



## MECHANISM OF ANTIDIABETIC MEDICATION IN TREATING COGNITIVE DYSFUNCTION

Dementia is a complication of diabetes mellitus and diabetes mellitus is risk factor for dementia. Prevalence of both conditions is increasing as the population ages. Diabetes mellitus increases the risk of dementia by about 70%, Alzheimer's type dementia by about 60%, and vascular dementia by more than 100%. There are several antidiabetic medications that may have a positive effect on preserving cognition of patients with dementia and diabetes. This issue of *CLIPs* briefly summarizes an article that reviews the mechanism of each antidiabetic medication and the evidence related to their prevention of cognitive dysfunction or preservation of cognition. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at (205) 726-2659.

**Umegaki, H. Therapeutic potential of antidiabetic medications in the treatment of cognitive dysfunction and dementia. *Drugs & aging*. 2016;33:399-409.**

### Mechanism of Cognitive Impairment

- The suggested mechanisms by which diabetes affects cognitive function is by insulin resistance; hyperglycemia; hypoglycemia; and inflammation and other mechanisms.
- Insulin resistance (IR) is associated with dementia, especially Alzheimer-type dementia due to a reduction in cerebral blood glucose metabolism or amyloid deposition.
- Hyperglycemia is associated with cognitive decline. One report indicated that increased glucose levels contribute to higher dementia cases in patients with or without diabetes. The Sacramento Area Latino Study on Aging (SALSA) showed, patients diagnosed with DM had more cognitive decline than those without diabetes. Antidiabetic treatment was thought to provide a decline in cognition in these patients.
- Hypoglycemia may contribute to cognitive impairment due to the reduction in the supply of glucose as an energy source for neurons. A positive association between hypoglycemia episodes and risk of dementia has been observed.
- Inflammation and other etiologies may contribute to cognitive impairment due to increased permeability of the blood brain barrier cause by elevated blood glucose. This change in permeability can cause peripheral cytokines to cross the blood brain barrier and induce more neuron inflammation

### Antidiabetic Treatments

- Several clinical trials have been performed to determine the effects of antidiabetic medications on cognition; however, only one large scale randomized control trial has shown beneficial effects.
- Previous studies have had short study periods and drug therapy regimens were complex and some were associated with hypoglycemic episodes.
- The effect of new diabetes agents on cognitive impairment has not been elucidated.

*Insulin.* Several small studies have been performed that indicate that insulin may be beneficial in cognitive dysfunction. Four studies have assessed this benefit. In one study, euglycemic patients experienced improvement in cognition after a single insulin injection. Another study showed positive effects on cognition after insulin administration; however, two studies showed an increase in cognitive decline with insulin administration. Intranasal administration of insulin has been shown to have beneficial effects without peripheral affects on blood glucose. A randomized controlled trial showed intranasal insulin improved delayed memory tasks. Other benefits of intranasal insulin are improved vasoreactivity and cerebral spinal fluid biomarker manipulation.

*Thiazolidinediones (TZDs).* TZDs inhibit proinflammatory gene expression and therefore improves insulin resistance and inflammatory response. A recent study reported long-term use of pioglitazone decreased the occurrence of dementia, and may be a good choice in the treatment of Alzheimer's related dementia.

*Biguanides.* Biguanides are thought to have a protective vascular effect due to its ability to increase responsiveness to insulin. Metformin crosses the blood–brain barrier and may have anti-inflammatory and neuroprotective effects. In a large study, however, metformin was shown to have a negative effect on cognition.

*Glucagon-Like Peptide-1 (GLP-1).* GLP-1 is an incretin peptide that is activated by the intestines and causes an increase in insulin, stimulated by food intake and increase in blood glucose. GLP-1 agents cross the blood–brain barrier and exert its effects on GLP-1 receptors in areas such as cerebral cortex and hippocampus, and improves insulin signaling in the brain. GLP-1 agonists are suggested to be neuroprotective, neurotropic and anti-inflammatory.

*Dipeptidyl-Peptidase-4 Inhibitors.* While GLP-1 is released to increase the release of insulin and suppress the release of glucagon, dipeptidyl-peptidase-4 (DPP4) acts by degrading GLP-1. DPP4 inhibitors act by inhibiting DPP4 activity, thus increasing insulin and decreasing glucagon to lower blood glucose. DPP4 inhibitors are also beneficial due to having a low risk of hypoglycemia and weight gain.

*Sulfonylureas (SUs).* This class of medication is used to stimulate insulin-secreting cells in the pancreas by binding to ATP-sensitive potassium channels to increase insulin release. This class has a strong blood glucose lowering effect and may cause hypoglycemia. Glimepiride may reduce synapse damage and delay the progression of cognitive decline in Alzheimer's dementia. An intervention study with type 2 diabetic subjects revealed glipizide improved cognition when compared to their condition before receiving medication.

*Glinides.* These agents stimulate the release of insulin from pancreatic cells. Glinides have a moderate blood glucose lowering effect and a low risk of hypoglycemia and weight gain. A clinical study demonstrated preserved cognitive function in a group treated with repaglinide compared with those treated with SUs.

*SGLT-2 Inhibitors.* This class promotes the excretion of glucose into the urine by inhibiting sodium-glucose cotransporter-2 in the proximal tubules of kidney. No clinical data on cognition in association with the use of this class of medication have been reported so far. This class may improve insulin resistance due to reducing body weight.

## Conclusion

- Diabetes is a risk factor for dementia.
- Insulin resistance, insulin signaling in the brain, hyperglycemia, and hypoglycemia may contribute the risk for dementia
- Antidiabetic medications help with cognitive preservation by lowering glucose, reducing insulin resistance, and improving central insulin signaling in the brain.
- There are several antidiabetic medications, with each having a different mechanisms of action that contribute to improving or preserving cognitive function
- More studies are necessary assess the benefit of antidiabetic medication use for improving or preserving cognitive function.

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