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COMMENTARY

Close Relationship of Alzheimer's Disease (AD) and Glucose Dysregulation

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Keywords

Mild cognitive impairment (MCI), Alzheimer's disease (AD), Low carbohydrate diet (LCD), Randomized controlled trial (RCT), Diabetes mellitus, Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

Abbreviations

MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; LCD: Low Carbohydrate Diet; MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay; RCTs: Randomized Controlled Trials

Introduction

One of the recent crucial medical problems in the world has been diabetes mellitus, which is increasing in developed and also developing countries [1]. Furthermore, dementia and Mild Cognitive Impairment (MCI) in the elderly has been also medical and social problems due to the extended life span. The both diseases are interrelated and there are many influencing factors on them [2]. These topics are involved and described in this article.

Concerning dementia and MCI, dietary intervention has been an important approach for long worldwide. For several nutrients related to cognitive function, major dietary sources have been found, such as B vitamins (B6, B12, folate), antioxidants (Vit C, E, carotenes, flavonoids) and Vit D [3]. In addition, macronutrients include carbohydrates, proteins, dietary fat, saturated fatty acids (FA), polyunsaturated FA (PUFA), monounsaturated FA (MUFA), and so on [4].

Several evidence have been reported about dietary types on cognitive outcomes. Among them, there were some well-known types with beneficial effects. They include Dietary Approaches to Stop Hypertension (DASH), Mediterranean diet, Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) [5], Low carbohydrate diet (LCD) [6]. In the light of LCD, the authors and colleagues have reported clinical studies for LCD so far. We have developed three meal types of LCD, which are super-, standard- and petite-LCD [6]. These LCD have been widely prevalent through the activity of Japan LCD promotion association (JLCDPA) [6].

There have been several factors involving pathophysiological cause for Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD). The presence of inflammation, defective insulin signaling, and mitochondrial dysfunction has been associated with obesity and the enhancement of stress signals [7]. Similarly, chronic inflammation in the brain has been supposed to contribute the development of the pathology of AD. Consequently, both of these could be suggested to be one of the risks of common molecular pathology [8].

Certain correlation was reported between glucose metabolism and AD. For the patients with established AD, the cognitive impairment has been correlated remarkably with the reduced level of glucose uptake [9]. Furthermore, various changes in energy metabolism of the brain has been found in the development for AD [10].

Diabetes has been one of the main risk factors for

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dementia. There were studies concerning glycemic control and the onset of dementia. Among these, ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study) has been known. As a result, no significant difference was found in the effect on cognitive function in the intensive treatment group (goal with A1 c < 6.0%) compared to the standard treatment group (goal with A1 c 7.0-7.9%) [11]. Similar results were observed with other reports [12]. There are few large-scale Randomized Controlled Trials (RCTs) of diabetes management including cognitive function as an endpoint. Consequently, it has been not clear whether strict management is effective for preventing the onset of dementia [1].

As for the relationship between glycemic control and dementia, the risk for developing dementia has been higher in the cases with severe hypoglycemic seizures. Conversely, the risk of severe hypoglycemic seizures has been higher in the cases with dementia [13]. Thus, both factors may interact each other to cause a vicious cycle. Consequently, prevention of hypoglycemia and stable glucose variability have been important according to the guideline of diabetic management [14].

There was a study for the patients with MCI or dementia due to AD, in which anti-diabetic agent metformin was provided [15]. As a result, metformin seemed to show improved executive function, associated with probable improvement of function for learning, memory and attention.

A study of a systematic review and meta-analysis was reported for the relationship between obesity and dementia [16]. From 1612 abstracts and 21 completely met the criteria, the result was that obesity with < 65 years showed a positive association on dementia with Risk Ratio (RR) 1.41. In contrast, the opposite result was found in those aged 65 and over as RR 0.83 [16]. Thus, the relationship between obesity and dementia varies with age.

There are various controversies concerning the relationship between Total Cholesterol (TC) value and increased risk of AD. Meta-analyses were conducted including 17 studies, 23,338 participants for 20 years [17]. The evaluation would vary by each study. For middle-aged studies, the results showed significant correlations. In contrast, studies for older subjects tended to show less significant correlations. Consequently, it seemed to be depending on the age of the subjects [17]. In general, cases of high TC in middle age may increase the risk of AD in later life or may increase the onset of AD pathology. Furthermore, there are many reports that HDL-C and triglyceride levels in the elderly are not related to the elevated risk of dementia [17].

Can administration of statins for the patients with dyslipidemia suppress the onset of dementia? Cochrane review analyzed two large-scale RCTs in high-risk patients (n = 26,340) with vascular disease [18]. As a result, statin administration in the elderly could not prevent the onset of dementia and the decline in cognitive function.

With regard to the blood pressure, age-related hypotension is significantly associated with dementia and AD onset. In the patients with dementia and MCI on the Antihypertensive Drugs (AHDs), cognitive function declines when daytime blood pressure has been lower. Furthermore, the progress for decreased cognitive function has been reported to be significantly faster [19]. Thus, excessive depression may reduce cognitive function.

In previous studies such as traditional Systematic Review (SR) and Meta-Analysis (MA), high physical activity has been shown to reduce the risk of dementia and cognitive decline [20]. In contrast, there has been an opposite report. The Cochrane Review concludes that the analysis of MA does not clearly show the evidence for its effectiveness on cognitive function in the patients with dementia [21].

There is a large RCT for aged patients with dementia. It has been Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Among them, modifiable vascular and lifestyle-related risk factors have been analyzed [22]. As a result, it has supposed that multi-domain intervention would relieve or maintain the cognitive function in elderly people with risk for dementia.

In summary, various health and medical problems including diabetes, dementia and MCI have been discussed. There are not simple and effective way to solve these complex problems. With multi-factorial analyses and integrative approach, multi-domain interventions would become the recommended treatments for clinical practice and research in the future.

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