Efficacy of Anti-Diabetic Medicines in the Treatment of Alzheimer’s Disease

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ABSTRACT
Alzheimer’s disease (AD) is a neurologic disorder that has affected more than 36 million patients all over the world and is expected to rise up to 100 million till 2050. AD cost has been calculated more than 600 million dollars worldwide during 2010. There are approximately 400000 AD cases in Iran. Indeed AD is a neuroendocrine disorder and named Type 3 diabetes mellitus (T3DM) and its reason is some insufficiency in insulin and IGF signaling pathway, which consist of impairments in synthesis of insulin and insulin-like growth factor (IGF) in the brain. T3DM has large overlap with Type 1 diabetes mellitus (T1DM) and particularly with Type 3 diabetes mellitus (T2DM) from the point of view in both biochemical abnormalities aspects as well as its effects on the brain. Recently some research are published which show cognitive improvement in patients of AD that were treated with intranasal insulin and other anti-diabetic medicines.

Keywords: Alzheimer’s disease, Type 3 diabetes mellitus (T3DM), Anti-Diabetic Medicines

Introduction
Nearly 10% of all persons over the age of 70 have signs of memory loss, and in more than 50% of these cases, the main reason is Alzheimer’s disease (AD) [1-3].

Epidemiology
There are over 36 million AD patients around the world. It has been estimated that these figures dramatically, will be rising to 65.7 million by 2030 and 115.4 million by 2050.

Although AD has involved people in all countries, more than half (58%) reside in low- and middle-income societies. According to the Alzheimer’s Disease International (ADI), 2010, Alzheimer’s disease is the third most common cause of death worldwide. It is the most common cause of death in elderly people, and there is a rapidly increasing number of Alzheimer’s disease cases in the world. Indeed AD is a neuroendocrine disorder and named Type 3 diabetes mellitus (T3DM) and its reason is some insufficiency in insulin and IGF signaling pathway, which consist of impairments in synthesis of insulin and insulin-like growth factor (IGF) in the brain. These impairments can lead to the neurodegeneration of the brain cortex and the hippocampus.

The characteristic microscopic findings of AD are brain deposition of two fibrillary proteins. The name of these proteins is amyloid-beta (Abeta) and including apolipoprotein E (APOE) and Tau proteins.

Progressive demolition and death of neurons plus attenuate of the cerebral cortical degeneration, particularly the temporo-parietal cortex and the hippocampus.

Atrophy of the cerebral cortex along with ventricular enlargement of the brain has been demonstrated by biopsy. These facts have shown the neurotic cortical degeneration, particularly the temporo-parietal cortex and the hippocampus.

The disease can affect a person’s physical coordination. Therefore, the patient would not be able to do daily activity such as eating, bathing, and dressing. It is a condition that is completely related to significant somatic and emotional problems for patients and their households [1,9-10].

Type 1 diabetes mellitus
The reason of this type of diabetes has been demolished pancreatic beta cells and concomitant reduced insulin secretion.

Cholinergic neurons are the first part which be damaged by AD. So, use of medicines that stop the decline of acetylcholine in the synapses has an important role in the treatment of AD.

Recent studies have shown low levels of insulin in the brain have reduced the amount of acetylcholine level and brain blood flow. Furthermore, the changes of insulin level in the brain lead to form Abeta and Tau proteins.

Aging is the main cause of AD. Emerging information has indicated that type 2 diabetes mellitus (T2DM) and dyslipidemic conditions are other major risk factors for progressing of AD.

Epidemiologic researches have proponed persuasive document for an important and considerable relation between T2DM and dementia and moreover offer that T2DM is a major risk factor for progressing of AD.

Insulin resistance (disability to react to insulin stimulation) differs between various organs and has been observed in only one or two organs and not in others, an event that could be described the incomplete overlap between T2DM and AD [9].

Increasingly, a great improvement is seen in the researches that mention insulin deficiency and insulin resistance as inductors of AD. In addition to pancreas, there is special insulin gene in the human brain. Deficit of endogenous insulin, insulin like growth factor (IGF-1), IGF-2, and their receptors in the brain cause the neurodegeneration of the brain related to dementia [6,7].

Clinical Manifestations
The cognitive changes in AD are started by memory impairment and develop to language and visuospatial deficits. Furthermore, it is described by a decay of intellectual performance, apathy, reduction of speech function, disorientation, and difficulty in walking. Decision-making power is reduced.

The disease can affect a person’s physical coordination. Therefore, the patient would not be able to do daily activity such as eating, bathing, and dressing. It is a condition that is completely related to significant somatic and emotional problems for patients and their households [1,9-10].

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Type 2 diabetes mellitus

This type is a heterogeneous group of disorders characterized by different degree of insulin resistance in peripheral organs, impaired insulin secretion and increased glucose production often has associated with a positive family history, obesity, aging, and sedentary condition. Hence, patients suffering from T2DM have hyperglycemia and hyperinsulinemia.

Type 3 diabetes mellitus

This kind is exclusive to the brain, but in some cases have overlap with T2DM. Actually, there is insulin resistance and insulin deficiency situation in the human brain.

According to researchers’ hypothesis, type 3 diabetes mellitus (T3DM) elucidates a main pathogenic mechanism of AD neurodegeneration.

Indeed AD is a neuroendocrine disorder and its reason is some insufficiency in insulin and IGF signaling pathway, which consist of impairments in the synthesis of insulin and IGF in the brain. As previously mentioned T3DM has large overlap with type 1 diabetes mellitus and particularly with T2DM from the point of view in both biochemical abnormalities aspects as well as its effects on the brain [6-8].

Treatment

In spite of numerous researches about AD and its proper treatment, there is not any effective method for prevention or complete treatment of this disorder. Some drugs such as donepezil, galantamine, and memantine reduce only cognitive signs for a limited time, but none of them treat basic problem.

By considering the role of insulin and IGF deficiency and insulin signaling pathway impairment in the pathogenesis of AD, some new medical approaches has been assumed control of AD symptoms including, utilization of insulin and some oral anti-diabetic agents which act primarily by increasing insulin sensitivity like peroxisome proliferator-activated receptor-γ agonist (rosiglitazone and pioglitazone) [11].

Recently, some researches have been published which show cognitive improvement in patients of AD that were treated with intranasal insulin.

According to the results of a randomized, double-blind, placebo-controlled trial of Craft et al. “treatment with 20 IU of insulin has improved delayed memory and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability” [12-14].

In one study, after administration of rosiglitazone to Tg2576 Alzheimer mice, has been observed that rosiglitazone decreased learning, and memory deficits [15].

Results of a randomized, double-blind, placebo-controlled clinical trial about the efficacy of rosiglitazone monotherapy in AD consists of: monotherapy with rosiglitazone did not have any positive effect on the cognitive or total function of AD patients [16].

In a comparison of APOE positive AD patients with APOE negative AD patients, after administration of rosiglitazone, APOE negative AD patients showed cognitive improvement, but there was not any change in cognitive or total function of APOE positive patients [17].

In a research effect of rosiglitazone was tested on the cognitive improvement of three groups of Tg2576 AD mice. Finally, in 5 months old and 13 months old mice have not been observed any improvement, whereas rosiglitazone attenuates learning and memory deficits in 9 months old mice .

Discussion

Recent studies reveal that Abeta plays a role of a direct competitive inhibitor of insulin binding to its receptor and function. Excessive amounts of Abeta in AD are connected to the relevant insulin resistance that has been found in this disease [18].

Presence of some evidence suggests that insulin resistance is one the secondary problems of AD, which is related to increased levels of Abeta neurotoxin, which leads to effects similar to other types of diabetes mellitus in the brain.

Hence, according to these facts the main reason of AD remains unclear and considering of AD as a pure form of diabetes mellitus cannot explain whole sides of this disease and is not responsive completely in terms of AD treatment.

Probably this is why anti-diabetic agents are not helpful in AD like their impacts on diabetes. Finally, it is recommended subsequent studies on the causes of increased Abeta production.

References