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The Presence of Dementia as one of Diabetic Complications: Hyperglycemia, Hypoglycemia and Glycemic Fluctuation are Associated with the Development of Dementia

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Abstract

The number of subjects with dementia has been increasing all over the world which has become one of the serious social issues. Mainly, there are two types of dementia; one type is Alzheimer's disease and another type is vascular dementia. Such dementia is often complicated in elderly subjects with diabetes and thereby it is thought that dementia is one of diabetic complications. There are many possible explanation about the mechanism by which dementia is easily induced in subjects with diabetes. Chronic hyperglycemia and repeated hypoglycemia are closely associated with the onset and/or development of dementia. In addition, the fluctuation of blood glucose level *per se* is also associated with dementia. In this review article, we would like to describe the current status of dementia and association between dementia and diabetes.

Keywords: Dementia; Diabetes

Dementia is One of Diabetic Complications: Hyperglycemia is Closely Associated with the Onset and/or Progression of Dementia

The number of elderly subjects has been markedly increasing all over the world. Consequently, the number of subjects with dementia has also been increasing which has become one of the serious social issues. It is well known that the presence of diabetes mellitus leads to various complications such as microangiopathy (nephropathy, retinopathy, neuropathy) and macroangiopathy (ischemic heart disease, stroke). Dementia is often complicated in elderly subjects with diabetes and thereby thought to be one of diabetic complications. Indeed, it was reported that the incidence of Alzheimer's disease and vascular dementia was significantly higher in subjects with diabetes compared to non-diabetic subjects [1-7]. Therefore, in order to obtain the quality of life in subjects with diabetes, it would be very important to understand the molecular mechanism for dementia and to explore the way to prevent the development of dementia.

There are many possibilities in the reason why dementia is often observed in subjects with diabetes. For example, it has been suggested that in the diabetic state chronic hyperglycemia leads to the formation and accumulation of advanced glycation end products in the brain which could lead to the development of dementia [8] (Figure 1). In addition, while it is known that hyperglycemia and subsequent oxidative stress reduce insulin signaling in various insulin target tissues [9,10], insulin receptors are highly expressed in the brain as well [11]. It was reported that such reduction of insulin signaling in the brain induced hyper-phosphorylation of Tau protein and accumulation of beta amyloid protein both of which are well known as main characteristics in Alzheimer's disease [8,12-14] (Figure 1). In subjects with diabetes, there are several macro- and micro-angiopathy. Diabetic macroangiopathy (e.g. atherosclerosis) leads to the onset of cerebrovascular disease such as stroke which is closely associated with the development of vascular dementia. In addition, diabetic microangiopathy brings out brain ischemia which is also closely associated with the onset and progression of vascular dementia (Figure 1).

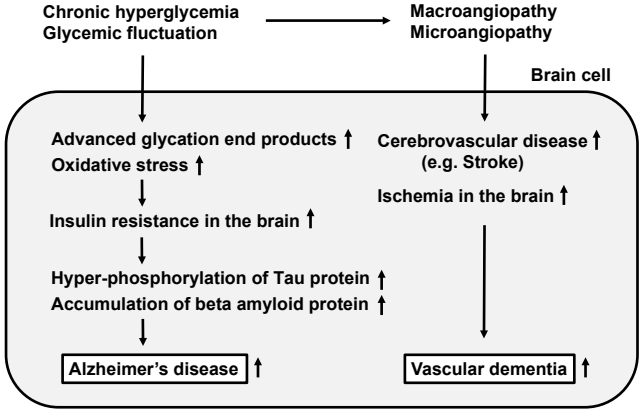

Figure 1: Association between diabetes and dementia.

Repeated Hypoglycemia is Closely Associated with the Onset and/or Development of Dementia in Subjects with Diabetes Mellitus

It has been thought that repeated and/or severe hypoglycemia is closely associated with brain damage especially in the cerebral cortex and hippocampus [15]. It is obvious that the maintenance of cognitive function for a longer period would provide good quality of life in each subject with diabetes. Recently, large and prospective cohort study in subjects with type 2 diabetes clearly showed that the incidence of dementia was significantly higher in elderly subjects who experienced hypoglycemia [16]. Hypoglycemia was significantly associated with increased risk for dementia even after adjustment with various parameters such as hemoglobin A1c (HbA1c) level. There was also a

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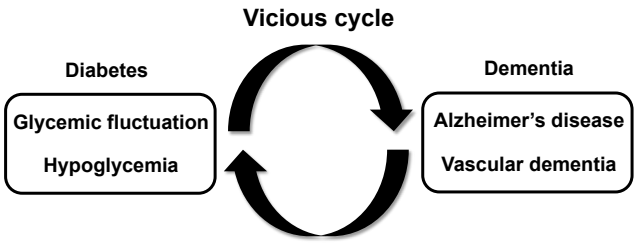

Figure 2: Vicious cycle between diabetes and dementia.

significant linear association between an increased risk of dementia and an increased number of hypoglycemia. It is known that recurrent hypoglycemia causes brain damage especially in the cerebral cortex and hippocampus [15]. Indeed, it was shown that hypoglycemia provided a substantial damage on the hippocampus in some animal study [17]. In addition, once dementia is brought out, it becomes very difficult to maintain good glycemic control and avoid the appearance of hypoglycemia. There is a kind of vicious cycle between the frequency of hypoglycemia and the development of dementia including both Alzheimer's disease and vascular dementia (Figure 2).

Some anti-diabetic drugs such as insulin or sulfonylureas easily bring out hypoglycemia in subjects with diabetes. Therefore, it would be better to use other types of anti-diabetic drugs such as dipeptidyl peptidase IV (*DPP-IV*) *inhibitor*s in order to avoid hypoglycemia especially in elderly subjects with type 2 diabetes. DPP-IV inhibitors inactivate DPP-IV which is a splitting enzyme of incretin and increases serum levels of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Since both incretins stimulate insulin secretion in a glucose-dependent manner, hypoglycemia is seldom observed in subjects using DPP-IV inhibitor alone. Needless to say, combination therapy with DPP-IV inhibitor and other anti-diabetic drugs such as insulin and sulfonylureas could bring out hypoglycemia. In addition, although insulin has the risk of hypoglycemia, insulin therapy should be introduced in subjects with very low insulin secretory capacity.

Taken together, hypoglycemia is closely associated with the onset and/or progression of dementia in subjects with type 2 diabetes. We should avoid hypoglycemia especially in elderly subjects with type 2 diabetes in order to avoid the development of dementia. In addition, we should avoid hypoglycemia in subjects with various diabetic complications such as proliferative diabetic retinopathy and/or ischemic heart disease, because the appearance of hypoglycemia could aggravate such diseases.

Glycemic Fluctuation is Closely Associated with the Onset and/or Development of Dementia in Subjects with Diabetes Mellitus

The fluctuation of blood glucose levels and repeated hypoglycemia likely leads to the onset and/or progression of dementia [18,19]. It was reported that the risk of Alzheimer's disease and vascular dementia was significantly associated with postprandial glucose levels but not fasting glucose levels [7]. These data support the hypothesis that the fluctuation of blood glucose levels is likely associated with the development of various types of dementia. Although self-monitoring of blood glucose levels and continuous glucose monitoring are useful to visualize the fluctuation of blood glucose levels, it is practically difficult to do such examination for all subjects in everyday clinical medicine. It has been reported that glycoalbumin (GA)/hemoglobin A1c (HbA1c) ratio is a good marker for the fluctuation of blood glucose levels regardless of glycemic control situations [20]

It was reported recently that GA/HbA1c ratio as well as age were significantly associated with Hasegawa dementia scale-revised (HDS-R) score in elderly subjects with type 2 diabetes [21]. Furthermore, in multivariate regression analyses, age, GA/HbA1c ratio and urinary albumin excretion were independent factors contributing to HDS-R score [21]. Although it was easily expected and quite reasonable that age was the strongest factor contributing to the HDS-R score, multivariate analyses showed that GA/HbA1c ratio was also an independent factor contributing to the HDS-R. It was known that GA/HbA1c ratio was associated with cognitive impairment in elderly subjects with type 2 diabetes, but it has been thought that increased hypoglycemia leads to the onset and/or progression of various types of dementia. However, the fluctuation of blood glucose levels, but not the incidence of hypoglycemia, was significantly associated with the decrease of cognitive impairment in this study [21]. These data suggest that the fluctuation of blood glucose level *per se* is likely associated with dementia even when hypoglycemia is not accompanied, although we still think that hypoglycemia has some bad influence for dementia. Taken together, in order to avoid the onset and/or development of dementia, we should be careful for reducing the fluctuation of blood glucose levels in addition to avoiding hypoglycemia. In addition, once dementia is developed, it becomes very difficult to reduce glycemic fluctuation. There is a kind of vicious cycle between the glycemic fluctuation and the development of dementia including both Alzheimer's disease and vascular dementia (Figure 2).

Some anti-diabetic drugs such DPP-IV inhibitors are expected to reduce the fluctuation of blood glucose levels. Since incretins stimulate insulin secretion in a glucose-dependent manner, fluctuation of blood glucose levels is thought to be reduced. Indeed, it was reported that DPP-IV inhibitors reduced glycemic fluctuation compared to sulfonylureas in subjects with type 2 diabetes [22].

Taken together, glycemic fluctuation is closely associated with the onset/of progression of dementia in elderly subjects with type 2 diabetes. We should avoid glycemic fluctuation especially in elderly subjects with type 2 diabetes in order to avoid the development of dementia. Since it is very easy to calculate GA/HbA1c ratio, a maker of the fluctuation of blood glucose levels, we should check this ratio so that we can reduce the fluctuation of blood glucose levels especially in elder subjects with type 2 diabetes.

Conclusion

Dementia is often complicated in elderly subjects with diabetes mellitus and thereby thought to be one of diabetic complications. Not only chronic hyperglycemia and repeated hypoglycemia but also the fluctuation of blood glucose levels is associated with the onset and/or progression of dementia in elderly subjects with diabetes mellitus.

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