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Mini Review

Diabetes increases risk for dementia and mild cognitive impairment (MCI)

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Summary

There have been large lifestyle and demographic changes across the world, and the diabetes and dementia become large challenges to healthcare system in each countries and districts. People with dementia seem to exist about 50 million, in which common types are Alzheimer's disease (AD) and Vascular Dementia (VasD) [1]. The number of people with dementia is expected to increase to 66 million by 2030, and 131 million by 2050 driven by rising numbers of older adults [2].

Before the development to dementia, mild cognitive impairment (MCI) has the prevalence of about 6% of the population, which is found in one out of five persons aged 65 or older [3]. MCI has the concern about the cognitive symptoms who does not show dementia yet, and associate with heterogeneous condition [4]. Subjects with MCI have higher risk for developing dementia with around 46% within 3 years. In contrast, age-matched subjects show about 3% [4].

There was the report of 6865 subjects with Metabolic Syndrome (MetS) from 15 articles [5]. The overall odds ratio for the progression of MCI to dementia in subjects of diabetes/MetS was 1.67, that of diabetes + MCI was 1.53, and that of MetS + MCI was 2.95. Thus, coexisting several risk factors would become a significant risk factors for developing from MCI to dementia in MetS.

There are some reports about modifiable risk factors for cognitive decline. A Mediterranean diet was reported to have beneficial effect of lowering risks for developing cognitive disorders and reduced rate of progression to dementia, which was analyzed by meta-analyses [6,7]. Nine cohort studies was investigated with 34,168 subjects by the analyses of pooled analysis [7]. It showed that Mediterranean diet score was highest, inversely associated with the developing of cognitive disorders and its pooled relative ratio (RR) was 0.79 [7]. Furthermore, there was a 10% reduced risk of dementia by leisure-time physical activity [8].

There is correlation between AD and glucose metabolism. In the case of patients with established AD, cognitive impairment level is strongly correlated with the reduced glucose uptake [9]. Further, there are several evidence that changes of the energy metabolism in brain become causative factors in the development of AD [9,10,11].

Ketone bodies include three kinds, in which Beta Hydroxybutyric Acid (BHB) and Acetoacetic Acide (AcAc) are produced in the body from the metabolism of the fat. They are utilized for producing energy throughout the body, such as brain and muscle [12].

Before clinical symptoms of AD was apparent, the reductions of glucose uptake in the brain can be found using the brain Fluorodeoxyglucose Positron Emission Tomography (FDG PET) imaging. [12,13]. Further, it would contribute the precipitation of the deposition of amyloid, which is causal substrate for AD [12].

Diabetics has increased risk of developing dementia. Recent epidemiological studies suggest that metformin treatment would prevent the decline of cognitive function for diabetics. Metformin showed the improved memory and learning in the SAMP8 mouse which is model of spontaneous onset AD. Due to biochemical analysis, metformin improved memory by decreasing APPc99 and p Tau [14].

Formerly, there was misunderstanding concerning ketone bodies, in which ketone bodies may indicate risky situation in medical practice. However, correct information and judgement has been

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prevalent about ketone bodies, which can become a source of energy for human metabolism. They are from the product of fat metabolism and are available even when glucose metabolism is not inadequate. Some situations are found that i) glucose supplies may be reduced in the case of severe carbohydrate deprivation, ii) glucose metabolism may be faulty in the case of AD.

There was a Randomized Clinical Trial (RCT) for the feasibility of a Modified Atkins Diet (MAD) with ketogenesis to the patients with MCI or early AD. The effect of MAD was monitored with the Memory Composite Score between the baseline and 6 week. From this preliminary data, the elder generation with even slight ketosis might increase their episodic memory ability and self-reported vitality in early stage of AD [15].

AD patients are known to show the decreased function of glucose metabolism. However, the brain metabolism for ketone bodies was not impaired by the analysis of Positron Emission Tomography (PET) examination [16].

LCD may induce hyperketonemia, in which our body can metabolized fat and produces ketone bodies that can be measured in blood and urine. Formerly, ketogenic diet has been used for the patients with drug-resistant epilepsy. It has been known to be safe treatment with remarkable clinical effects [17]. Similar hyperketonemia can be found when LCD has been continued, including original Atkins diet and recent MAD. MAD has proven to be a safe treatment associated with efficacy for reducing seizure in patients with epilepsy [18].

There are some reports concerning cognition, LCD, high-fat diet and metabolic ketosis in the elderly people [19]. About 1000 elderly were evaluated for the effects of some diet on the risk for dementia. Subjects were usually consumed a high carbohydrate diet showed the increased risk value of MCI and dementia. Its Hazard Ratio (HR) was 1.89 with significantly high value. In contrast, elderly who had high fat and high protein showed reduced HR which were 0.56 and 0.79, respectively.

In another report, the effect of high carbohydrate and VLCD (very low carbohydrate diet) for the cognition and mood situation in patients with MCI. As a result, subjects of VLCD only showed the improved scores on memory tests after 6 weeks. These effects were correlated with urinary ketone excretion significantly.

Furthermore, there was a study of ketogenic diet and a Medium-Chain Triglyceride (MCT) fat [20]. They enrolled 15 patients with AD, and 10 case was completed the protocol. According to the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog), the completers showed moderate improvement on the regimen at 3 months [20].

As for diabetes, about 450 million diabetes patients are present in the world [21]. There are some discussion concerning the adequate nutritional therapy including calorie restriction diet (CRD) and low carbohydrate diet (LCD) in several diabetic associations [22].

In Western countries, LCD has been introduced and gradually prevalent for years. In contrast, author and colleagues have started LCD in Japan and developed LCD promotion movement until now [23]. We have proposed super-LCD, standard-LCD and petite-LCD and continued clinical research for LCD and CR [24]. Furthermore, the significance and physiological role of Ketone Bodies (KB) has been reported in the case of LCD and in the circumstances of the axis of foetus-placenta-new-born-mother [25].

In summary, the topics concerning dementia, MCI, diabetes and glucose variability were described in this article. We hope that these would become the reference of future development of research and clinical practice.

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