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Review

Nutritional approaches in the risk reduction and management of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous and devastating neurodegenerative disease with increasing socioeconomic burden for society. In the past 30 y, notwithstanding advances in the understanding of the pathogenesis of the disease and consequent development of therapeutic approaches to novel pathogenic targets, no cure has so far emerged.

This contribution focuses on recent nutritional approaches in the risk reduction and management of AD with emphasis on factors providing a rationale for nutritional approaches in AD, including compromised nutritional status, altered nutrient uptake and metabolism, and nutrient requirements for synapse formation. Collectively these factors are believed to result in specific nutritional requirement in AD. The chapter also emphasizes investigated nutritional interventions in patients with AD, including studies with single nutrients and with the specific nutrient combination Fortasyn Connect and discusses the current shift of paradigm to intervene in earlier stages of AD, which offers opportunities for investigating nutritional strategies to reduce the risk for disease progression.

Fortasyn Connect was designed to enhance synapse formation and function in AD by addressing the putative specific nutritional requirements and contains docosahexaenoic acid, eicosapentaenoic acid, uridine-5'-mono-phosphate, choline, phospholipids, antioxidants, and B vitamins. Two randomized controlled trials (RCTs) with the medical food Souvenaid, containing Fortasyn Connect, showed that this intervention improved memory performance in mild, drug-naïve patients with AD. Electroencephalography outcome in one of these clinical studies suggests that Souvenaid has an effect on brain functional connectivity, which is a derivative of changed synaptic activity. Thus, these studies suggest that nutritional requirements in AD can be successfully addressed and result in improvements in behavioral and neuro-physiological alterations that are characteristic to AD.

The recent advance of methodologies and techniques for early diagnosis of AD facilitates the investigation of strategies to reduce the risk for AD progression in the earliest stages of the disease. Nutrition-based approaches deserve further investigation as an integral part of such strategies due to their low risk for side effects and their potential to affect pathological processes of very early AD.

Introduction

Alzheimer's disease (AD), the most common form of dementia, is estimated to reach 100 million cases worldwide by 2050 [1,2]. It imposes a significant burden on patients, caregivers, and health care systems—the estimate in the United States alone is for an increase in health care budget for AD and other dementias from $200 billion in 2012 to $1.1 trillion in 2050 [3]. Thus, more effective therapies and novel strategies leading to improved disease management or risk reduction would have enormous socioeconomic effect.

Although AD was first identified more than 100 y ago, mechanistic studies and therapeutic developments for this devastating disease have gained momentum mostly in the past 30 y. Extraneuronal senile plaques and intraneuronal neurofibrillary tangles are two hallmarks of disease pathology in AD brain. Clinical manifestations include cognitive impairment and dementia. However, more subtle synaptic changes may occur years before such pathological and clinical symptoms manifest. Such

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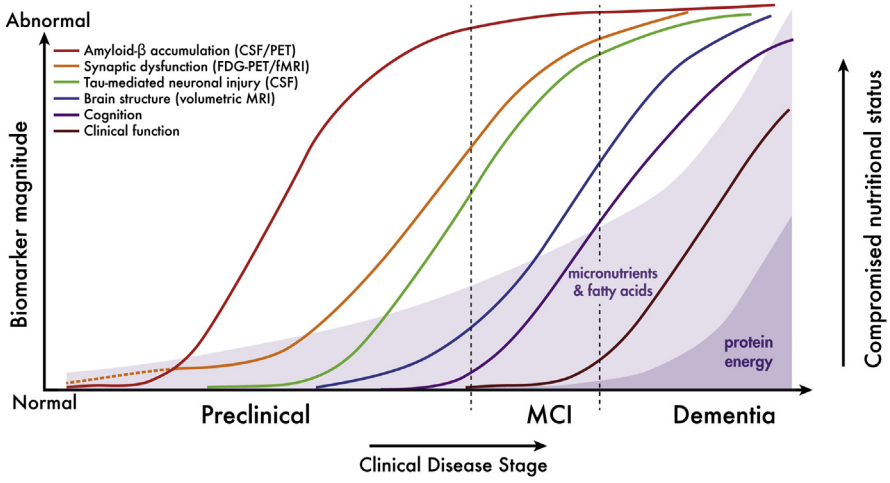

Fig. 1. Hypothetical model of dynamic biomarkers and nutritional status across the AD spectrum (adapted from Sperling et al, 2011 [8], with permission from Elsevier). Biomarkers including Aβ, synaptic dysfunction, tau-mediated neuronal injury and brain structure, change from normal to maximally abnormal (left *y*-axis) as disease progresses (details referred to [8]). The temporal trajectory of two key indicators for clinical stages of disease, cognition and clinical function, are also included. Compromised nutritional status has been highlighted with purple shades. Compromised micronutrients and fatty acids status have been implicated throughout the whole disease spectrum. Such compromised nutrient status may result from alterations in nutrient intake, reduced endogenous biosynthesis of nutritional compounds, and compromised nutrient absorption and uptake. With the disease progression, protein-energy malnutrition becomes prevalent at the demented stage of AD and the resulting weight loss is a common problem at this stage. Protein-energy malnutrition has been reported to be present in 50% of AD patients with severe AD [16].

a continuum of synaptic loss is strongly correlated with cognitive impairment [4–7]. With the recent advance in methodologies and techniques for early diagnosis of AD, especially the continuing maturation of structural, functional, and molecular imaging (i.e., magnetic resonance imaging [MRI], positron emission tomography [PET] or single-photon emission computed tomography [SPECT]) and identification of reliable cerebrospinal fluid (CSF)/plasma biomarkers, the research focus has shifted to the earliest stages of AD and strategies to reduce the risk for disease progression [8].

Mounting evidence points to the important role of nutrition in relation to cognitive function, especially during aging [9]. The maintenance of healthy neurons relies on adequate supply of nutritional compounds, which are mostly acquired from the diet. For instance, docosahexaenoic acid (DHA) from dietary intake is important for the formation of neuronal membranes. Choline is a precursor for the neurotransmitter acetylcholine and it also is used in the synthesis of neuronal membrane. For other nutrients' roles in the structure and function of the nervous system one can refer to a review by Bourre [10]. Furthermore, lower intakes of certain nutrients (i.e., DHA, B vitamins, and antioxidants) have been linked to increasing risk for AD and a diet rich in the aforementioned nutrients has shown to decrease the risk for AD [11–14]. Hence, in addition to pharmaceutical therapeutic approaches and lifestyle modification, we postulate that nutritional approaches are set to play an important role in future management options for AD. This contribution focuses on nutritional approaches investigated so far and their potentials as risk reduction measures of AD.

Rationale for nutritional approaches in AD

Protein-energy malnutrition in AD

Impaired nutritional status has been reported in AD. Protein-energy malnutrition is prevalent at the demented stage of AD and increases with disease severity (Fig. 1). In mild to moderate AD, 3% of the patients were reported to be malnourished [15], whereas another study indicated that 50% of patients with severe AD had protein-energy malnutrition [16]. Such compromised protein-energy status could be due to worsening of appetite, taste, and smell, which lead to reduced food consumption, food neglect, and changes in food preferences [17–19]. Additionally, compromised nutritional status has been shown in older individuals with AD living at home with their spouses; and among them weight loss and malnutrition (undernutrition) are a common problem [20–22]. Body mass index (BMI) and mini-nutritional assessment (MNA) are two widely accepted screening tools for the indication of malnutrition in the elderly [23,24].

Lower micronutrients and fatty acid status in AD

In addition to the fact that patients with AD are at risk for a compromised protein-energy status at the demented stage, there also might be compromised micronutrients/ω-3 fatty acids during the entirety of disease progression (Fig. 1). Recent meta-analysis has shown significantly lower plasma levels of vitamins A, C, E, folate, and vitamin B_{12} in patients with AD compared with cognitively intact elderly controls [25]. A trend toward lower levels of vitamin D and zinc also was observed [25]. Plasma levels of other nutrients and vitamins have been reported low in AD compared with age-matched healthy individuals (i.e., ω-3 polyunsaturated fatty acids [PUFAs] [26–29] and selenium [30,31]). Reduced uridine has been reported in the CSF of patients with mild AD [32], whereas a trend toward lower plasma uridine levels in mild AD compared with healthy controls has been reported for the first time in a recent study [33]. Interestingly, increased cysteine associated with decreased uridine is the best-paired combination to identify mild AD with specificity and sensitivity levels of above 75% [32]. Furthermore, lower nutrient status has been shown in subjects with mild cognitive impairment (MCI), that is, DHA content in phospholipids [26]; vitamins A, C, and E, lutein, zeaxanthin, and α-carotene [34,35]; and folate [36]. Taken together, observational studies suggest that lower nutrient status is a consistent finding during disease progression: It not only is a risk factor for onset of AD, but also