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Review Article

DIETRY FACTORS IN ALZHEIMER'S DISEASE: A COMPILATION OF HELPING EVIDENCES

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ABSTRACT

The increasing life expectancy of Indians is likely to result in an increase in age-related disorders like Alzheimer's disease. Alzheimer's disease is a chronic, progressive, untreatable neurodegenerative disorder characterized by apraxia, aphasia, agnosia and severe cognitive deficits. Several behavioural changes like anxiety, hallucinations, depression and delusions are also experienced. AD have a serious impact on families, caregivers, and the healthcare system in general. Although lot of theories and treatments have been proposed targeting pathophysiology of AD yet, current treatments are merely palliative and do little to slow the progression of the disease. Yet, a great deal of progress has been made in the understanding of AD and many promising therapies have entered clinical trials. Several of key areas have been recognized and out of them life style modifications and role of food stuff has been regarded as inseparable and crucial factor involved. Present review is an effort to investigate the status and role of different common food stuffs and supplements in pathogenesis of AD.

Keywords: Alzheimer's disease, vitamins, cholesterol, ketogenic.

INTRODUCTION

The elderly population is currently one of the fastest growing segments of society. Elderly population of individuals with mental retardation and other developmental disabilities have been on rise which may be attributed to the change in life style, altered food habits environmental pollution and stress etc.

With the dramatic increase in the population of adults over the age of 65, there has been a concomitant increase in the prevalence of age-associated diseases including dementias. Alzheimer's disease (AD) is the most common form of dementia, affecting millions of people around the world. Every four seconds, a new case of dementia occurs somewhere in the world. This epidemic has enormous implications for society, in terms of both human suffering and monetary cost [1-3].

Worldwide, nearly 36(35.6) million people are believed to be living with Alzheimer's disease or other dementias, increasing to nearly 66 (65.7) million by 2030 and more than 115 (115.4) million by 2050. The number of people with dementia will double by 2030 and will be more than triple by 2050[4].

Alzheimer's disease is the sixth leading cause of death in the United States and 1 in 3 seniors dies with Alzheimer's or another dementia. Every 68 seconds, someone in America develops Alzheimer's. By mid-century, someone in America will develop the disease every 33 seconds [5]. Approximately 13% of people over the age of 65 years and 45% over the age of 85 years are estimated to have AD [6].

AD is characterized by three primary groups of symptoms.

The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (i.e. loss of higher level planning and intellectual coordination skills). The second group comprises psychiatric and behavioral disturbances such as depression, hallucinations, delusions, and agitation, collectively termed as non-cognitive symptoms [7]. The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided) [8].

The pathophysiology of Alzheimer disease is complex and multifactorial. Characteristic pathologic features include the accumulation of amyloid cerebral plaques and neurofibrillary tangles of abnormally insoluble tau, an axonal protein. Synaptic levels of acetylcholine decrease as a result of cholinergic neuron involvement. Many other factors may contribute to the pathophysiology, such as depletion of other neurotransmitters, loss of neural synapses, mitochondrial dysfunction, oxidative stress, inflammation, ischemia, insulin signaling, and cholesterol metabolism [9].

AD resembles other chronic diseases, whereby a myriad of interconnected factors, including those associated with lifestyle, are involved in disease development [10, 11]. Foods, beverages, single food constituents, and unusual eating patterns have been included in several epidemiological risk factor studies [12, 13]. Among risk factors oxidative stress and lipid peroxidation may be associated with high fat diets and the pathogenesis of AD [14]. Moreover, dietary antioxidants have been investigated as protection against free radical formation and neurodegenerative disorders [15]. Total dietary fat and specific fatty acids have been linked to neurological disorders. High calorie intakes have also been reported to be associated with the development of AD [16]. Recently, dietary pattern analysis has emerged as an approach to examining diet-disease relations in Alzheimer's disease [17-19].

The present review aim to elaborate and help to understand the role and status of various dietary factors involved in pathobiology of most dreadful geriatric disorder, Alzheimer's disease.

CHOLESTEROL

The brain represents only 2% of the body's total mass, but contains 25% of the total cholesterol [20]. Cholesterol is required everywhere in the brain as an antioxidant, an electrical insulator (in order to prevention leakage), as a structural scaffold for the neural network, and a functional component of all membranes. Cholesterol is also utilized in the wrapping and synaptic delivery of the neurotransmitters. It also plays an important role in the formation and functioning of synapses in the brain [21]

Cholesterol is an essential component of the plasma membrane of all cells, where it increases membrane rigidity reducing lipid disorder; found mainly in the cytofacial leaflet, where, together with sphingolipids and gangliosides, is concentrated in detergent-resistant membrane fractions (lipid rafts) and plays key roles in neuronal development as well as in the maintenance of neuronal plasticity and function.[22].

Cholesterol is a major lipid component of eucaryotic plasma membranes, imparting both flexibility and stability, and it is the precursor for the biosynthesis of bile acids as well as adrenal, pituitary, and sex hormones. In these capacities, cholesterol is essential for life. However, elevated concentrations of plasma cholesterol are a well established risk factor for cardiovascular disease, and emerging evidence suggests that cholesterol metabolism plays a direct role in the pathogenesis of AD [23].

Neuronal cells appear to synthesize cholesterol during development, whereas mature neurons progressively lose such ability, getting cholesterol from glial cells, particularly astrocytes.[24,25]. In brain, the astrocytes not only synthesize, but internalize and recycle the cholesterol released from degenerating nerve terminals to deliver it back to neurons[26].

Statins (an inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, catalyzing the early rate-limiting reaction in cholesterol biosynthesis) protect against dementia and AD prevalence. Whereby increased plasma cholesterol concentration through the increased net sterol turnover to the brain enhances the production of AB protein and neuritic plaques, the key histochemical feature of the disease [27**].**

Prompted largely by results of epidemiological studies [28] the concept of alteredcholesterol homoeostasis as an important factor in the pathogenesis of Alzheimer's disease has emerged. In cell cultures, increased and decreased

cholesterol levels promote and inhibit the formation of AB from APP,respectively [29,30].

ANTIOXIDANTS

The brain utilizes about 25% of respired oxygen even though it represents only 5% of the body weight. Free radicals are generated in the brain during the normal intake of oxygen, during infection and during normal oxidative metabolism of certain substrates [31]. According to this hypothesis, reactive oxygen species (ROS) and reactive nitrogen species (RNS) play important roles in the initiation and promotion of neurodegeneration in the brains of patients with AD [32]. Some of these free radicals are released during inflammatory reactions, whereas others are formed during normal oxidative metabolism and auto-oxidation of certain neurotransmitters and by beta amyloid [33].

The brain is particularly sensitive to oxidative stress due to increased levels of oxidative agents and decreased levels of antioxidants. Increased oxidative stress may enhance intracellular accumulation of Amyloid beta in neurons [34]. Like many other chronic degenerative diseases, Alzheimer's appears to be caused to a large degree by oxidative damage. There is mounting evidence that antioxidant factors may help prevent or delay the onset of the disease. Natural dietary antioxidants include vitamin A, C, and E, carotenoids, flavanoids and polyphenols. Spices and herbs often contain active phenolic substances with potent antioxidant, antiinflammatory, and anti-cancer properties [35-38].

A free radical is any chemical species that contains one or more unpaired electrons. Unpaired electrons alter the chemical reactivity of an atom or molecule, usually making it more reactive than the corresponding non-radical, because they act as electron acceptors and essentially "steal" electrons from other molecules. This loss of electrons is called oxidation, and free radicals are referred to as oxidizing agents because they tend to cause other molecules to donate their electrons [39]. We are constantly exposed to freeradicals created by electromagnetic radiation from the environment, both natural (e.g., radon, cosmic radiation)and man-made, and by internal cellular metabolism. The most common cellular free radicals are hydroxyl radicalOH•), superoxide radical (O2?•), and nitric oxide (NO•) [40].

Free radicals and related molecules are often classified together as reactive oxygen species (ROS) to signify their ability to promote oxidative changes within the cell. Cells normally employ a number of defense mechanisms against damage inducedby free radicals [41]. Problems occur when production of ROS exceeds their elimination by the natural antioxidant defense system, or when the latter is damaged. This imbalance between cellular production of ROS and the ability of cells to efficiently defend against them, is called oxidative stress (OS) [42]. OS can cause cellular damage and subsequent cell death mainly by apoptosis in neurodegeneration because the ROS oxidize vital cellular components such as lipids, proteins, and DNA [43].

The central nervous system is especially sensitive to free radical oxidative damage. Ccompared with other organs, the brain consumes a large fraction (20%) of the oxygen that the body takes in, suggesting a high metabolic rate. This high oxygen consumption and possibly metabolic rate may increase the amount of free radicals produced in the brain [44].

Aging, the major risk factor for AD [45] leads to loss of free radical scavenging ability by endogenous mechanisms [46]. Hence, the normal balance between free radical generation and free radical scavenging is disrupted with aging and other oxidative stress conditions [47].

There are two general classes of antioxidants, endogenous and exogenous. Among the former are the tripeptideglutathione (GSH), various vitamins, and products of reactions catalyzed by enzymes that are upregulated in response to oxidative stress, e.g., bilirubin from heme oxygenase and products of antioxidant response elements (ARE) [48]. Among the exogenous, nutritionally derived anti-oxidants are different classes of molecules: those moieties that increase endogenous GSH levels or otherwise have reactive SH functionalities; vitamins; and phenolic and polyphenolic compounds [49,50]

Currently, the only Food and Drug Administration (FDA) approved treatment for AD is the administration of the cholinesterase inhibitors (AChEI) donepezil, galantamine and rivastigmine and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine [51, 52]. Nevertheless, to date, these drugs have demonstrated to produce only modest symptomatic improvements in some of the patients, but not to cure or stop the disease progression. Moreover, AChEI are expensive and may have side effects resulting from

activation of peripheral cholinergic systems [53]. Then, effective treatments are greatly needed. The current therapeutic strategies being investigated for AD include targeting neurotransmission with multifunctional compounds, anti-amyloid and anti-tau therapies, drugs targeting mitochondrial dysfunction, neurotrophins, statins and also other approaches such us PUFAs and antioxidants. Among them, antioxidant therapies and PUFAs are particularly attractive due to their low toxicity, low cost and their ability to target earlier changes of the disease (e.g oxidative stress) which are linked to cognitive and functional decline [54].

VITAMINS

Vitamin A-Vitamin A is an essential component of the human diet. It is derived from vitamin-A-rich foods as well as from foods containing beta-carotene, composed of two retinol molecules [55]. Retinoic acid (RA) is the active metabolite of vitamin A and is a critical signaling molecule for both the developing and adult central nervous system (CNS) [56]. Vitamin A, which has been traditionally considered to be an anti-oxidant compound, plays a role in maintaining higher CNS functions in older subjects [57].

Vitamin A, and more particularly its precursor, beta carotene, contribute to the stabilization of biological membranes. Vitamin A and the carotenoids (among them beta carotene, provitamin A) participate with other micronutrients (notably vitamins E, C, and selenium) in the protection of tissues, in particular nervous tissues, from aggression by free radicals or active forms of oxygen. Vitamin A and b-carotene dose-dependently inhibit the formation of b-amyloid fibrils (fAb) from fresh Ab, and also dose-dependently destabilized preformed fAb *in vitro*.[58].

Vitamin A has been traditionally considered as antioxidant and it seems essential for learning, memory and cognition. Retinoic acid, a metabolic product of vitamin A, is known to slow cell death and protect from AB [59]. Thus, since levels of vitamin A decline with age and are found lower in AD individuals [60]. Vitamin A supplementation might be useful for the treatment of some features in the ageing process.

Vitamin B

AD patients tipically present high levels of homocysteine (Hcy) [61] and low levels of vitamin B12 and folate which appear to be associated with an increased rate of cognitive decline [62]. B-vitamins (B6, B12 and folic acid) are lipid soluble antioxidants involved in the methylation of homocysteine (Hcy) which is highly cytotoxic. Cellular catabolism and cellular export mechanisms are the responsible for keeping low intracellular Hcy concentration.[61].

Vitamin B12

As early as 1959, Droller and Dosset reported that aged individuals with senile dementia have significantly lower serum vitamin B12 levels as normal persons of a similar age [62]. This was followed by Dawson and Donald [1966], who found that low serum vitamin B12 levels were correlated with both age and mental symptoms [63].

Deficiency/low level of vitamin B12 is more frequently found in AD patients than non demented individuals [62,63]. Vitamin B12 also known as cobalamin, comprises a number of forms including cyano-, methyl-, deoxyadenosyl- and hydroxy-cobalamin. The cyano form, which is used in supplements, is found in trace amounts in food [64]. The other forms of cobalamin can be converted to the methyl- or 5-deoxyadenosyl forms that are required as co factors for methionine synthase and L-methyl-malonyl- CoA mutase[65].

Vitamin C

Vitamin C (ascorbic acid), found in many fruits and vegetables, is the major water-soluble antioxidant and acts as first defence against free radicals in blood and plasma. Bagi et al, 2003, have shown that chronic vitamin C treatment is able to decrease high levels of isoprostanes in animal models [66].

Among the antioxidants, vitamin C has been regarded as the most important one in neural tissue. It also decreases β-amyloid generation and acetylcholinesterase activity and prevents endothelial dysfunction by regulating nitric oxide, a newly discovered factor in the pathogenesis and progression of AD [67].

Vitamin D

Whether vitamin D deficiency is a cause or consequence of AD is unknown. In addition, abnormal cellular calcium homeostasishas been noted in AD. There is evidence of aberrations in the vitamin D-endocrine system in patients with AD [68].

Vitamin D is a neurosteroid hormone which crosses the blood-brain barrier and binds to vitamin D receptors (VDR) present in neurons and glial cells of the central nervous system

including the hippocampus, the hypothalamus, the cortex and the subcortex [69-71].

More precisely, 1.25-dihydroxyvitamin D (active form ofvitamin D) regulates the intra-neuronal calcium homeostasis via the regulation of voltage-gated calcium channels - thus preventing necrosis [72], and has also exhibited neuroprotective properties against glutamate toxicity through antioxidant effects - thus preventing apoptosis [73].

Acetylcholine (ACh) and norepinephrine (NorEpi) are the most common neurotransmitters associated with the pathophysiological conditions observed in AD. It is hypothesized that these neurotransmitters are hypoactive in AD [74]. Vitamin D has been shown to be neuroprotective in several experimental models of Alzheimer's disease by normalizing the hypofunctioning of these neurotransmitters [75].

Prostaglandins (PGs) play a role in inflammatory processes.[76]. Cyclooxygenase (COX) participates in the conver-sion of arachidonic acid into PGs. Prostaglandin receptors are found in the hypothalamus, thalamus, and limbic system,[77] and COX-2 is expressed by excitatory neurons at postsynaptic sitesin rat cerebral cortex.[78] Overexpression of COX-2 has been demonstrated in the perinuclear, dendritic, and axonal areas ofpyramidal neurons as well as in subregions of the hippocampal formation in AD.[79,80].

Calcitriol has been reported to regulate the expression of several key genes involved in the PG pathways, causing a decrease in PG synthesis [81]. Calcitriol and its analogs have also been shown to selectively inhibit the activity of COX-2.[82].

Vitamin E

Vitamin E is an essential nutrient in humans. It functions as a natural antioxidant, scavenging free radicals in cell membranes and protecting unsaturated fatty acids from lipid per-oxidation. Normal plasma concentrations of vitamin E in humans range from 11.6 to 30.8? Mol/L [83].

Because of the high concentration of easily oxidizable lipids combined with high oxygen consumption, the brain is particularly vulnerable to oxidative stress and lipid peroxidation. Due to their restricted regeneration capacity, nerve cells require highly efficient protection mechanisms. Chain-breaking anti-oxidants, such as the lipophilic antioxidant vitamin E (a major form of which is a-tocopherol), are capable of aborting the LPO chain reaction. In this action they are supported by coantioxidants like vitamin C (ascorbate) or ubiquinol [84].Vitamin E, which is found in membranes and on lipoprotein particles is considered to be the major lipophilic antioxidant in humans [85] and, especially, is essential for normal brain function [86].

Vitamin E is a generic term for a group of naturally occurring tocopherol and tocotrienol derivatives with biologic activity similar to that of alpha-tocopherol. The natural isomer, RRR-alpha-toco-pherol, has the highest bioactivity [87].

In Alzheimer's disease beta amyloid can induce cytotoxicity through a mechanism involving oxidative stress and hydrogen peroxide. Vitamin E can block hydrogen peroxide production and the resulting cytotoxicity [88]. Vitamin E reduces beta amyloid–induced cell death in rat hippocampal cell cultures [89] and PC12 cells [90] and attenuates excitatory amino acid–induced toxicity in neuroblastoma cells [91].

In an animal model vitamin E has-been shown to accumulate in the brain and decreases lipid per oxidation [92, 93]. It also decreases the neurotoxic effect of Ab [94] as well as the toxicity of 24-S-hydroxycholesterol, a product of enzymatic cholesterol oxidation that is increased in plasma and brains of AD patients [95]. The antioxidant action ofvitamin E can be restored by vitamin C, which acts as acoantioxidant by the reduction of the a-tocopherylradical. By this mechanism the possible prooxidant effect of vitamin E can be prevented.

Vitamin E slows symptomatic progression in patients with AD, presumably because of interaction with freeradicals and interruption of processes that result in cel- lular damage.

vitamin E and other antioxidants effectively improve cognitive performance in aged animals and prevent oxidative damage in animal models of AD.

Ketone bodies

Normal brain accounts for two percent of our total body mass, consumes 250ml02/minute (16 percent of the body's total oxygen), and metabolizes 110 to 140 grams per day of glucose. Most of the brain oxygen use is for oxidation of glucose for ATP synthesis, which is required for cycling neurotransmitters and function-al neuronal signaling. The brain mostly relies on glucose in the circulation for the majority of its function and stores very little energy in the

form of glycogen. Glycogen provides approximately five minutes of normal brain function when glucose levels drop very low. In our culture, ketones work as a source of energy for brain cells in only very unusual circum-stances, such as starvation and poorly controlled diabetes. Throughout human evolution, ketosis likely served as a valu-able survival mechanism to fuel the brain metabolism during times of food scarcity [96].

Comparing Alzheimer's disease patients with normal controls, early studies showed a 24 percent decline of cerebral metabolic rate of glucose (CMR glc) across the whole brain, and this correlated directly with low cognitive scores[97].

In 1920 it was discovered that the ketogenic diet, which is very low in carbohydrate and protein and high in fat was successful in treating refractory childhood epilepsy[98].

Crafts,et al. in 2000[99] and Reger in 2004[100] showed that infusion of ketones in rodents protected them from ischemia, glutamate and MPTP toxicity. Constantine, et al. in 2007[101] exposed cultured hippocampal cells from 18-day embryonic rats toAB42. This resulted in a 50 percent decrease in cell numbers. When exposed to ketones at the same time, doubling of cell survival was noted suggesting that ketones protects against AB 42 toxicity[98].

A ketogenic diet has been found to be therapeutic in AD patients [102-103]. It involves an extremely high fat diet, with up to 88% ofcalories derived from fats. This benefit may be likely due in part to the bioavailability of a plentiful supply of fats to repair damaged membranes. However, this diet leads to the generation of a significant concentration of ketone bodies in the blood serum, which can be usedas an alternative fuel to glucose (metabolized by ABAD). In a mouse model, it was found that ketosis leads to a greater production of cetyl CoA in the forebrain, which would allow neurons to consume relatively less glucose, while achieving an increased production of glutamine and GABA, important nutrients for neurotransmission [104].

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