It is well known that nicotinic cholinergic dysfunction is the leading neurochemical feature of Alzheimer’s disease, and nicotinic acetylcholine receptors have attracted much interest as possible targets for therapy [14].

As in many diseases, genetic and environmental factors interact in the development of clinical disease. Early-onset Alzheimer’s is associated with mutations in the presenilin 1 gene on chromosome 14, presenilin 2 gene on chromosome 1, and the amyloid β precursor protein on chromosome 21. On the other hand, late-onset Alzheimer’s is associated with genetic polymorphisms that act as risk factors. Thus far, two genetic risk factors have been identified: the α2-macroglobulin on chromosome 12 and the ApoE gene on chromosome 19 [15, 16]. ApoE E4 allele is associated with a higher risk for the disease and a higher rate of cognitive decline [17, 18]. However, environmental factors are known to play a very important role in the cognitive decline of Alzheimer’s disease [19]. The increased knowledge of the pathogenesis of dementia and less severe forms of neurocognitive impairment described above, coupled with the rise in the number of elderly people expected to be affected by cognitive impairment, has stimulated the research on dietary manipulations to reverse or retard the progression of dementia and other forms of neurocognitive impairment in the elderly. We will discuss in detail the roles of antioxidants, dietary modulation of inflammation, dietary manipulation of cholinergic transmission, use of phytoestrogens, glucose enhancement of memory mechanisms and the importance of homocysteine, vitamin B12 and folic acid deficiencies, and alcohol intake.

**Antioxidants**

The hypothesis that ‘increased’ antioxidant intake may inhibit or reverse age-related cognitive dysfunction, whether it involves simple memory deficits or more severe dementia, has grown primarily from the knowledge that
Alzheimer’s disease involves substantial oxidative damage, neuronal damage, and free radical accumulation, and lipid peroxidation which may all contribute to the deteriorating clinical picture. Neurons can be specially susceptible to oxidative damage since their glutathione content is low, their membranes contain a high proportion of polyunsaturated fatty acids and brain metabolism requires substantial quantities of oxygen [20]. Observational studies relating tests of cognitive function to either (1) concentrations of antioxidant vitamins, (2) markers of oxidative stress, or (3) assessments of intake of foods with antioxidants and/or of antioxidant supplements have been performed but there are almost no randomized clinical trials to study the cognitive effects of antioxidants.

Analysis of the data obtained from the Third National Health and Nutrition Examination Survey in the United States, after adjusting the data for age, education, income, trace elements and minerals and for vascular risk factors revealed an association between decreasing blood levels of vitamin E per unit of cholesterol and poorer memory whereas it showed no association between selenium, vitamin C, β-carotene or vitamin A and memory [21]. Other investigators reassessed a sample of 137 elders after 6 years of an initial evaluation and related changes in cognition with vitamin intake. They observed that people using vitamin supplements fared better than those not using them, but no consistent association between memory performance and a specific vitamin was found [22]. A study done in Mexican elders showed that cognitive performance improved with increasing intakes of carbohydrate, fiber, thiamine, vitamin C, iron, zinc, β-carotene and vitamin E [23].

There are few reported prospective clinical trials on the effects of antioxidants and cognitive function. Sano et al. [24] studied the effects of 2,000 IU/day of α-tocopherol and selegiline 5 mg/day during 2 years on the occurrence of death, institutionalization, loss of the ability to perform at least two of the three basic activities of daily living and severe dementia. They observed that selegiline and tocopherol delayed the appearance of these endpoints by approximately 200 days. The main effect was observed on institutionalization. However, neither α-tocopherol nor selegiline had any effects on cognitive function tests and there was a significantly higher incidence of falls among those receiving the medications, an effect which could be due to the direct effects of selegiline on catecholamine production. However, the study by Sano et al. [24] used a very high dose (2,000 IU/day) and has been challenged [25] on the basis of its design, assumptions, and statistical interpretations. However, there is enough basis to propose new controlled trials on vitamin E and cognitive decline [26].

Another nutritional product with antioxidant properties is *Ginkgo biloba* extract (GbE). The effects of this product on cognition were assayed in 309 patients during 52 weeks in a double-blind, placebo-controlled trial. The authors observed a lower decline in ADAS-Cog and GERRI scales in treated
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patients, compared with controls. However, as they point out in the discussion, a major concern of this study is the large number of patients lost to follow-up before the assessment at 26 weeks, since only 202 patients were able to provide evaluable data at that point of the study. Although the authors conducted an intention-to-treat analysis, there are always doubts about the fate of lost patients and its effects on the final results [27]. An analysis of 50 articles on the use of GbE on cognitive decline selected four papers that used standard inclusion criteria and a double-blind, placebo-controlled design. The overall analysis of these four papers showed a 3% difference in the Alzheimer Disease Assessment Scale cognitive subset between treated and placebo groups [28]. Clearly, new placebo-controlled prospective trials on the effect of nutrients with antioxidant properties on the cognitive function of the elderly are needed.

Dietary Modulation of Inflammation

The possibility the amyloid β exerts its damaging effects eliciting an inflammatory response has stimulated the research on pharmacological or nutritional modulation of inflammation as preventive or therapeutic measures for cognitive decline. Long-term users of nonsteroidal anti-inflammatory drugs have lower odds ratios for the development of cognitive decline [29]. The use of indomethacin was demonstrated to have a significant effect of cognition, but with a high incidence of gastrointestinal side effects [30]. A more recent study tested the association of diclofenac and misoprostol (to reduce the incidence of gastrointestinal complications) in patients with a diagnosis of Alzheimer’s disease, in a double-blind fashion, during 25 weeks. These authors did not find any significant difference between the active drug and placebo in cognitive outcomes, however they claim a nonsignificant trend towards improvement in the treatment group, that should be tested in a larger sample [31].

Besides pharmacological means, there are dietary manipulations that can modulate inflammatory reactions, namely changes in the dietary intake of fats. Fatty acids of the n-3 series compete with arachidonic acid for cyclooxygenase and lipoxygenase, producing less active prostaglandins and leukotrienes [32]. Several epidemiological studies have looked for an association between dietary fat intake and cognitive decline. In a study performed in the Netherlands in 5,385 subjects aged 67 years, followed for 2 years, 58 individuals became demented. Dietary surveys showed that subjects with the highest intakes of total fat, saturated fat and cholesterol had an increased risk for dementia. Likewise, fish consumption, a source of n-3 fatty acids, was associated with a reduced risk of dementia, and specially of Alzheimer’s disease [33]. Another study in the Netherlands, involving 342 subjects aged over 65 years, followed for 3 years, showed a mean decline in Mini Mental Score of 0.27 ± 2.62 points and 15% of subjects had a decline of more than 2 points. In this
study, fish consumption was inversely but not significantly associated with cognitive decline. Linoleic acid consumption appeared as a risk factor for cognitive decline, when subjects with cognitive impairment at the baseline of the study were withdrawn from the statistical analysis [34]. A cross-sectional study of the effects of dietary fat was done in Italian subjects aged 65–84 years, who were either free-living or institutionalized, with mild but objective memory or cognitive decline, but without dementia, and whose dietary intake was measured by a 77-item semiquantitative food-frequency questionnaire. Subjects indicated how often during the previous year, on average, they had eaten a certain food, choosing from pictures of three different serving sizes or natural units, e.g. a glass of wine. Results showed that monounsaturated fat intake was associated with an improvement in the odds ratio of global cognitive functions and selective attention. Moreover, the effect of education on the odds of having a cognitive impairment decreased exponentially with monounsaturated fat intake [35]. In an ecological study comparing the incidence of cognitive impairment with dietary fat intake across different countries, a positive correlation between total fat intake and the incidence of Alzheimer’s disease was noted and fish consumption apparently reduced the incidence of the disease in European and North American populations [36]. Finally, a pathological study showed that patients with Alzheimer’s disease have lower concentrations of n-3 fatty acids in cholesterol esters from the central nervous system, compared to control subjects [37].

Unfortunately, all the evidence linking fat consumption with cognitive decline is epidemiological or circumstantial and, to our knowledge, there is no published prospective study designed to test the hypothesis that a high consumption of n-3 fatty acids could modulate central nervous system inflammatory responses and protect against memory decline.

Another possible dietary means of modulating inflammatory responses associated to the aging process is dietary restriction. This nutritional modulation has been shown to prolong longevity in mice and possibly in nonhuman primates [38, 39]. The most accepted explanation for the effect of caloric restriction is a protection against peroxidative processes, but inflammation could also be modulated. The activity of the inducible form of cyclooxygenase (COX-2) is enhanced in old animals [40]. A recent study in rats showed an age-related increase in COX-2 mRNA expression in the kidney. Dietary restriction blunted the age-related increase in COX-2 activity and reduced the generation of radical oxygen species and the production of several prostanoids such as thromboxane A2, prostaglandin I2 and prostaglandin E2 [41]. Also, the production of interleukin-6 by peripheral mononuclear cells from nonhuman primates can be reduced with dietary restriction [42]. Therefore it is possible that dietary restriction could modulate not only the generation of radical oxygen species but also the production of several mediators of inflammation. There is no clinical proof that such a dietary manipulation has an effect of cognition and the design of experiments to test
this hypothesis will be complicated, if not impossible, but we must have an open mind towards nutritional modulation of inflammation and its possible role to prevent cognitive decline.

**Dietary Manipulation of Cholinergic Transmission**

The defects in cholinergic transmission observed in Alzheimer’s disease have provoked the development of cholinergic augmentation therapies. Most drugs marketed at the moment for the treatment of the disease act by inhibiting acetylcholinesterase at the synaptic cleft. Most of these medications have significant, albeit very modest positive effects on the cognitive faculties of patients with Alzheimer’s disease and are not completely devoid of adverse effects [43].

Dietary manipulation of cholinergic transmission has also been attempted with less than modest results. The use of lecithin and choline for Alzheimer’s disease proved to be useless [44]. A more recent report assessed the effect of acetyl-L-carnitine in the disease [45]. This sterified form of carnitine may, among other actions, act as a partial direct cholinergic agonist and can be converted to acetylcholine. The authors studied 431 patients with a diagnosis of Alzheimer’s disease, that received in a double-blind fashion the active compound or placebo during 1 year. No significant effect of acetyl-L-carnitine was observed on the evolution of a series of cognitive tests. In a subset of patients with early-onset disease, a nonsignificant trend towards an improvement with acetyl-L-carnitine was observed, an observation that could deserve further interest in this product.

Thiamine could also have a role in the enhancement of cholinergic transmission. There is pathological and clinical evidence that patients with Alzheimer’s disease have low brain, plasma and red blood cell levels of thiamine [46, 47]. In clinical experiments with young subjects, the provision of large amounts of thiamine with young subjects improves the memory impairment induced by scopolamine injections, an experimental model of cholinergic transmission impairment [48]. Again, there is no prospective trial in which the effects of thiamine supplementation on elderly cognition has been assessed.

**Phytoestrogens**

There is clinical and epidemiological evidence that postmenopausal women receiving estrogen replacement therapy experience less cognitive decline than unsupplemented women [49]. Estrogens can act as important neurotrophic and neuroprotective factors. In rats, estrogen increases the levels of acetylcholine in the basal forebrain, hippocampus and frontal cortex [50]. Estradiol
promotes formation of functional dendritic spines and stimulates synaptogenesis, it also protects against injury induced by transient cerebral ischemia and can even protect against the damaging effects of amyloid β [51]. Unfortunately, postmenopausal women tend to discontinue estrogen replacement therapy due to side effects or fear of acquiring a hormone-dependent cancer.

A safer alternative to classical estrogen replacement could be the use of plant estrogens. This is a promising area, but clearly more studies are required to propose these substances as a replacement therapy. Isoflavones are chemical substances occurring naturally in plants that belong to the class of ‘phytoestrogens’. These isoflavones are exclusively found in legumes and soy is the main source [52]. Isoflavones are hydrolyzed by intestinal glycosidases and release the aglycones daidzein, genistein and glycitein, that have a half-life of 8 h after administration. Isoflavone supplementation decreases menopausal symptoms and has a trophic effect on vaginal epithelium [53]. In neuronal cell cultures, the phytoestrogen kaempferol is protective against amyloid β toxicity [54]. In ovariectomized rats, phytoestrogens significantly increased mRNA levels of brain-derived neurotrophic factor [55].

As always, the clinical trials to test the neuroprotective effects of phytoestrogens are lacking, but their design seems worthwhile.

**Glucose Enhancement of Memory Mechanisms**

There is evidence from rodents and humans that modest increases in circulating glucose regulate many brain and behavior functions, including learning and memory. On the other hand, aging is accompanied by alterations in glucose metabolism, specially in the brain. There is clinical and experimental evidence that the provision of a beverage with glucose enhances memory performance in young, healthy and demented human beings. The mechanisms of actions of glucose are not well known but probably related with a more efficient energy metabolism [56]. In elderly patients with and without Alzheimer’s disease, there is a correlation between brain glucose metabolism and cerebrospinal levels of amyloid β₁₋₄₂, a marker of residual brain function in demented patients [57]. In another study, the insulin response to a 75-gram carbohydrate load and changes in plasma amyloid precursor protein was measured. Subjects possessing the apo ε-4 allele had a milder plasma amyloid precursor protein reduction than subjects not bearing the allele. Therefore, insulin could be involved in the regulation of amyloidogenesis in patients with Alzheimer’s disease [58].

These results allow us to think that glucose and energy metabolism could also be associated with cognitive decline. Moreover, the enhancement of glucose transport and oxidation could have positive effects on cognition, among other effects. One of the most efficient ways to improve glucose metabolism is aerobic exercise [59]. This metabolic effect of exercise could
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	herefore explain the reported positive effects of training on cognition in elderly people [69].

The beneficial effects of training in the quality of life of old people are well known and a closer look at the effects on cognition is warranted.

**Homocysteine, Vitamin B12 and Folic Acid Deficiency**

The association between hyperhomocysteinemia and dementia in the elderly is becoming increasingly important. Elderly people are at increased risk for vitamin B12, vitamin B6, and folate undernutrition due to increasing prevalence of atrophic gastritis with hypochlorhydria or achlorhydria. The pH of the gastrointestinal tract is thus increased and the pH-dependent absorption of these nutrients, particularly of B12 and folate, is reduced. The prevalence of atrophic gastritis ranges from 20 to 50% depending on the population studied and how the diagnosis is made [61]. The physiological basis for deficiencies of these nutrients suggests that deficiencies of these nutrients may exist despite a dietary intake considered ‘adequate’ for younger individuals and thus suggests that supplementation with these nutrients may be especially relevant for people as they age. Riggs et al. [62] found that lower folate and B12 concentrations in plasma were associated with poorer spatial copying skills ($p = 0.003$ and 0.04, respectively) and plasma homocysteine, which varies inversely with folate and B12 concentrations, was a stronger positive predictor ($p = 0.0009$) of spatial copying performance than either folate or B12 concentrations [63].

Mechanisms by which B6 absorption may be reduced in elderly people are reduced pyridoxal phosphate (PLP) transport protein (albumin), increased PLP degradation, and alterations in B6 absorption and metabolism [64]. Vitamins B12, B6, and folate are involved in the metabolism of homocysteine, a sulfur amino acid. Metabolism of homocysteine requires folate as a methyl group donor and vitamin B12 as a cofactor. Another step in the metabolic pathway of homocysteine involves an enzyme which requires vitamin B6 as a cofactor. Thus, deficiencies of vitamin B12, vitamin B6, and folate can lead to the accumulation of homocysteine, which appears to have multiple etiologic roles in various neuropathologies and dysfunction of the nervous system. It is also possible that the loss of neurocognitive function due to deficiency of folic acid and vitamin B12 is caused by an impairment in methylation reactions as a consequence of a lower production of S-adenosylmethionine [61]. Epidemiological studies have consistently demonstrated that high plasma homocysteine is an independent risk factor for atherosclerosis [65–67]. As for hypercholesterolemia, both dietary and genetic factors contribute to elevate homocysteine levels. Folate, cobalamin and vitamin B6 nutritional status influence homocysteine levels [68]. Any alteration in folate metabolism leads to a deficiency of methyltetrahydrofolate impairing remethylation of homocysteine. Several
clinical studies have shown an inverse relationship between homocysteine and folate plasma levels in normal subjects [69, 70]. Folate supplementation leads to significant reductions in homocysteine levels [71, 72]. Approximately 10% of the population is deficient in enzyme methyltetrahydrofolate reductase and becomes extremely sensitive to marginal folate deficiency, and tends to have higher homocysteine levels [73].

Successive reports have shown an association between homocysteine levels and cognitive impairment in the elderly. A study showed lower folate and vitamin B12 and higher homocysteine levels in patients with histologically confirmed Alzheimer’s disease as compared with age-matched healthy controls [74]. The results of this paper suggest that the damaging effects of homocysteine in the central nervous system may go beyond its deleterious effect on vasculature. Maybe, the prooxidant capacity of the molecule also plays a role [75]. Finally, a recent paper reports much higher homocysteine levels in patients with subcortical vascular dementia, as compared to healthy subjects and patients with cerebral macroangiopathy. This suggests that homocysteine injures the small penetrating cerebral arteries and arterioles rather than larger brain-supplying arteries [76].

Vitamin B12 deficiency has also been related to cognitive impairment, even in the absence of the typical hematological manifestations of the deficiency [77]. Vitamin B12 also influences homocysteine levels, but it also has a direct trophic effect on the central nervous system [78].

The drawback of all these studies is that they are cross-sectional and cannot discriminate if these lower vitamin or higher homocysteine levels are a consequence rather than a cause of the cognitive impairment. Very few prospective studies have addressed this issue. A prospective study of vitamin B12 supplementation in elders failed to demonstrate a positive effect on their cognitive function [79].

As with the other nutrients, large prospective trials are badly needed to define the real role of high homocysteine, folic acid, vitamin B6 and vitamin B12 deficiencies as independent cardiovascular risk factors and their importance in the cognitive decline of the elderly. In many countries, staple foods are being enriched with folic acid, an intervention that will certainly contribute to lower homocysteine levels in the population. The usefulness of this intervention in terms of cardiovascular or brain health, remains to be established [80].

**Alcohol Intake**

Excessive and occult alcohol intake is frequent among the elderly. Alcohol can cause central nervous system damage in young and old individuals and many of the potential pathogenic mechanisms for alcoholic dementia are similar to the proposed brain-damaging mechanisms of Alzheimer’s disease, namely peroxidative damage, depletion of brain thiamine and excitotoxicity.
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[81]. Therefore it is not surprising that alcohol intake can potentiate the cognitive decline of the elderly. Alcohol abuse is 1.5 times more frequent in people with cognitive impairment and alcohol is probably responsible for approximately 5% of dementias. A study performed in Sweden showed that people with heavy alcohol use had a 4.4 times higher risk of dementia diagnosed as Alzheimer [82].

However, protective effects of moderate alcohol ingestion on cognition have also been reported. A French study showed a lower odds ratio for cognitive impairment among moderate wine consumers as compared to teetotalers [83]. Also, the consumption of light to moderate amounts of alcoholic beverages was associated with an odds ratio of 0.79 for stroke among North American male physicians followed for 12 years [84].

Although there is no reason to advise against moderate alcohol consumption, it is important to ask about heavy alcohol ingestion during the initial assessment of elderly patients. As they will probably deny an excessive alcohol intake, interrogation of close relatives living with the elderly or the use of short questionnaires such as CAGE can provide a reliable estimation of alcohol ingestion. Every effort should be made to discourage excessive alcohol intake in the elderly.

The association of nutritional or dietary factors with cognitive decline in the elderly provides a fascinating field of clinical and experimental research. However, for the moment the only nutrient that has demonstrated to be mildly useful to prevent cognitive decline in a well-designed prospective trial is \( \alpha \)-tocopherol. All the other hypotheses about the association of specific fatty acids, flavonoids or vitamin deficiencies require prospective clinical trials before they can be recommended for clinical use.

References

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Discussion

Dr. Rosenberg: This gives us an opportunity to focus on an issue which we need to keep in mind, and that is that, even though you were talking about intervention studies which might be considered as treatment, or designed to reverse cognitive decline, you are implicitly talking about prevention as well. One of the things that we need to be more precise about, and I think the SANO study is a good example, is whether we are talking about an intervention that constitutes treatment, secondary prevention (seeking to prevent new events or recurrent events), or primary prevention. There is a serious lack of good controlled intervention trials, but when they are done, we need to be precise about whether we’re talking about primary prevention, secondary prevention, or, as in the case of the SANO study, progression. I think the most egregious problem with the misinterpretation of the SANO study was that it was immediately taken as evidence that vitamin E prevents Alzheimer’s disease. As you pointed out, it probably doesn’t prevent anything, and it certainly doesn’t prevent Alzheimer’s disease!

Dr. Bunout: I agree with you. Our normal trend as clinicians is to intervene only with the sicker patients, but you are right, we should indeed look at primary prevention. Dr. Vellas may like to comment on that as he likes to work on patients with very mild impairment. However, patients with mild impairment also have very minor changes in cognitive function over time, so it’s difficult to study them.

Dr. Vellas: If we want to examine the protective effects of nutrition, we will need to do long-term studies, as was done with cholesterol or blood pressure. We need at least a 4- to 5-year study. I don’t think it will be possible to reverse the condition in people who already have severe dementia. Could you tell us about the studies that were done on energy restriction, mostly in animals? It was shown that a low-energy intake produced a reduction in cognitive disorders and pathological lesions.

Dr. Bunout: Yes, that was a beautiful experiment. Unfortunately I cannot see a way to study that effect in elderly people, neither do I see any way of convincing young people to restrict their intakes for long periods, maybe for 10 years, to see an effect. But in rats and monkeys, energy restriction certainly appears to retard the appearance of most age-related changes.

Dr. Frautschy: I think energy restriction would be a really bad idea in dementia. These patients lose a lot of weight anyway, and Alzheimer’s patients have severe glucose hypometabolism. With regard to Dr. Rosenberg’s comment on intervention vs. prevention, the NIH is trying to recruit patients for prevention studies. Although a recent paper showed unequivocally that estrogen does not help reduce the cognitive decline in Alzheimer patients, the NIH is committed to seeing whether it can prevent the onset of the disease, because there are extensive epidemiological data implying that it does.
Dr. Bunout: Again on energy restriction, I would like to see studies in young people. This is feasible if we confine ourselves to preventing obesity. Even in the monkey experiments, the energy restriction regimen was targeted at avoiding weight gain in comparison with monkeys fed ad libitum. This could certainly be done in young people.

Dr. Vellas: It is clear that energy restriction would have to be applied before the development of Alzheimer’s disease, not after. If energy restriction is protective against neurodegeneration in rats and monkeys, then maybe it is in humans as well. It is certainly possible that too high an energy intake, as we have now, may be a risk factor for an increasing incidence of Alzheimer’s disease in 20 or 30 years’ time. One problem is that, although we now have a high prevalence and incidence of Alzheimer’s disease, we don’t really know whether the incidence is higher than it was 20 years ago. Many people say the increase is apparent because of an increasing population of old people and better diagnosis.

Dr. Uauy: The data from the 1930s and 1940s on aging and prolongation of life span showed that it was a reduction in energy intake in the first third of the life span that had the greatest impact on overall survival, so we need to re-examine the possibility that early effects have long-term benefits. Unfortunately in human populations energy restriction early on in life is usually associated with infectious morbidity in a dirty environment, so we don’t have an appropriate epidemiologic model. We need to see what happens to children who have been energy-restricted early on but then later have been maintained on a healthy diet.

Dr. Bunout: Unfortunately I will have to disagree with my boss! There really are lots of studies in rats showing that if you start energy restriction after puberty you have the same effects. And if one is thinking about the possibility that energy restriction might be beneficial in adults, one is not aiming to impose undernutrition, only to avoid obesity.

Dr. Rosenberg: There has been another experiment of low energy intakes in humans which involves people who are considered to be restricted eaters. These are people who for behavioral reasons choose to eat less than others, and some even fall into the anorexia category. The intakes of these people are quite different from controls. A long study was done in an effort to see whether they had any of the early metabolic changes that are associated with the energy restriction experiments, but none were found, so I think we’re still some distance away from finding a human model that will examine that phenomenon. Although I think it’s fair to say that you can get many of the same effects by instituting energy restriction after puberty, my reading of the literature is that the effects are much more profound if you start earlier in life. The main reason, I think, that life expectancy at birth is affected by improvements in health in the first third of life is because we’re talking about average life expectancy at birth. That’s a quantitative arithmetic phenomenon. I don’t think we know that those improvements in health in the first third of life actually result in extending life to the age of 50 and beyond.

Dr. Frautschy: Energy restriction interacts with exercise. If you impose a 40% reduction in energy intake you get quite an extension of life in rats, but if you make those rats exercise, they die. However, if you impose a 10% reduction in energy intake and exercise the rats, you get a life extension equivalent to the 40% reduction, without so much stress. One of the first investigators of energy restriction – he’s retired now – has been practicing caloric restriction on himself for decades. He runs an internet company with his daughter where they teach caloric restriction, which
includes good nutrition and how to calculate the appropriate energy intake for your activities.

Dr. Bunout: That’s important. There are many people doing this type of energy restriction on a personal basis who know nothing about nutrition. Another point is that I recently learned that the control rats in the energy restriction experiments had to have a restricted intake as well because they become obese if they were allowed to eat \textit{at libitum}. Those so-called control rats had a 20\% energy restriction compared with \textit{truly ad libitum} fed fat rats, and also showed increased life span. So lesser amounts of energy restriction could prove effective in preventing age-related problems.

Dr. Freeman: I have a nice model of energy restriction – the ketogenic diet. We maintain children at their weight by adjusting the diet on the basis of the amount of energy used. These children don’t gain weight but grow quite normally.

Dr. Cole: There’s been a study from Wisconsin showing that long-term energy restriction in mice will virtually eliminate the inflammatory changes that occur spontaneously with aging – that is, large-scale increases in the expression of complement protein, interleukins, and other proinflammatory cytokines. So energy restriction does have an impact, at least on inflammation and on heat-shock proteins. It also reduces protein anabolism in rat brain, which might not be good for cognition but could have an impact on the development of the inflammatory disease in the brain that is associated with Alzheimer’s disease.

My second comment is that in the SANO study they used 2,000 IU of \(\alpha\)-tocopherol. There is a very nice study showing that the higher the intake of \(\alpha\)-tocopherol, the more competition you have with \(\gamma\)-tocopherol, and that \(\gamma\)-tocopherol – one of the natural tocopherols – is much more effective at scavenging nitric oxide peroxynitrite than \(\alpha\)-tocopherol. So it’s quite possible that high-dose vitamin E as \(\alpha\)-tocopherol may actually reduce your capacity to protect yourself from radicals produced by inflammatory processes.

Dr. Bunout: That’s an important point. There’s an ongoing vitamin E trial at the moment. What are they using now?

Dr. Vellas: That is the Alzheimer’s Disease Cooperative Study. They are again using 2,000 IU. There was a recent paper in \textit{Neurology} which seems to show that a supplement of vitamin C and E combined has a protective effect against Alzheimer’s. This needs to be looked at in depth.

Dr. Bourdel-Marchasson: You spoke about glucose administration in normal elderly subjects. I remember a Canadian paper about 5 years ago which showed that glucose had no effect on Alzheimer’s disease patients. Has there been any other trial on glucose?

Dr. Bunout: I’m not aware of any clinical trial on glucose.

Dr. Woods: I think the studies on glucose and improvement in memory and other cognitive functions were confounded. They were all associated with raised plasma insulin, and we and others have found that if you put insulin into the brain and don’t change the glucose at all, you get the same improvement in cognitive function, so it’s probably insulin rather than glucose that’s having the effect. The hippocampus is loaded with insulin receptors.

My other comment has to do with energy restriction and the lack of studies on its effects. In fact, in the USA, millions of people voluntarily go on an energy-restricted diet to try to reduce obesity. The problem is that the longer they go on with it, the more miserable they get, and the statistics are that over a few years the recidivism rate is 99 point something per cent. Such studies are doomed to failure unless you
Nutritional Reversion of Cognitive Impairment in the Elderly

absolutely restrict these people from eating. Neither people nor animals will maintain
a restricted diet in the long term unless they have no choice. There’s a quality-of-life
issue that goes with it.

Dr. Williams: My colleagues and I have been doing research for a number of
years on the effects of prenatal treatment with the nutrient choline in rats and mice.
We have shown that if you give supplements early in development you can actually
protect against the age-related decline in cognitive function, at least in a rodent
model. We’re not ready to test this in humans as we are not exactly sure how it
works; nevertheless, the work has been published and it’s quite a potent and powerful
effect. In the light of such findings that suggest to me that brain aging actually starts
prenatally, I wonder if there have been epidemiological studies looking at brain aging
and relating it to nutrition very early in development, in babies and in very young
infants.

Dr. Bunout: I do not know of any data on cognitive decline, but there are data on
the use of choline in the treatment of Alzheimer’s disease, and it had no effect.

Dr. Williams: But our effects are all from giving the supplement only during early
development, not throughout life, so this is prevention not treatment.

Dr. Grantham-MacGregor: Are there any epidemiological data on the prevalence of
Alzheimer’s disease across populations, and is there any tendency in countries where
infant malnutrition is high for there to be a high level of Alzheimer’s disease?

Dr. Uauy: In most countries where you have high infant mortality from malnutrition,
few people reach old age.

Dr. Grantham-MacGregor: It would be nice to know the prevalence.

Dr. Uauy: The ones who reach old age are usually not the ones who were
malnourished.

Dr. Bunout: I can tell you that countries that have a high intake of fruit and
vegetables have a low incidence of Alzheimer’s disease.

Dr. Peirano: I want to stress that people who have a fragmented sleep/wake cycle
throughout the 24 hours have cognitive decline. There is a highly effective way of
converting a healthy young subject into an elderly subject: you only have to reduce the
number of hours they sleep a day. This results in the appearance of insulin resistance,
high cortisol levels, and an increase in sympathetic tone; they also prefer to eat
carbohydrates.

Dr. Uauy: There have been many interventions involving different experiments,
with different models, and with uninterpretable data. I think we’re going to have to get
to grips with an animal model to screen nutrients and nutrient combinations. We’re
never going to be able to explore this in humans because it will take far too long.

Dr. Cole: As I study animal models of Alzheimer’s disease I can tell that if
your endpoint is pathogenesis you can study that in lots of different animal
models – transgenic and inhibitor models or infusion models. We are learning a
lot about nutritional endpoints. For example, the group at Eli Lilly is studying the
effects of cholesterol and high fat diet on the development of amyloid plaques and
finding an impact. Of course that’s not Alzheimer’s disease, and right now we don’t
have an animal model for the cognitive deficits and the real clinical symptoms. That’s
the animal model that people are all working to get.

Dr. Vellas: Though animal models are fine, I think it is now time to start doing
big interventional studies. Studies have shown that if you treat hypertension, you can
prevent vascular dementia and Alzheimer’s disease. We need to know if we can treat
high cholesterol in elderly people and prevent Alzheimer’s, or if we can treat diabetes
and prevent Alzheimer’s. It would be interesting to do interventional studies with
homocysteine and antioxidants. Now is the time to undertake a really big study with
thousands of people over a number of years. This is an important disease and it needs investigation on a large scale.

*Dr. Bunout:* The first thing we have to do is to sit down and agree on an endpoint for such studies. That’s the biggest problem. Cognitive function is clearly not a good endpoint. We will probably have to use a morphological endpoint.

*Dr. Vellas:* I think a good endpoint is the prevention of Alzheimer’s disease!

*Dr. Bunout:* But we have to measure it, that is the problem.

*Dr. Vellas:* I think the methodology for studying intellectual decline is adequate. What we need now is to design an interventional study.