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EARLY-BEGINNING DEMENTIA IN TYPE 2 DIABETES MELLITUS

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ABSTRACT
The incidence of both diabetes and dementia is rising. The coexistence of the two can have enormous consequences – complications from one condition having a significant effect on the course of the other. The incidence of type 2 diabetes is rising because of changing lifestyles and increasing longevity. Contributory factors include a diet rich in sugar and fats, poor exercise regimes and obesity. However, with early diagnosis and treatment, people are living with diabetes into old age. Diabetes mellitus is a risk factor for dementia, especially for vascular dementia (VaD).[1]

KEYWORDS: Diabetes mellitus type 2 (DM2); Alzheimer's disease (AD); hypoglycemia; vascular dementia (VaD); amyloid precursor protein amyloid-β (APP-Aβ).

INTRODUCTION
Diabetes is a set of chronic conditions that affect the production and regulation of the hormone insulin. Insulin helps blood cells take up glucose, which means that for diabetics, getting glucose to the brain is a difficult task. If the brain is starved of energy, it's possible that neurological problems like dementia and Alzheimer's disease are more likely to develop.[1]

The number of people affected by diabetes mellitus has been growing worldwide. In 2015, the International Diabetes Federation estimated that 415 million people aged 20-79 years had diabetes worldwide, and nearly 75% lived in low-to-middle-income countries (LMIC). The number of diabetics will continue to rise with diabetes set to affect 642 million people by 2040, and this will take place especially in regions where economies are transitioning from low-income to middle-income levels. The World Alzheimer Report 2015 estimated that 46.8 million people worldwide had dementia in 2015 and 58% of these lived in LMIC. The proportion of people with dementia living in LMIC will reach 63% in 2030 and 68% in 2050. Dementia and type 2 diabetes are more prevalent with aging.1, 2 Diabetes is a known risk factor for dementia and vascular dementia (VaD), but the association between diabetes and Alzheimer's disease (AD) needs to be better clarified. Several longitudinal studies have shown that diabetes was associated only with VaD, but not with AD.[1]

Diabetes is the seventh leading cause of death in the U.S., according to the Centers for Disease Control and Prevention (CDC). It seems that among older adults with diabetes, there is also an association between low blood sugar (hypoglycemia) and dementia, say researchers at the University of California, San Francisco (UCSF) in a new study published in the Journal of the American Medical Association. This can create a dangerous spiral, in which a hypoglycemic event caused by diabetes can lead to mental deterioration and vice versa. "The brain uses glucose as a primary source of energy. Cognitive function becomes impaired when blood glucose drops to low levels, and severe hypoglycemia may cause neuronal damage,".[2]

The UCSF researchers found that the relationship between dementia, Alzheimer's, diabetes, and hypoglycemia is mutual. "scientist found that clinically significant hypoglycemia was associated with a two-fold increased risk for developing dementia similarly, participants with dementia were more likely to experience a severe hypoglycemic event,".[2]

Persons with type 2 diabetes mellitus (DM2) have an increased incidence of cognitive decline and dementia. An increased cortical and subcortical atrophy has been found after controlling for vascular disease and inadequate cerebral circulation. A possible role of insulin resistance and hyperinsulinemia has been suggested to mediate the link between DM2 and Alzheimer's disease (AD). Altered insulin signaling may contribute to AD biochemical and histopathological lesions. Both hyperglycemia and hypoglycemia may contribute to cognitive decline in DM2.Recurrent symptomatic and

asymptomatic hypoglycemic episodes have been suggested to cause subclincal brain damage and permanent cognitive impairment.[3]

Alzheimer's disease (AD) has characteristic histopathological, molecular, and biochemical abnormalities, including cell loss; abundant neurofibrillary tangles; dystrophic neurites; amyloid precursor protein, amyloid-β (APP-Aβ) deposits; increased activation of prodeath genes and signaling pathways; impaired energy metabolism; mitochondrial dysfunction; chronic oxidative stress; and DNA damage. There is an evidence that (1) T2DM causes brain insulin resistance, oxidative stress, and cognitive impairment, but its aggregate effects fall far short of mimicking AD; (2) extensive disturbances in brain insulin and insulin-like growth factor (IGF) signaling mechanisms represent early and progressive abnormalities and could account for the majority of molecular, biochemical, and histopathological lesions in AD; and (3) experimental brain diabetes is treatable with insulin sensitizer agents, i.e., drugs currently used to treat T2DM.[4]

Population-based longitudinal studies have shown that the risk of dementia in general is increased in people with diabetes. Even pre-diabetes has been associated with an increased risk of dementia and Alzheimer disease. Although diabetes may be linked to dementia through several biologically plausible pathways, our understanding of the mechanisms for such an association is still limited. Both dementia and diabetes are complex age- and lifestyle-related disorders. In addition to strong influence of environmental elements, genetic components also play a part in both Alzheimer's disease and diabetes Epidemiological and clinical studies have reported that environmental factors acting in early life, such as birth weight and childhood socioeconomic situation, are also involved in the development of diabetes as well as dementia. Evidence from genetic and epidemiological studies has indicated that genetic and environmental factors may interact to affect the association between diabetes and dementia during the life course.[5]

Dementia and diabetes mellitus are common long-term conditions and may co-exist in a large number of older people. Worldwide, there are an estimated 35.6 million people with dementia. By 2050, this number will rise to over 115 million. Although there are differences in the physical and cognitive effects of the different types of dementias, all are progressive, involve increasing physical and mental deterioration and lead to a person with dementia to become increasingly dependent. Diabetes mellitus is seen in 10–25 % of older people and in nursing homes, up to 27 % of residents may have diabetes. As with dementia, the prevalence of type 2 diabetes is increasing globally and there is evidence to suggest there is a link between cognitive dysfunction and type 2diabetes.[6]

Diabetes can cause small scale and macro vascular confusions like retinopathy, neuropathy, nephropathy, stroke, and coronary corridor sickness. Raised A1C is related with a greater amount of these intricacies. Glycemic control has likewise been connected to discernment issues in individuals who have type 2, however very little research has done on the impact of this with individuals who have type 1 diabetes. There is even less research on individuals who have type 1 diabetes and a danger of creating age-related ailments like dementia.[7]

DISCUSSION

Early detection of dementia associated with diabetes.

With the increasing ageing population, the epidemiology of diabetes is shifting towards old age with increasing prevalence of comorbidities. Geriatric syndromes; especially cognitive dysfunction is emerging as a third complication category in addition to the traditional macro and micro vascular disease in older people with diabetes.[8]

Type 2 Diabetes and Alzheimer's disease Dementia The importance of the connection between type 2 diabetes and Alzheimer's disease dementia is perhaps best captured by the term "type 3 diabetes," coined to describe a portion of patients who develop Alzheimer's disease dementia presumably as a result of diabetes-related injury and degeneration.[9]

To effectively target and treat dementia associated with type 2 diabetes, such treatment would be most effective when implemented as early as possible, preferably during a latent or prodromal phase when the neuropathological changes are not yet significant enough to result in significant overt clinical symptoms. Importantly, both type 2 diabetes and dementia are associated with prolonged prodromal phases, and although symptoms may not be overt, current advances permit early identification of both syndromes.[10]

Older people with diabetes and dementia experience difficulties in performing self-care tasks. In a community based study of 1,398 older patients with diabetes, mean (SD) age 70 years, adherence to diabetes self-care tasks (taking diabetes medication, performing regular exercise, following a recommended eating plan, undertaking blood glucose monitoring and feet inspection) decreased as cognitive impairment increased. Specific self-care tasks of exercise and diet adherence were the most strongly associated with cognitive impairment. These individuals are also more likely to experience treatment-related complications such as severe hypoglycemia—requiring assistance. Due to erratic eating patterns, associated with dementia, older people with diabetes are also at risk of malnutrition, dehydration and thus; worsening diabetic control. Carer's of patients with diabetes and dementia will face extraordinary challenges to care for both conditions especially in those individuals who develop

behavior changes. Their needs should be identified early for greater support from the healthcare system.[11]

Type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD) are among the fastest growing epidemics of the third millennium, which are both associated with aging of the population. DM2 is characterized by impairment in insulin action, insulin resistance and hyperinsulinemia. AD is pathologically distinguished by the presence of several hallmarks including neuronal loss, deposits of amyloid beta (senile plaques), intracellular neurofibrillary tangles composed of aggregated hyper phosphorylated tau proteins in brain, proliferation of astrocytes, and activation of microglia, associated with mitochondrial dysfunction and alterations in neuronal synapses. Most studies have suggested that the deposit of the toxic amyloid beta peptide (amyloid cascade hypothesis), may be a triggering factor contributing to the pathogenesis of AD. DM2 is associated with several and an important change in cognition and it has been strongly associated with an increased risk of developing dementia.[12]

Role of Insulin in Learning and Memory

The salutary effects of acute insulin administration on cognition are well documented. In rats, acute intracerebroventricular insulin administration improves memory on a passive avoidance task and enhances spatial memory via potentially age-dependent inflammatory reduction processes. In humans, acute intravenous and intranasal insulin administration (while maintaining euglycemia) consistently improves declarative memory performance. Learning also appears to influence insulin receptor expression and function in the dentate gyrus and CA1 area of the hippocampus. Together, these studies support insulin as an important factor in normal memory functioning. Potential mechanisms for the influence of insulin on memory include regional effects of insulin on cerebral glucose metabolism, influence on components of the long-term potentiation cascade, and modulation of acetylcholine and norepinephrine, neurotransmitters that are known to influence cognitive function.[13]

Collected data suggest that higher glucose levels may be a risk factor for dementia, even among persons without diabetes. Late examinations propose that the cerebrums of individuals with Alzheimer's sickness are in a diabetic state, incompletely because of the diminishing in or lack of care to insulin. There are numerous likenesses in the minds of individuals with diabetes and the cerebrums of individuals with Alzheimer's infection; be that as it may, diabetes just remains a hazard factor. A few people with diabetes may proceed to create dementia, yet many won't. Reducing your risk for diabetes and dementia. What's good for your heart is good for your brain. Living a healthy lifestyle that promotes cardiovascular health will benefit your brain.

- Eat a healthy diet rich in vitamin D, folate, and B6 and B12 vitamins.
- Exercise regularly – both your body and mind.
- Stay socially active and challenge yourself daily.
- Protect your head when playing sports.

CONSLUSION

With an aging population and concurrent rise in chronic health conditions has come a rapid escalation in the incidence of both type 2 diabetes and dementia. The risk for cognitive impairment and dementia is increased among those with type 2 diabetes, and insulin resistance represents a potential mechanism by which both Alzheimer's and vascular disease can develop. Fortunately, type 2 diabetes is amenable to intervention, and promising therapeutic interventions are under investigation. The abilities to establish risk among specific populations identify and perhaps prevent progression of the disease early in its process.[14]

Dementia and cognitive dysfunction have many causes. There is strong evidence that diabetes mellitus (DM) increases the risk of cognitive impairment and dementia. Optimal glycemic control, identification of diabetic risk factors, and prophylactic approach are essential in the prevention of cognitive complications.[15]

Type 2 Diabetes and Vascular Dementia Vascular disease represents a principle factor in accelerated brain aging, and vascular brain injury is an important contributor to cognitive dysfunction in older adults. Type 2 diabetes is a known risk factor for cardiovascular and cerebrovascular disease and may increase susceptibility to large and small caliber vessel-mediated injury to the brain, including hypoxic events, ischemia, and blood-brain barrier leakage. Dysfunction of vascular endothelial cells secondary to insulin resistance and inflammation is a characteristic consequence of type 2 diabetes, and disruption of white matter networks is seen on neuroimaging in patients with type 2 diabetes. Furthermore, white matter dysfunction is associated with poorer cognitive performance in patients with type 2 diabetes. Type 2 diabetes is frequently reported to be more strongly correlated with vascular dementia than with other types, including Alzheimer's disease dementia. Indeed, a recent meta-analysis of prospective studies that examined the risk of dementia in patients with type 2 diabetes reported a pooled relative risk of 2.27 for vascular dementia. Interestingly, new evidence suggests the increased risk for vascular dementia may be especially prominent in women; women with type 2 diabetes had a 19% greater chance of vascular dementia than men. In addition, those with longer duration and earlier age of onset of type 2 diabetes were more likely to develop vascular dementia.[16]

Neuroimaging studies have recently demonstrated that people with type 2 diabetes had moderately elevated risk for lacunes, hippocampal atrophy, and deep white matter lesions, which support the notion that the increased risk of cognitive decline and dementia in people with diabetes is probably due to dual pathological processes

involving both cerebrovascular damage and neurodegenerative changes. In addition to micro vascular and macro vascular disease, there are other pathophysiological mechanisms through which diabetes could increase the risk of dementia, including glycaemia, insulin resistance, oxidative stress, advanced glycation end products, and inflammatory cytokine. Hyperinsulinemia is suggested to explain the increased risk of Alzheimer's disease in diabetic patients, as the effect of high levels of insulin on dementia risk is independent of diabetes and blood glucose. These pathways may act separately or interactively, but which of these mechanisms are clinically relevant is unclear. In addition, the different mechanisms may interact during the long prodromal phases of both diabetes and dementia.[17]

As we studied diabetes happens when the body can't make enough insulin or utilize the insulin it makes appropriately. Insulin is a hormone utilized by the body to control glucose levels, or the measure of sugar, in your blood. Glucose is one of the primary wellsprings of fuel for the body, giving vitality the body needs to play out every fundamental capacity. There are two primary kinds of diabetes type 1 and sort 2. A third kind, gestational diabetes, happens incidentally amid pregnancy. Studies have demonstrated that type 2 diabetes can be a hazard factor for Alzheimer's malady, vascular dementia and different kinds of dementia on the grounds that cardiovascular issues related with diabetes are likewise connected with dementia. These include: Obesity, Heart ailment or family ancestry of coronary illness, impaired veins, Circulation issues, High cholesterol, and High circulatory strain.[18]

Especially in the old, Alzheimer's infection is ordinarily the most widely recognized type of dementia; be that as it may, different factors enormously add to advancement of the condition. Dementia may hit people with deficiently overseen diabetes, hypertension, elevated cholesterol and coronary illness significantly harder, as these infirmities increment the hazard for 'vascular dementia 'brought about by a progression of little strokes that extremely harm or demolish cerebrum tissue and repress oxygen from achieving the mind.[19]

All the studies have reliably demonstrated that people who have type 2 diabetes are bound to create dementia in contrast with those without. Being a standout amongst the most widely recognized metabolic clutters, type 2 diabetes designates for different obsessive difficulties, which influence various organs, including the cerebrum. Practically identical to diabetes, glucose isn't used suitably in the minds of individuals with Alzheimer's ailment. This might be activated by nerve cell passing, which decline the mind's capacity to interpret messages. While thinking about vascular dementia, mind cells terminate because of a need or deficiency of oxygen, turning away cerebrum cells from speaking with each other. The development of beta amyloid plaques in individuals with Alzheimer's illness has additionally appeared to frustrate insulin receptors in the mind from doing their typical assignments. This specifically impacts insulin generation and causes cerebrum cells to wind up delicate to insulin. This reduction in, or obtuseness to, insulin is one of the essential focal points of momentum explore since it suggests that the minds of people with Alzheimer's sickness are in a diabetic state.[20]

Practical management of Diabetes and dementia

Although there is an association between hyperglycemia and cognitive dysfunction, it has been shown that tight glycaemia control is not able to prevent a decline in mental function. As discussed, once dementia develops-diabetes self-care deteriorates therefore, checking for cognitive dysfunction should be high priority on a clinician's mind if a patient's noncompliance with self-care tasks is observed. Clinicians should also be aware that dementia may be associated with language impairment, disorientation and personality changes which may mimic the symptoms of hypoglycemia. The Mini Cog test is a simple screening tool for dementia which has a sensitivity of 86.4% (95% CI 64.0 to 96.4%) and a specificity of 91.1% (85.6 to 94.6%) and takes only three minutes to perform; ideal for clinicians with limited consultation times.[20]

As the decline in cognitive function continues, older people with diabetes and dementia will have complex needs due to increased dependency and unpredictable behavioral changes. For example, hydration should be maintained due to impaired thirst sensation to avoid risk of volume depletion and hyperglycemic crises. In insulin treated patients the new class of long acting insulin analogues may be a good option as they reduce the risk of hypoglycemia and can be conveniently injected once daily. Patients who have erratic eating patterns and unpredictable caloric intake could be managed with a regime where short-acting insulin analogues are administered only after meal consumption, thus preventing insulin induced hypoglycemia if a meal is missed or only partly consumed.[21]

In contrast to late-life diabetes, mid-life diabetes was associated with an increased risk of dementia even when controlling for genetic and familial factors, suggesting that mid-life diabetes–dementia association might be exogenous and is more likely attributable to adulthood environments (e.g., occupation and lifestyle such as exercise, diet, smoking, and social activities as well as glycemic control in patients with diabetes). Researcher results indicate that genetic and unmeasured early-life environmental factors are likely to play a role in the association of late-life diabetes with dementia but could not explain mid-life diabetes in association with dementia, which implicated the involvement of adulthood environments in the development of mid-life diabetes–dementia association and highlighted the need to maintain a healthy lifestyle during adulthood in order to reduce the risk of dementia late in life.[22]

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