Nutritional Factors and Alzheimer’s Disease

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Nutritional factors are integrally linked with Alzheimer’s disease (AD). Although AD patients have no changes in energy metabolism, fluctuations in weight are fairly common. The potential role of vitamin B₁₂ and folate, with the production of hyperhomocysteinemia, in the pathophysiology of AD is explored. The role of free-radical damage in AD is discussed. It is stressed that alterations in dietary lipids may play an important role in cognitive defects in AD secondary to their effects on neuronal membrane lipids. More research is needed on the role of nutrition in the ongoing development of cognitive changes in AD.

This article gives a broad overview of the research linking various nutritional factors with Alzheimer’s disease (AD). Increased scientific interest in recent years has led to a large number of publications covering a huge range of plausible nutritional hypotheses. We have concentrated our attention on those areas that we feel are most important in terms of the validity and weight of research. This review breaks down broadly into three sections: energy and weight change; the role of vitamins, with a marked emphasis on B vitamins; and fat and cholesterol.

Weight Change

Loss of weight was described in Alois Alzheimer’s (1) original case report of the first AD patient. It is also included as a “clinical feature consistent with the diagnosis of AD” in the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association Work Group report (2). There was reasonable consensus among early authors that patients with AD or other dementias seemed to have a higher risk of weight loss (3–5). However, a 1989 study by Burns and colleagues (6), which compared hospitalized versus nonhospitalized demented patients, showed that the nonhospitalized patients did not lose weight. To quantify these changes more precisely in a larger cohort, White and colleagues (7) observed 362 AD patients and 317 controls over a 2-year period. They showed that AD patients were twice as likely to lose weight (mean weight gain, 3 kg). Wang and colleagues (8) observed the weight of 362 AD patients and 317 controls over a 2-year period. They showed that AD patients were twice as likely to lose weight (mean weight loss, 5% of their initial body weight and also twice as likely to lose 5% of their initial weight). Unexpectedly, they were also shown to be more likely to gain 5% of their initial weight. This suggests a more generalized dysregulation of energy balance rather than simply weight loss. These results are consistent with those of Gillette-Guyonnet and colleagues (9), who observed a cohort of 50 AD patients for 30 months. Forty-eight percent of the cohort lost >4% of their initial weight (mean weight loss, 7.6 kg), while the rest of the cohort actually put on weight (mean weight gain, 3 kg). These results are consistent with those of Gillette-Guyonnet and colleagues (9), who observed the weight of 79 AD patients (divided into severe and less-severe groups) and 26 controls for 4 years. Although at baseline the controls had significantly higher mean weight than the AD groups, none of the three groups showed a significant mean weight change over the course of the study. Consistent with White and colleagues and Gillette-Guyonnet and colleagues, they also noted that the AD group was more likely to have a weight loss of >4.5 kg. These studies therefore point to the possibility of one particular subgroup of AD patients who are at risk of quite marked weight loss. However, this finding may also be due, at least in part, to regression to the mean for previously heavy or light eaters, once the patient no longer controls his or her own portion size.

Correlation Between Weight Loss and AD

Because of the variable times between disease onsets and study entrances, the previously described studies do not shed much light on the timing of the weight loss with regard to disease onset or progression. Barrett-Connor and colleagues (10) reported on a 20-year prospective cohort study of 299 elderly people that showed a very significant correlation between weight loss and subsequent development of AD. This result is important, as it suggests that the weight loss seen is not due to reduced energy intake because of dementia, but may itself be a risk factor for AD, or at least related to the causative pathology of AD. Further evidence for such a link comes from Grundman and colleagues (11). They showed a significant correlation between median temporal cortex (MTC) atrophy and decreased body mass index in AD patients. There was no significant relationship between MTC atrophy and cognitive function, leading the authors to hypothesize that the weight loss may be directly linked to the MTC atrophy and not as a consequence of cognitive decline. Although this correlation does not prove causation, if it were backed up by longitudinal evidence, it may help in targeting those patients who would be more likely to benefit from specific intervention to help prevent weight loss.

Weight Loss and Energy Expenditure

Weight loss occurs either by decreased energy intake or increased expenditure. Increased expenditure occurs, in turn, because of increased exercise or increased basal metabolic rate caused by catabolic states (e.g., inflammation, infection, or malignancy). Because of difficulties with dietary diaries and estimations of energy expenditure, the cause of weight loss reported in the earlier studies was unclear. A
Cambridge team (12) developed a doubly labeled water (D$_2$O$^{18}$) technique to evaluate total energy expenditure (TEE) in 14 “chronically ill mental patients.” Their results showed no increase in TEE, and this finding was duplicated by Poehlman and colleagues (13), who combined the measurement of TEE by the doubly labeled water technique with body composition by means of dual-energy x-ray absorptiometry scanning. These tests were performed on 30 AD patients, with a wide range of cognitive dysfunction, and 103 controls. The AD patients had a lower TEE and lower fat-free mass (FFM) than the control group, and, after correcting for FFM (as increased FFM increases energy expenditure), there were no significant differences in TEE between the groups. A separate study (14), using the same techniques, demonstrated that higher appendicular skeletal muscle mass had an association with higher levels of physical activity and energy intakes.

**Dietary Intervention**

Given the association between weight loss and frailty, disability, and mortality (15,16), strict attention to dietary intake and nutritional status must be seen as an important part of care offered to AD patients. There is evidence to suggest that, with careful attention, weight loss in AD patients can be minimized or prevented (17,18). One of the problems regarding dietary intervention is that patients at particular risk of weight loss or malnutrition are not discovered quickly enough. A widely used and well-validated nutritional screening tool is the mini-nutritional assessment tool (19), which quickly identifies those elderly patients who would benefit from further assessment and possible intervention.

**Dietary Restriction**

Paradoxically, although much work has gone into trying to elucidate the causes, and prevention, of weight loss in AD, there is a growing body of opinion that caloric restriction earlier in life may reduce the risk of developing AD in old age. The basis of this theory is that caloric restriction reduces oxidative stress, which has an important role in AD-related neurodegeneration. It is beyond the scope of this review to discuss the evidence supporting the theory of caloric restriction, but it has been thoroughly reviewed by Mattson (20).

In summary, weight loss does seem to be associated with AD early in its course, and some AD patients may have periods of weight gain. However, AD is consistently associated with weight loss in end-stage patients in nursing homes (21). Atrophy of the MTC may play a role, but this is probably only one of many genetic biological and behavioral causative factors.

**The Role of Vitamins**

Vitamin B$_{12}$ and folate both play vital roles in the one-carbon metabolism necessary for the production of nucleic acids. Thus, the dietary deficiency of either can block effective DNA synthesis, due to an inability to methylate deoxyuridine monophosphate to deoxythymidine monophosphate. The methyl group for this reaction is provided by a folate coenzyme, tetrahydrofolate (THF) polyglutamate. At one point in the pathway that results in the conversion of folate to THF polyglutamate, methyl THF is converted to THF in a reaction catalyzed by vitamin B$_{12}$. During this reaction, homocysteine is methylated to methionine. Thus, deficiency of vitamin B$_{12}$, in addition to blocking DNA synthesis, will also cause a build-up of homocysteine. It is also worth noting that methionine, after conversion to $s$-adenosyl methionine, is itself an important provider of methyl groups necessary to maintain normal brain metabolism. The other route by which homocysteine is metabolized is via a vitamin B$_{6}$ catalyzed conversion to cysteine.

There is longstanding clinical evidence that vitamin B$_{12}$ deficiency causes neuronal dysfunction in the form of dementia, peripheral neuropathy, or subacute combined degeneration. Folate deficiency is a recognized cause of depression, while vitamin B$_{6}$ deficiency also causes peripheral neuropathy.

**Biochemical Evidence**

A number of epidemiological studies have linked B vitamin status and neurological dysfunction (22). Recently, epidemiological evidence has emerged that specifically links AD with vitamin B$_{12}$, folate, and associated metabolites. Joosten and colleagues (23) compared serum levels of vitamin B$_{12}$, folate, total homocysteine (tHCY), and methylmalonic acid (MMA), a vitamin B$_{12}$ metabolite and marker of B$_{12}$ deficiency (24), in three groups of subjects: 52 AD patients, 50 hospital-bound controls, and 49 healthy controls. They found no significant differences between groups for serum B$_{12}$ or folate. However, MMA and tHCY levels were significantly higher in the AD group than in the healthy controls. For homocysteine, the AD group mean was also significantly higher than the hospitalized non-AD group. These findings were mirrored by smaller studies by McCaddon and colleagues (25) and Kristensen and colleagues (26). These results emphasized the potential pitfalls in the interpretation of B$_{12}$ status, and the authors felt that tHCY and MMA should be included in subsequent studies. The fact that only vitamin B$_{12}$ was measured, and not MMA or tHCY, may explain why Basun and colleagues’ (27) cross-sectional population-based study of 545 individuals with cognitive impairment did not reveal any correlation between AD and vitamin B$_{12}$ levels. The hypothesis that vitamin B$_{12}$ deficiency plays a role but that serum B$_{12}$ levels alone are a relatively insensitive marker is consistent with a carefully conducted study by Clarke and colleagues (28). They compared the serum tHCY, folate, and vitamin B$_{12}$ levels in 164 AD patients (76 histologically confirmed) and 108 controls. There were significantly higher tHCY levels and significantly lower levels of serum folate, red-cell folate (RCF), and vitamin B$_{12}$ ($p = .01$) in the histologically proven AD group than in the controls. Comparing the larger, clinically diagnosed AD group with the controls showed there were still significant differences for tHCY, serum folate, and RCF, but not for vitamin B$_{12}$.

**Pathological and Radiological Evidence**

Snowdon and colleagues (29) recently published data from the Nun Study comparing serum levels of numerous vitamins with postmortem pathological markers for AD and
neocortical atrophy. The 30 subjects were divided into two groups according to the numbers of AD-related brain lesions. Among the subset with significant numbers of lesions, it was found that folate deficiency correlated significantly with neocortical atrophy. This suggests that, in the presence of AD, folate deficiency may contribute to cortical atrophy. Clarke and colleagues (28) suggested a similar relationship. Of the 164 AD patients who originally participated in their study, 30 were followed up for 3 years with annual computed tomographic head scans. The authors then compared rates of atrophy of the mesial temporal lobe (MTL) with tHcy levels. Unsurprisingly, whatever the tHcy level, there was progressive decrease of the thickness of the MTL, but the tertile with the highest tHcy demonstrated the highest rate of atrophy (p = .03).

It seems reasonable to accept that, overall, these studies do at least point to a link between AD and low vitamin B₁₂ or folate levels, or raised homocysteine levels; the important question is whether these changes contribute to causing AD, or are an effect of the disease due to reduced intake. Clarke and colleagues’ (28) study showed that tHcy levels remained stable over the few years that patients were followed up, suggesting that raised tHcy may be causative.

There are various theories about possible mechanisms by which hyperhomocysteinemia is related to AD. There is strong evidence that hyperhomocysteinemia probably plays a role in cerebrovascular disease (30). There are also lines of evidence pointing to a more important role for cerebrovascular disease in AD than had previously been thought (31). If AD does indeed have common risk factors with cerebrovascular disease or ischemia is a contributory factor to AD, then it may well be that hyperhomocysteinemia is one of the factors linking the two.

With regard to molecular level mechanism, the possibility of a role for apoptosis in AD was suggested by Su and colleagues (32) in 1994. This idea has been backed by a great deal of evidence, although debate about mechanisms continues (33). However, Kruman and colleagues (34) have recently published a series of experiments demonstrating homocysteine-induced apoptosis in rat hippocampal neurons via a series of events, beginning with DNA damage. If this mechanism holds true for homocysteine in humans, it would provide an explanation for the role of vitamin B₁₂ or folate deficiency in AD.

Other Vitamins

The evidence for the role of oxidative stress in the neuropathology of AD has led to speculation that dietary vitamins with antioxidant properties may have a role in the prevention or slowing of cognitive decline in AD. The epidemiological evidence for this has been reviewed by Launer (35) and is at best inconclusive, in that Launer’s conclusion is that we need to await the results of larger, better designed trials. Sano and colleagues’ (36) trial of α tocopherol (vitamin E) and selegeline fits that description and showed a reduced risk of death, institutionalization, and loss of ability to perform activities of daily living for those in the selegeline and tocopherol treatment groups. However, with the high doses used, this must be considered in the role of medical treatment and not nutrition.

**Fat and Cholesterol**

Interest in a possible link between AD and cholesterol arose for two reasons. First, an association was noted between coronary heart disease (CHD) and increased risk of AD (37), which led to a search for relationships between CHD risk factors and AD; more theories than clear correlations were demonstrated in which cholesterol figures strongly (38,39). Second, it was discovered that the presence of the epsilon-4 allele of the apolipoprotein E (APOE) gene was related to increased risk of developing AD (40). The ApoE protein, coded for by APOE, is present in plasma and cerebrospinal fluid and serves as a ligand for low-density lipoprotein receptors and, through its interaction with these receptors, appears to be involved in the transport of cholesterol and other lipids between neurons (39).

Although the APOE epsilon-4 allele is related to increased AD risk, and also to increased serum cholesterol (39,41), there is conflicting evidence regarding a link between raised serum cholesterol and AD. Evans and colleagues’ (42) cross-sectional population-based study of 87 of 411 African Americans diagnosed with AD demonstrated a higher mean total cholesterol (TC) in those with AD than those without AD among the group of patients not carrying the epsilon-4 allele. However, among those with epsilon-4, this relationship was not statistically significant. Jarvik and colleagues’ (43) data on 206 AD cases and 276 controls showed that the significant interaction between APOE and AD was dependent on TC, age, and sex, although TC levels did not fully explain the APOE epsilon-4—AD association. Kuo and colleagues (44) performed immediate postmortems on 64 neuropathologically diagnosed AD cases and 36 controls. They found that serum TC and low-density lipoprotein cholesterol were correlated with the amount of Abeta 42 in brain tissue, independent of the ApoE4 allele. In Notkola and colleagues’ (45) longitudinal study of 444 elderly Finnish men, a cholesterol level of ≥6.5 was found to be a significant risk factor for AD after controlling for age and the epsilon-4 allele. However, they also showed that in men who subsequently developed AD, the serum cholesterol decreased before the onset of cognitive decline. However, Romas and colleagues (46) examined this relationship in 178 AD cases and 680 controls and found that after adjustment for confounders there was no relationship between fasting serum lipids and AD risk. Kuusisto and colleagues (47), in their study of hyperinsulinemia in AD in 980 elderly Finns, demonstrated that low total serum cholesterol was independently associated with increased risk of AD. Therefore, the relationship between serum cholesterol and AD is unclear on current evidence.

**Dietary Fat Intake**

Despite the arguable relationship between serum cholesterol and AD, there is some epidemiological evidence linking dietary cholesterol intake to AD. The strongest comes from two studies by Kalmijn and colleagues. In the Rotterdam study (48), 5434 subjects aged older than 55 years were interviewed regarding dietary habits, then observed for up to 4 years. In the Zutphen study (49), 476 men were observed for 5 years. In both studies, relative risks for incident dementia were calculated for various dietary factors. In
both, total fat, saturated fat, and cholesterol intakes correlated with the risk of developing dementia. Both studies also showed that fish consumption of >20 g daily reduced the risk of cognitive decline, dementia, and, particularly, AD. However, there was no statistically significant difference in N-3 polyunsaturated fatty acid intake between those who went on to develop AD and those who did not. Other epidemiological studies have linked dietary fat intake and cognitive decline, but not specifically with a diagnosis of AD.

In Vitro Evidence for the Role of Cholesterol

There have been a number of in vitro studies examining the relationship between cholesterol and beta amyloid (Abeta), the insoluble form of the protein found deposited in AD brains as a result of beta then gamma secretase cleavage of amyloid precursor protein (APP). Cholesterol decreases secretion of the secreted form of APP (50) through its inhibition of the glycosylation of APP (51). Reduction of cellular cholesterol levels in living hippocampal neurons completely inhibits beta-secretase cleavage of APP in forming Abeta while not affecting the generation of nonamyloidogenic secretory APP (52). Subsequently supplementing the cholesterol-depleted cells with cholesterol caused a 1.8-fold increase in secretion of Abeta 1-40 (53).

High Cholesterol Diet in Animal Studies

Animal studies using cholesterol-fed rabbits have shown them to have a twofold increase in beta-amyloid concentration in the hippocampal cortex (54). Other investigators (55) have studied the effects of a high cholesterol diet on a doubly transgenic mouse that expresses human presenilin 1 and mutant human APP. They showed that diet-induced hypercholesterolemia results in increased levels of Abeta deposition. These levels correlated with both plasma and TC in the central nervous system. Similar to the previously described in vitro studies, the hypercholesterolemic mice had decreased APPs and increased C-terminal fragments as a result of beta cleavage of APP. Brain sections revealed both increased size and number of Abeta deposits compared with basal-diet-fed controls. Until very recently there were obvious concerns about the applicability of such results as there was no evidence to suggest that a reduction in beta-amyloid deposits correlated with a decrease in cognitive decline. However, two recent studies published simultaneously used variations of Morris’ water maze to show that AD-model transgenic mice, with reduced beta-amyloid deposition after vaccination, showed significantly less age-related decline in their ability to navigate a maze, in comparison with controls. Taken together, these in vitro and animal studies provide hope that dietary manipulation could have at least a disease-modifying effect.

Of particular interest are data emerging in a spontaneous mouse AD model, the SAMP8 mice (56,57). This mouse spontaneously overproduces Abeta protein and develops early learning and memory deficits. This mouse has a 50% (58) decrease in Δ9 desaturase with age, altering the ratio of saturated to unsaturated fatty acids in the brain. It is believed this results in altered membrane mobility and in the deterioration in cognition. Umezawa and colleagues (59) found that perilla oil (rich in α-linolenate oil) improved learning and memory in the SAMP8 mouse. These studies strongly support the concept that dietary lipids can modulate cognition.

Cholesterol-Lowering Drugs and AD

Finally, two recent studies have suggested that a group of cholesterol-lowering drugs, the Hmg-CoA reductase inhibitors (statins) can reduce the risk of developing AD. Wolozin and colleagues (60) performed a cross-sectional analysis on data from the hospital records of more than 50,000 patients and compared the likelihood of patients in the whole population developing AD with that of the group taking statins and those taking antihypertensives or cardiovascular drugs not affecting cholesterol levels. They found that the risk for AD was 60% to 73% lower in the statin group (pravastatin and lovastatin, but not simvastatin) than in the non-cholesterol-lowering drug group or the total population. In the second study, Jick and colleagues (61) used a nested case-control design on data from the U.K. General Practice Research Database. They found an adjusted relative risk of dementia for those prescribed statins of 0.29 as opposed to a relative risk of close to 1.0 for those with either untreated hyperlipidemia or hyperlipidemia treated with nonstatin agents. However, once AD has developed, the role of cholesterol lowering is uncertain. Two out of four studies using statins have shown a small but significant decline in cognition during short-term studies (62–64).

CONCLUSION

It seems likely that dysregulation of energy balance, vitamin B12, folate, and homocysteine, as well as dietary fats, all play a role in the pathogenesis of AD. It remains a disease with a complicated, multifactorial pathology, and, at the moment, exactly how such factors interact with various genetic, environmental, and biological factors is far from clear.

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