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Review Article

Lower brain and blood nutrient status in Alzhiemer's disease: Results from meta-analyses

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Abstract

Introduction: Alzheimer's disease (AD) patients are at risk of nutritional insufficiencies because of physiological and psychological factors. Recently, we showed the results of the meta-analyses indicating lower plasma levels of vitamins A, B_{12}, C, E, and folate in AD patients compared with cognitively intact elderly controls (controls). Now, additional and more extensive literature searches were performed selecting studies which compare blood and brain/cerebrospinal fluid (CSF) levels of vitamins, minerals, trace elements, micronutrients, and fatty acids in AD patients versus controls.

Methods: The literature published after 1980 in Cochrane Central Register of Controlled Trials, Medline, and Embase electronic databases was systematically analyzed using Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines to detect studies meeting the selection criteria. Search terms used are as follows: AD patients, Controls, vitamins, minerals, trace elements, micronutrients, and fatty acids. Random-effects meta-analyses using a linear mixed model with correction for age differences between AD patients and controls were performed when four or more publications were retrieved for a specific nutrient.

Results: Random-effects meta-analyses of 116 selected publications showed significant lower CSF/brain levels of docosahexaenoic acid (DHA), choline-containing lipids, folate, vitamin B_{12}, vitamin C, and vitamin E. In addition, AD patients showed lower circulatory levels of DHA, eicosapentaenoic acid, choline as phosphatidylcholine, and selenium.

Conclusion: The current data show that patients with AD have lower CSF/brain availability of DHA, choline, vitamin B_{12}, folate, vitamin C, and vitamin E. Directionally, brain nutrient status appears to parallel the lower circulatory nutrient status; however, more studies are required measuring simultaneously circulatory and central nutrient status to obtain better insight in this observation. The brain is dependent on nutrient supply from the circulation, which in combination with nutrient involvement in AD-pathophysiological mechanisms suggests that patients with AD may have specific nutritional requirements. This hypothesis could be tested using a multicomponent nutritional intervention.

Keywords: Alzheimer's disease; Brain; Cerebrospinal fluid; Plasma; Nutrient; Nutritional requirement; Metabolism; Omega-3 polyunsaturated fatty acids; DHA; Choline; Vitamins; Phosphatidylcholine; Phospholipid synthesis; Synapse; Neuronal membrane

1. Introduction

The link between nutrition and the risk of developing Alzheimer's disease (AD) has been recognized for several decades. Specific dietary patterns have been associated with increased risk of developing AD, whereas others are linked to protection. Dietary patterns such as the Mediterranean diet that is characterized by high intakes of legumes, fruits,

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fish, unsaturated fats, and high in antioxidants offer protection [1]. Conversely, diets high in saturated fats, high trans-fat, and low antioxidants levels have been linked to an increased risk for developing AD [2]. In addition, diet-related disorders such as obesity, hypertension, hypercholesterolemia, and diabetes have consistently been shown to be associated with AD [3–5].

Since understanding the pivotal importance of B-vitamins for neuronal functioning and cognition, at the beginning of the 20th century [6–8], several nutrients, including antioxidants, choline, and omega-3 fatty acids, have been suggested to influence cerebral functioning (reviewed in Bourre [9] and in Smith and Blumenthal [10]). It is no surprise, therefore, that these nutrients have been postulated to play roles in the pathophysiological processes in AD. For example, antioxidants reduce reactive oxygen species–induced damage and stabilize membranes; the fatty acid docosahexaenoic acid (DHA) affects abnormal membrane–located protein processing (amyloid-b, tau); and DHA, choline, and uridine modulate neuronal membrane formation (reviewed in van Wijk et al. [11]). Neuronal membrane function has been shown to be dependent on its phospholipid composition, and alterations could lead to membrane instability and synaptic loss and, in that way, contribute to AD pathology [12]. Recent evidence suggests that a multinutrient intervention which enhances phospholipid formation comprising DHA, eicosapentaenoic acid (EPA), uridine monophosphate, choline, folate, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, selenium, and phospholipids modulated functional connectivity measures (assessed by electroencephalography) in AD, indicative of preserved synaptic function [13,14]. These data suggest that adequate supply of specific nutrients may preserve synaptic

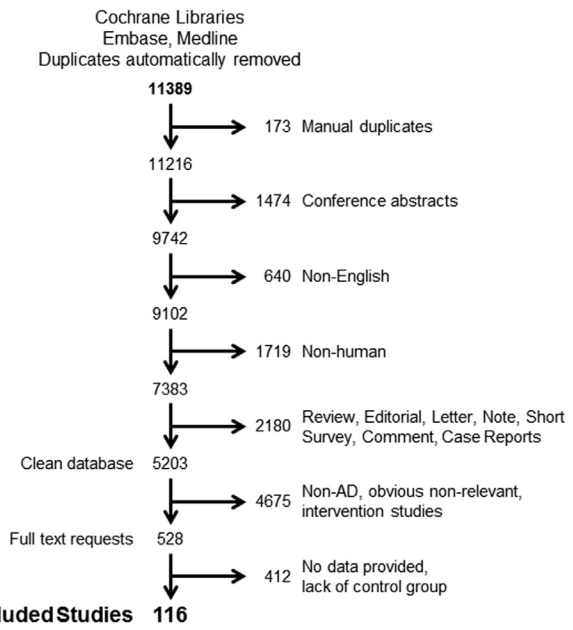

Fig. 1. Breakdown of the retrieved publications leading to the selection of the 116 publications suitable for meta-analysis. Abbreviation: AD, Alzheimer's disease.

Table 1
Summary of the included publications for the meta-analysis

Compartment	Nutrient	Total number of publications	Total number of AD patients/average age (years)	Total number of control subjects/ average age (years)	Studies reporting significantly lower levels in AD patients than in controls	Studies reporting no significant differences between AD patients and controls	Studies reporting significantly higher levels in AD patients than in controls
Circulation	DHA	13	488/78	1245/72	Six studies [24-29]	Seven studies [30-36]	
	EPA	13	488/78	1245/72	Six studies [24-26,28,32,35]	Seven studies [27,29-31,33,34,36]	
	Choline (as PC)	4	87/76	76/73	Two studies [37,38]	Two studies [24,39]	
	Vitamin B_6	6	192/76	199/75	Two studies [40,41]	Four studies [34,42-44]	
	Selenium	17	660/77	536/72	Seven studies [34,45-50]	Eight studies [51-58]	Two studies [59,60]
Brain	DHA	12	237/77	220/75	Four studies [61-64]	Eight studies [65-72]	
	Choline (^{1}H-MRS)	31	828/73	791/70	Four studies [73-76]	Twenty-seven studies [77-103]	
	Folate	9	307/73	538/65	Four studies [104-107]	Five studies [108-112]	
	Vitamin B_{12}	4	92/70	208/69	Two studies [110,113]	Two studies [114,115]	
	Vitamin C	5	102/74	79/70	Four studies [41,116-118]	One study [119]	
	Vitamin E	5	127/73	100/70	Three studies [116,120,121]	Two studies [117,118]	
	Selenium	13	487/76	353/76	Three studies [122-124]	Ten studies [46,58,125-132]	
	Zinc	16	496/73	306/71	Five studies [122,123,133-135]	Ten studies [46,125,127,128,130,132,136-139]	One study [126]

Abbreviations: AD, Alzheimer's disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.