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IMPACTS OF DIABETES ON COGNITIVE FUNCTION AND BRAIN STRUCTURE.

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Abstract:
Diabetes mellitus is associated with the major decrements of brain functioning with the passage of time. People with both type 1 and type 2 diabetes have been shown to have mild to moderate reductions in cognitive function as measured by neuropsychological testing compared to non-diabetic controls.

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INTRODUCTION:

Type 2 diabetes (T2DM) has also been associated with 50% increased risk of dementia as compared to type 1 diabetes [1] Diabetes has been known to have an effect on the brain for one hundred years or more. In the early twentieth century, researchers and clinicians recognized that people with diabetes frequently complained of poor memory and attention. A research in 1922 showed that people with diabetes performed poorly on cognitive tasks examining memory and attention. [2] The term 'diabetic encephalopathy' was introduced in 1950 to describe central nervous system related complications of diabetes. [3] Other terms like functional cerebral impairment and central neuropathy have also been used to describe diabetes related cognitive dysfunction. [4] With the growing epidemic of diabetes and the ever increasing number of people who live to old age, diabetes related cognitive dysfunction could have challenging future public health implications.

Type 1 diabetes (T1DM):

Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin. Insulin is a hormone needed to allow sugar (glucose) to enter cells to produce energy.

Magnetic resonance imaging (MRI) techniques of brain structure are used to examine the diabetes impact on regional brain volumes. The structural MRI studies of brain has determined us that how lower gray and white volumes effects with the person having type 1 diabetes mellitus as compared to a non-diabetic person. [5] The voxel-based morphometry is used to examine brain changes in 82 patients with type 1 diabetes mellitus. Person with diabetes had lower gray matter density primarily in the temporal, cerebellar and posterior regions of the brain. With age of onset of diabetes and its duration shown that lower gray matter density was severely affected with higher frequency of severe hypoglycemic events, poor glycemic control. Another study has shown that patients with uncontrolled diabetes have the frontal lobe appeared to be the location of reduced with volumes. [6] A reduction in the white matter volumes has also been identified patients with T1DM by Wessels et al and these major changes of brain leads to loss of executive function , speed of information processing and volume loss was associated with lower performances. [7] Duration and age of onset of diabetes was also associated with the major eye problems such as presence retinopathy have also seen in type 1 diabetes mellitus patients and with major structural changes in imaging studies.[8,9] White matter lesions which represent vascular abnormalities in intraparenchymal cerebral arterioles have shown to have increased patients with type 1 diabetes mellitus. [10,11] Increased severity of white matter lesions was seen patients with type 1 diabetes mellitus as compared to patients with controlled diabetes. [12]

A study shown that adults with type 1 diabetes mellitus did not find any difference in hippocampal volumes and adults with controlled type 1 diabetes mellitus. [13] On examination on large sample of adults with type 1 diabetes on comparison with their siblings not having type 1 diabetes mellitus. [14] Adult study overall shown that there were no difference in hippocampal volumes but in children with type 1 diabetes mellitus and have episodes of severe hypoglycemia in the past, hippocampal gray matter volume was larger. Overall studies in both adults and children shows that type 1 diabetes mellitus is associated with reduction in brain volume compared to non-diabetic and with controlled diabetes, the distribution of brain areas involved appear to be variable and the changes in brain structure has been associated with decline in cognitive performance.

The impact of type 1 diabetes mellitus on brain functional connectivity is still poorly characterized as compared to type 2 diabetes mellitus. Few recent functional connectivity studies have been conducted on type 1 diabetes mellitus patients with neuropathic pain such studies revealed abnormalities in networks involving attention [15] but with or without microangiopathy which effects motor and visual areas ,working memory, auditory and language processing. [16] In particular, reduced functional connectivity in the attention network was found in diabetics with microangiopathy compared to patients with controlled type 1 diabetes, but not in patients who did not have microangiopathy. [16] Subclinical macroangiopathy was also found to be a factor that likely contribute to development of diabetes-related cognitive changes in type 1 diabetes mellitus patients. More extensive studies aimed at establishing the impact of other clinical features of the disease including hyperglycemia or hypoglycemia episodes needs to be perform.

Type 2 diabetes (T2DM):

Type 2 diabetes is a common condition that causes the level of sugar (glucose) in the blood to become too high. It can cause symptoms like excessive thirst, needing to pee a lot and tiredness. It can also increase your risk of getting serious problems with your eyes, heart and nerves.

Patients having type 2 diabetes mellitus have seen also lower total and regional white and gray matter volumes including brain atrophy compared to non-diabetic npatients. [17] Cross sectional studies have shown total gray, white and hippocampal volumes are relatively lower in patients with type 2 diabetes. [17] Regions with loss of gray matter include the medial frontal lobes, medial temporal and anterior cingulate. White matter loss was found in the frontal and temporal regions. These investigators determined that brain volume loss was associated with poor performance in cognitive testing in type 2 diabetes mellitus patients. Another study have shown that atrophy may be greater in the hippocampal region in type 2 diabetes mellitus patients.[18,19] Patients having type 2 diabetes mellitus have increased white matter loss. [17,20] white matter loss and brain atrophy were associated with cognitive dysfunction. [20] but not in all studies. [21]

Patient having type 2 diabetes mellitus showed an accelerated progression of white matter loss and brain atrophy over 3–4 years 71–74 in relative to controlled diabetes. Diabetes related risk factors are retinopathy, hypertension, glycemic control duration of diabetes and glycemic control have associated with brain structural changes in diabetic patients.[22,20,23] In recent studies using ultra-highfield magnetic resonance imaging at 75 did not find any differences in the presence and number microvascular lesions (micro bleeds and micro infarcts) in patients with type 2 diabetes mellitus as compared to the controlled type 2 diabetes mellitus patients, nor did they find that any microvascular lesions were associated to performance on the cognitive testing. As in type 1 diabetes mellitus, studies in type 2 diabetes mellitus also show the distribution of volume loss across brain areas is variable but medial temporal lobe appears to be more susceptible. Future work will need to be done to determine if particular groups of patients with type 2 diabetes are at greater risk for changes in brain structure and function.

By using diffusion magnetic resonance imaging abnormalities in microstructure of brain and disruptions in the white matter network were seen in type 2 diabetes mellitus patients as compared to the controlled ones. These abnormalities were related to slowing of information-processing speed. [24,25] In obese adolescents with type 2 diabetes mellitus reduction in white and grey matter microstructural integrity has been seen, [26] suggesting that these structural changes are related to diabetes specific factors other than the atherosclerotic vascular disease related changes seen in older people with diabetes.

Decreased connectivity of the posterior cingulate cortex (PCC) within the default mode network is not only commonly observed in patients with Alzheimer's disease [27] but with mild cognitive impairment, [28] but specifically seen in patients with type 2 diabetes mellitus. [29] Abnormal functional connectivity of the posterior cingulate cortex to selected brain regions in patients with type 2 diabetes mellitus also appear to correlate with lower fractional anisotropy (FA) in the cingulum bundle and uncinate fasciculus,[30] and with the insulin resistance has been seen. [31]

Reduction in functional connectivity within the resting state default mode network, but also show abnormal involvement of the default mode network during task performance was seen in the subject of type 2 diabetes mellitus[32] including a reduced activation of the dorsolateral prefrontal cortex during encoding and reduced deactivation of the default mode network during recognition, with these effects being possibly exacerbated by acute hyperglycemia.

Alterations in the brain functional connectivity have been reported in type 2 diabetes mellitus patients [33] these type of patients are at higher risk of getting Alzheimer's disease [28] which leads to the reduction in the resting-state connectivity between the hippocampus and other brain regions. [30,33] A major reduction in functional connectivity of the hippocampus and decline in cognitive performance was associated with the type 2 diabetes mellitus patients. [33] These observation seems to be interesting, because patients with type 2 diabetes mellitus have an increased incidence of both Alzheimer's disease [34-39] and a vascular type of dementia [35,38,39] therefore abnormal functional connectivity has been seen which might constitute an early marker of subsequent cognitive decline for patients with type 2 diabetes mellitus. Future longitudinal studies are however necessary to determine whether these changes are predictive of cognitive dysfunctioning. Cognitive dysfunctioning in type 2 diabetes mellitus has associated with functional connectivity of other brain regions outside the default mode network and hippocampus. In type 2 diabetes mellitus patients. In type 2 diabetes mellitus a decreased amplitude of low frequency fluctuations (possibly indicative of reduced functional connectivity) was observed in the occipital lobe and postcentral gyrus as compared to controlled diabetes patients. The absence of structural brain changes and was associated with worse memory performance and executive functioning in type 2 diabetes mellitus patients. Disturbances of low frequency fluctuations

have been observed in several additional brain areas. [40,41] The observations of smaller fluctuations in the bilateral middle temporal gyrus have been associated with higher A1C values, poor neurocognitive performances and impaired β-cell function. [40] It is likely that the microvascular complications of diabetes largely contribute to the development of brain functional abnormalities, which possibly even precede the cognitive decline observed in type 2 diabetes mellitus. Diabetic retinopathy is considered to be an independent risk factor for cognitive decline in diabetes. Pathophysiology of the cognitive decline and brain structural changes in subjects with diabetes is not well known. Genetic predisposition, insulin resistance, poor glycemic control, amyloid disposition, vascular disease and oxidative stress have been proposed as major contributors.

Imaging studies on diabetes and brain structure:
Various neuroimaging techniques have been applied to study the impact of diabetes on brain structure and cognitive function. This approach has also been used to define the structural correlates of cognitive dysfunction in diabetes and to provide insights into the mechanisms of the central nervous system complications of the disease. The techniques related magnetic resonance like structural MRI, magnetic resonance spectroscopy (MRS), functional MRI (fMRI) and diffusion tensor imaging (DTI) have been used to assess brain structure and function in diabetes.

CONCLUSION:

Both type 1 and type 2 diabetes mellitus are associated with mild to moderate decrease in cognitive function which leads to the major changes in brain structure. They are significant differences in the underlying pathophysiology of cognitive impairment between type 1 and type 2 diabetes. Type 1 diabetes mellitus is usually diagnosed at an early age and may have effects on brain development. Chronic hyperglycemia and microvascular complications are important risk factors common to both type 1 and type 2 diabetes. Type 2 diabetes mellitus is usually diagnosed at an older age and is commonly associated with obesity, insulin resistance, hypertension and dyslipidemia, all of which can have negative impact on brain.

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