

Common Pathophysiological Issues in Diabetes and Dementia

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Commentary

Recent medical problems in elderly people include dementia and metabolic syndrome such as diabetes and impaired glucose tolerance. Both are not different disease, but has common pathophysiological basis including glucose and ketone bodies and insulin resistance. Such topics would be described in this article.

Firstly, there have been various topics concerning brain and glucose, protein and fat. As brain uses glucose as main energy source, carbohydrate is necessary for ordinary function. Brain is only 2% of weight in the body, but it consumes about 25% of total glucose energy [1]. In contrast, excess consumption of glucose for long may cause decreased synaptic plasticity and increased inflammation, leading to probable cognitive impairment [2]. According to decreased sensitivity of brain for insulin with age, neuronal glucose utilization would gradually decrease with impaired cognitive function [3,4].

As a role of dietary protein, it is important to supply amino acids for necessary neurotransmitters, such as serotonin and catecholamines [5]. Especially, tryptophan, precursor of serotonin and essential amino acid would have important role in human. It includes cognitive function, information processing and feeling the mood.

There is a blood brain barrier (BBB) in human for protecting neural system. Serotonin itself cannot pass the BBB, while tryptophan can enter BBB through specialized channels with conversion to 5-hydroxyl-tryptophan (5-HTP) and lastly converted to serotonin [6]. Serotonin level would be decreased with age, probably influencing cognitive level [5,7].

Dietary fat is necessary for the brain, because of the structure of neuronal membranes [5]. There are rich in poly unsaturated omega 3 fatty acids (PUFA) in all neurons. Omega-3 fatty acids have been in focus, because it occupies approximately 30% of the membrane phospholipid composition. Especially, the omega-3 fatty acid docosahexaenoic acid (DHA) has been in considerable interest. It includes providing membrane fluidity and synaptic integrity, leading to affecting cognitive function [8]. Furthermore, MRI study showed that DHA scan may contribute for brain protection for aging process [9].

As mentioned above, research among three macronutrients and cognitive function has been progressing for many years. Among them, detail balance of major- and micro-nutrients seemed to be necessary for the proper function for brain [10]. In elderly people, appropriate changes in ordinary diet would be effective on cognitive function with reducing dementia [11]. One example is the Mediterranean diet, which is a standard meal for people living around the Mediterranean Sea. It is mainly composed of fresh seafood, red wine, bread, pasta, fruit, vegetables, olive oil [12,13]. People on Mediterranean diet seem to retain cognitive function [14].

Secondly, impressive reports were found about cognitive and diet. An intervention study was found, which was Finish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). It included exercise, cognitive training, balanced meal of macronutrients with less than 10% of carbohydrate [15]. With such a multimodal approach, decreasing the rate of cognitive decline in the elderly cohort was successful [16].

As described above, the common point of Mediterranean meal and FINGER is characterized by rather high intakes of fruits, vegetables and whole grains, as well as low added sugar intake. Both diets can be compared. FINGER is based on Finish Nutritional Recommendations, developed based on a strict set of specific nutrition guidelines [17]. In contrast, the Mediterranean pattern is not as strict as the nutritional guidelines, and the food intake restriction is loose [18].

Another difference is the origin of food lipids. FINGER uses rapeseed oil, vegetables, margarine, while Mediterranean style uses olive oil and nuts. People on the Mediterranean will consume much amount of legume that affects the proportion of animals and plant proteins, besides the amount of fiber and phytic acid. Furthermore, moderate intake of red wine and resveratrol source is recommended for Mediterranean diet [19].

Clinically, the pathophysiological background is different between young and elderly people. In the former one cause can be usually speculated, but in the latter multifactorial possibility due to various tissues damage would be present. Therefore, dementia including Alzheimer's disease (AD) draws the same trajectory as other related disorders and diseases. The mortality rate and the effect of age on AD are similar, the mortality rate doubles every 7.5 years from 30-years-old, and dementia doubles every 5 years [20]. Dementia is also closely related to multiple prevalence of diseases and frailty/locomotion syndrome [21].

Thirdly, the metabolism of ketone bodies and glucose has been in focus. Glucose is the brain's principal energy substrate. AD seems to have a pathological decrease in the brain's ability to use glucose. Due to the study of very low carbohydrate, ketogenic diet was effective for memory improvement in older adults with AD risk [22]. Its improved neurocognitive function would be supposed from correction of hyperinsulinemia, hyperketonemia, reduced inflammation and enhanced energy metabolism.

In the aged rats, ketogenic diet improved cognitive performance under normoxic and hypoxic conditions [23]. These data suggested that diet-induced ketosis may be beneficial for neurodegenerative conditions [23].

In clinical application, elevated ketone bodies (KB) through an oral dose of medium chain triglycerides (MCTs) may improve cognitive functioning in older adults with memory disorders [24-26]. In addition, higher KB was associated with greater improvement in

paragraph recall with MCT treatment relative to placebo across all subjects [26]. There was a report that the derivative of 3-hydroxybutyrate (3HB), 3-hydroxybutyrate methyl ester (HBME) was used by cells as an alternative to glucose [27]. As a result, HBME inhibited cell apoptosis under glucose deprivation, rescued activities of mitochondrial respiratory chain complexes that were impaired in AD [27].

Finally, recent topics include diabetes and ketogenic diet, as well as KB and beneficial effect of KB. Author and colleagues have continued clinical research about KB, Low Carbohydrate Diet (LCD) and Calorie restriction (CR) [28-30]. As to the oxidation of the substrate, CR has rather incomplete oxidation from glucose metabolism, while LCD has rather complete oxidation from KB metabolism [31].

Regarding hyperglycemia in diabetes, advanced glycation end products (AGEs) has been in focus, which are the conjugation of glucose and protein [32]. They cause diabetic macro-angiopathy, micro-angiopathy, arteriosclerosis including dementia and various impaired function [32].

In summary, several related topics among cognitive problem, glucose, ketone bodies and macronutrients were described in this article. We expect further development of clinical study for correlation among glucose and KB, diabetes and dementia in the future.

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