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*OBM Geriatrics*

Article Type: Review

Title: A consideration on the current treatment methods for dementia

Author: Miyako Tazaki [1]

1. Department of psychology, Faculty of Medicine, Toho University, Tokyo, Japan: mtazaki@med.toho-u.ac.jp

* **Correspondence:** Miyako Tazaki: mtazaki@med.toho-u.ac.jp

**Academic Editor(s):** Name(s)

**Special Issue**:

*OBM Geriatrics*
2018, volume 2, issue 1
doi:10.21926/obm.geriatr.1801xxx

**Received:**
**Accepted:**
**Published:**

***Abstract***

***Background*:** The number of people with dementia has been steadily increasing in developed countries. Particularly in Japan, 55 % of more than 85 years old are diagnosed as dementia. Although various experiments and researches have been conducted, no definitive treatment has been established to date. Current research indicates metabolic dysfunction may play an important role of occurrence of the disease.

***Methods:*** The author first conducted database search with key words of dementia, Alzheimer's disease, and prevention of dementia so on in the databases of Cochran, PubMed, and Cinii Article, then selected methods which proof of effectiveness.

**(3) *Results*:** The author summarises the recommended methods in six fields as follows; 1) Diet: The Mind-Dash diet and omega-3 intake, 2) Exercise: walking and "cogni-cises", an exercise developed in Japan, 3) Appropriate communication, 4) Drugs controlling of Aβ of the brain, 5) Neurofeedback and 6) Control of insulin resistance, whose extensive clinical researches are currently underway.

**(4) *Conclusions*:** To keep healthy life style with good communication are the key for the prevention of the disease. The research results of control of insulin resistance and neurofeedback are anticipated as potential tools for drastic improvement of the disease.

**Keywords;** dementia, Alzheimer's disease, prevention and treatment methods of dementia

## 1. Introduction

Japan leads the world in the average life expectancy with females reaching the age of 87.14 years and males 80.98 years, while the healthy life expectancy for females is at 74.79 years and for males 72.14 years[1]. It means, for the period of more than 7 years, many of the Japanese are too frail to be active and need to be taken care of. A report by Dai-ichi Life Research Institute in 2014 [2] said that 70% of Japanese wish to die in "pinpinkorori" which means to be energetic without pain until sudden death. In reality, however, it is nearly inevitable that as they live longer, they become bedridden or suffer from dementia. According to the estimates by the Japanese Ministry of Health, Labour and Welfare in 2016[3], about 4 million people have a mild cognitive impairment, with over 65 years accounting for about 13% of them, and 4.62 million people have dementia disease, with over 65 years accounting for 15% of them. In other words, there is a possibility that one in three over 65 years with some cognitive problems may develop dementia. According to the Organization for Economic Co-operation and Development (OECD) survey[4], the incidence is the highest at 2.33% of the 35 developed countries and there is a large deviation from the OECD average of 1.48%.

According to the Ministry of Health, Labour and Welfare[3], about 70% of dementia in Japan is Alzheimer's disease, 20% is cerebrovascular dementia, and the rest is frontal temporal dementia that is likely to occur in young people such as Lewy body dementia or 50's. Alzheimer's disease occurs when senile plaques are formed from the amyloid beta (Aβ)protein, which is the trash of the brain, and furthermore, the proteins called tau are entangled among the nerve cells to denature the nerve cells and the brain is atrophied. It is considered that cerebrovascular dementia caused by cerebrovascular disorders such as cerebral infarction and cerebral haemorrhages is closely related to hypertension and diabetes. Currently, psychotherapy such as meditation therapy 5) and cognitive behaviour therapy [6] and reminiscence methods [7] are the main treatments for dementia, which can slow the progress. However, if the brain atrophy occurs, it is not possible to expect a complete recovery. Therefore, early detection, early treatment, and prevention are keys, and care after onset is important.

In recent years, developed countries have positioned dementia control as one of the top priorities of social security policy, formulated a comprehensive national strategy, and are actively promoting the reform of institutions and services. For example, in Japan, in 2015, "Comprehensive Strategy to Accelerate Dementia Measures- To Realize Age and Dementia-Friendly Community - (New Orange Plan)[8]" was formulated. This means that the administrative agencies responsible for medical care, nursing care, etc., the private sector that carries out daily living support services, and the communities act voluntarily and collaborate each other, and the entire community as a whole will support the elderly with dementia. We are aiming to realize a regional inclusive care system. At the moment, dementia has become one of the challenges to be overcome by mankind of the 21st century where the discovery of therapeutic method is urgent as it goes beyond merely one individual's brain diseases.

Lifestyle diseases such as hypertension, diabetes, dyslipidaemia not adequately treated are likely to develop Alzheimer's disease, and in the case of diabetes, the risk is doubled. This lifestyle-related disease accelerates arteriosclerosis and risks causing cerebral infarction and cerebral

haemorrhage, which causes cerebrovascular dementia. Diabetes promotes the arteriosclerosis of the brain, and as the arteriosclerosis progresses, the risk of developing cerebral infarction increases and thus it leads to vascular dementia [9].

## 2. Methods

The authors first searched PubMed, Cinii, Cochran databases with same searched strategies for studies published up to July 2018. The search strategy using Medical Subject Headings [mh], and keywords was: "dementia" OR "Alzheimer's Disease AND "prevention" OR "treatment," AND "a systematic review," OR "meta-analysis," The specific search strategy retrieved 379 results in PubMed, 461 in Cinii Article, and 192 in Cochran. The same searching strategies used with keywords of "diet," "physical exercises," "diabetes," "communication, " "insulin resistance, " and "neurofeedback". Going through article titles and selected and full texts were reviewed, then 26 review papers were chosen. In this paper, the author selected 7 review papers and introduced related 25 articles.

## 3. Results

The author summarises the recommended methods for prevention and treatment of dementia in six fields as follows; 1) diet, 2) exercise, 3) appropriate communication, 4) drugs as treatment are described, then future possible treatments which may improve the disease drastically or to some extent, 5) control of insulin resistance and 6) neurofeedback.

1) Diet

Diet is very important for dementia in preventing Cholesterol from accumulating in blood vessels. Eating vegetables and fish, especially blue fish such as mackerel, sardine, soybeans, DHA (docosahexaenoic acid) or EPA (eicosapentaenoic acid) that reduces cholesterol, is recommended.[10] In the United States, the Mediterranean-DASH Intervention for Neurodegenerative Delay diet, the MIND diet which combines the portions of the DASH (Dietary Approaches to Stop Hypertension) diet.[11] The MIND diet consist of eating whole grains, green leaf, vegetable, nuts, berries, fish, poetry, wine, supplemented with either extra-virgin olive was proven to be effective to recover of memory loss with 923 participants diagnosed as the Alzheimer's Diseases.[12] Probably because green vegetables, fruits, almonds and nuts contain polyphenols and vitamins C and E, which act to reduce the damage of nerve cell membranes received by active oxygen, and soy products contains a large amount of lecithin, which acts to lower blood cholesterol and neutral fat, and also has the function of dissolving fibrin as the main component of thrombus. Recent research reveals that the Mediterranean diet[13] is proven to improve cognition, which is more effective at reducing cognitive decline than either the Mediterranean or DASH diets alone.[14]

In Japan, it is also recommended to have Omega 3 (DHA, EPA, α linoleic acid) which is indispensable for maintaining the cognitive function of the brain.[15] More than 60% of the tissues in the brain are lipids, and the majority of them are omega-3 fatty acids such as DHA and EPA. There is also a survey result that the risk of Alzheimer's disease will rise if there is a shortage, so it is important nutrients. Because this ingredient is not made in the body, ingestion from food is indispensable. The vegetable α-linoleic acid changes into DHA, EPA in the body when taken.

2) Exercises

According to the literature review [16] of physical activity and Alzheimer's dementia suggest that elderly people living in the area are treated for 2.5 years. 24 follow-up observations from 24 papers reported that physical activity and exercise have a defensive effect on cognitive decline and development of dementia in 20 papers. Specifically, walking is recommended mainly from 2 to 3 times or more per weeks, exercising for more than 30 minutes. Those who exercised more than 30 minutes more than 3 times a week showed significantly less decreased cognitive function and the decreased onset of dementia in the elderly. Recently, it is said that a combination of exercise and other training is more effective for prevention of dementia than simply performing one exercise. For example, the report of the National Institute of Longevity Sciences in Japan[17] recommended exercising while "exercising", "clapping hands at multiples of 4" or exercising, named ‘cogni-cise’, which is Japanese coined word, and has promoted the exercise to penetrate the public by promoting all kinds of media that ‘cogni-cise’ is effective for dementia prevention.

3) Appropriate Communication

Alzheimer's type dementia is caused by the fact that the hippocampus and temporal lobe, which controls memory in the brain, are contracted by aging. The symptoms appear loss of the memory of the words of daily items, the face and name of the family members living together, and also today's date and meals taken just before. Then, getting confused with the names of children and grandchildren gradually appear, which is a sign of common dementia. As the symptoms progress, memories of the age and the name of oneself, and the location of home are getting lost. Wandering of elderly people is one of the social problems, but many of them are happening because they cannot remember the place of their home. When these symptoms and troubles arise, the family receives a big shock, but the one most hurt is the elderly person himself. Therefore, families have to know that people with dementia are psychologically uneasy about having communication.

According to Dementia care network in Japan,[18] people with diseases would lose the ability to communicate, and problems we can expect to see throughout the progression of the disease include;

- Difficulty in finding the right words
- Using familiar words repeatedly
- Describing familiar objects rather than calling them by name
- Easily losing a train of thought
- Difficulty in organizing words logically
- Reverting to speaking a native language
- Speaking less often
- Relying on gestures more than speaking.

There, the better ways of communicating with people with dementia are as follows;

- Speak slowly with a loud voice
- Talk at the height of your eyes
- Keep communication simple
- Give one command at a time
- Make eye contact before beginning to speak

- Keep distractions to a minimum, for example, turn off the TV or radio and stop background conversations, when you are interacting with someone with dementia.

4) Drugs

Since1980s, an immense amount of research taking place into new drug treatments for Alzheimer's disease and the other dementias, and drugs which acetylcholinesterase inhibitors that suppress the decline of acetylcholine have long been used for a decade, as nervous communication substance called acetylcholine in the brain was lacking in the brain of the patients with dementia. The treatment to directly compensate for acetylcholine was initially conducted, but it turned out to be ineffective. So, drugs that increase acetylcholine system by further suppressing enzymes suppressing acetylcholine system, and agents that regulate the effect of neurotransmitter such as glutamate are used. Although it is not possible to ameliorate memory impairment itself with these drugs, it is said that progress can be delayed for at least one year.[19] Currently, drug therapy for dementia can be divided into treatment for core symptoms such as memory disorder, disorientation disorder, performance disorder and treatment for mental behaviour such as depression and anxiety, and hallucinatory delusions, wandering and violent behaviors.[20]

In addition, almost all of the currently developed therapeutic drugs for Alzheimer's disease are those that prevent dementia by stopping the mechanism of disease occurrence.[21] As the accumulation of a Aβprotein in the brain causes Alzheimer's disease, most pharmaceutical companies are developing various ways to exclude this Aβfrom within the brain. Specifically, immunotherapy such as amyloid vaccine, drugs that inhibit and modify the action of beta-secretase and gamma-secretase enzymes necessary for the production of amyloid beta, and polymerization inhibitor of A $\beta$ are being carried out in various strategies.[22] It has also been shown that worsening can be prevented by appropriate treatment and care if a doctor examines at an early stage 2. However, up to date, there is no drugs to cure the disease yet. [23]

5) Control of Insulin resistance

Recently, eliminating insulin resistance has been an issue in the prevention of dementia, [24], [25], because insulin resistance is thought as a risk factor for the development of Alzheimer's disease. Insulin regulates sugar energy metabolism in the brain as well as neurotransmission and synapse. It has also been reported from experiments using animals that insulin promotes the release of Aβ from cells thereby suppressing intracellular accumulation of Aβ. Insulin is transported into the brain through the cerebrovascular barrier, but in hyperinsulinemia it is considered that insulin action in the brain and the neuroprotective effect decrease as insulin transport to the brain decreases. It is also known that insulin receptors are highly localized in the olfactory bulb, hypothalamus and hippocampus in the brain.

Insulin resistance is thought to affect not only the blood glucose but also the metabolism of blood pressure, cholesterol, triglyceride (neutral fat), so that leads to obesity (especially visceral obesity), hypertension. When insulin resistance occurs, insulin does not work normally in the liver, muscle, adipocytes, etc., and even if insulin is secreted from the pancreas by sensing the elevated blood glucose level in the meal, muscle and liver are in the blood. As it does not take in glucose, it is explained that the blood glucose level does not decrease, leading to the onset of

diabetes. In fact, it is recognized that the elderly people with diabetes commonly develop dementia.[26)]

Since 1993, Kyushu University's "Hisayama-cho study" [27)] reveals that there are many mergers of dementia in elderly diabetic patients. People with diabetes have a 2-4-fold increase in the risk of developing Alzheimer's disease and vascular dementia compared with those who do not. In this research, when the participant of the research dies, pathologic dissection is carried out, and the cause of death is analysed. Among them, we are pursuing how much difference in the proportion of people who had diabetes when they were middle-aged and those who did not, in the incidence of dementia after 20 years and 30 years later. According to it, the behaviour of genes in brain neurons is greatly different between those who died of Alzheimer's disease and those who did not, and more than half of the genes worked well in people without Alzheimer's disease. On the other hand28), in the neurons of the brain of a person with Alzheimer's disease, genes necessary for the function of insulin worked, and genes that interfered with the function were active.

Another reason diabetic persons are more likely to develop Alzheimer's disease is that diabetes promotes arteriosclerosis of the brain. As the arteriosclerosis progresses, the risk of developing cerebral infarction increases. It is likely to become vascular dementia. Furthermore, if "postprandial hyperglycaemia" that increases the postprandial blood glucose level continues, oxidative stress, inflammation, "terminal glycation end product" which is a harmful substance that can be generated when burning sugar and the like cause damage to nerve cells of the brain. Surprisingly, even in the case of "impaired glucose tolerance" which is a preliminary stage of diabetes mellitus, the risk of dementia is said to be high.

A research team at the Georgetown University in the United States[28)] also examines sugar uptake in the brain for many years and clarifies how it changes. According to it, in people without Alzheimer's disease, sugar uptake has not changed so much even as the age progresses, but in people with Alzheimer's disease, sugar uptake has clearly declined about 10 years before onset. It is thought that when the blood glucose level is high, insulin works poorly in the brain and Aβ tends to increase. In the United States, researches on therapy for administering insulin from the nose are under way.[29)] It is a treatment that absorbs insulin from the mucosa of the nose and sends insulin directly to the nerve cells of the brain to improve the function of nerve cells. If good results are obtained in these studies, practical application is expected.

6) Neurofeedback

Little is known about the effect of neurofeedback in patients with dementia. However, the research to examine efficacy of neurofeedback to patients with dementia has emerged, and showed that patients with Alzheimer's diseases who received neurofeedback treatment had stable cognitive functions, and improvement in memory and in recall of information and recognition.[30)] Currently, clinical trials of National Institute of Health is underway[31)] to examine the efficacy of neurofeedback on dementia patients. Neurofeedback[32)] also called EEG Biofeedback, is simply biofeedback applied to the brain directly by giving feedback with visual and auditory stimuli if brain functions properly, which is self-regulation of brain. Self-regulation is a necessary part of good brain function. Self-regulation training allows the system (the central nervous system) to function better. Neurofeedback addresses problems of brain dysregulation, such as the anxiety-depression spectrum, attention deficits, behaviour disorders, various sleep disorders, headaches

and migraines, PMS and emotional disturbances. It is also useful for organic brain conditions such as seizures, the autism spectrum, and cerebral palsy. In the normal aging process, the EEG changes in the pattern of brain electrical activity concern decreases in frequency and amplitude. Patients with Alzheimer's diseases present a greater amount of theta activity compared to normal aging individuals. An excess of delta and a decrement of alpha and beta are also observed.

## 4. Discussion

Dementia is associated with functional and structural alterations in a distributed network of the brain regions supporting memory and other cognitive domains. The research results indicated that the MIND-DASH diet or taking EPA/DHA, walking or 'cognicise', appropriate communication treating the elderly with dignity, and drugs of polymerization inhibitor of Aβ are effective to prevent and slow down the progress of the disease. As there are many merged dementia with diabetes in elderly patients, it was also found that control of insulin resistance may be strongly associated with occurrence of dementia. In an animal experiment[33)], a rat where insulin was made not to be effective in the brain was released to the pool filled with water and the time to swim to arrive at the hill was measured. The rat got round the same place over and over again. After all, it took 13 minutes. Next, the same rat was injected with insulin only once in the brain and released to swim the pool. This time, it arrived in just 11 seconds after a week. Insulin injection in the brain showed to improve memory power dramatically. The mobility of dementia among the people who have healthy life styles without insulin resistance has not been investigated, but it seems highly possible that control of insulin resistance is the definitive treatment of dementia. If so, the treatment of diabetes might be also applicable to the early stage of dementia treatment. Further research is needed to see relationship between insulin resistance and onset of dementia.

## 5. Conclusions

Current research indicates metabolic dysfunction may play an important role of occurrence of the disease. The key of preventing and slowing progress of the disease are to keep healthy life style with good communication with others. The research results of control of insulin resistance and neurofeedback are anticipated as potential tools for drastic improvement of the disease.

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