Diabetes and Alzheimer’s disease: association or cause

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Diabetes is a chronic metabolic disease characterized by hyperglycaemia. It is categorized into three types: type-I diabetes (T1D), type-II diabetes (T2D) and gestational diabetes (GD). Alzheimer’s disease (AD), a neurodegenerative disorder, is slowly gaining the attention of scientists due to its undeniable connectivity to diabetes. Multiple epidemiological studies have found a direct correlation between T2D and AD, with patients suffering from T2D developing AD-like symptoms at an advanced age. With a multitude of similar cellular and molecular mechanisms existing between the two diseases, AD can be categorized as ‘Type-3 diabetes’.

Diabetes is arguably emerging as one of the largest epidemics ever to be witnessed globally. It is a chronic metabolic disease that affects glucose metabolism in the body. It is characterized by hyperglycaemia, i.e. the presence of a high amount of glucose in the bloodstream as the hormone required by the body to utilize is either not produced or produced in enough quantities, or the body cannot effectively utilize the same produced by the insulin-producing pancreatic β-cells. Broadly, diabetes mellitus (or simply diabetes) is categorized into three different types: type-I diabetes (T1D), type-II diabetes (T2D) and gestational diabetes (GD). T1D is a heterogeneous, idiopathic, autoimmune disease where the body attacks and destroys its β-cells of the pancreas, thereby hindering the insulin production, and leading to absolute insulin deficiency. It is also known as insulin-dependent diabetes as the patients need to take a daily dose of insulin for proper metabolism. It is mainly diagnosed in children and young individuals, accounting for more than 85% of all diabetes cases in the youth population, contributing to about 5% of all diabetic caseloads worldwide. On the contrary, T2D is characterized by persistent hyperglycaemia caused primarily due to insufficient insulin production by the β-cells of the pancreas or unresponsiveness of the body to insulin due to a condition called insulin resistance; it is also known as insulin-resistant diabetes. Therefore, it results from insulin insensitivity, caused due to insulin resistance (presence of adequate insulin, but desensitization of the insulin receptors leading to disruptive cellular insulin signalling), diminished insulin production and/or a complete failure of insulin production by the pancreatic β-cells. Obesity, advanced age, family history of T2D, physical inactivity, unhealthy lifestyle and high blood pressure are some common risk factors associated with the disease. According to the International Diabetes Federation (IDF), at present diabetes follows a trend of affecting 1 in 11 adults worldwide, with approximately 90% of them ascribed to be T2D and its current caseload at 537 million affected people in 2021. Another 84.1 million people are suspected to be prediabetic. It is projected to affect nearly 643 million people by 2040 and about 783 million people by 2060. These distressing numbers of the disease progression have quadrupled since 1990, with a high prevalence rate of about 9.3% in adults. Gestational diabetes, as the name suggests, develops in certain women during their gestational period of pregnancy. Generally, the blood sugar returns to its usual level in mothers after delivery, but exposes both the mother and child to a greater risk of developing T2D later in life. Apart from these three, there exist some other less common types of diabetes that contribute to the etiological classification of the disease and are all categorized under the umbrella of ‘type-3 diabetes (T3D)’.

Monogenic diabetes syndrome occurs due to genetic mutations inherited by the offspring from the parents. It accounts for about 4% of the total diabetic caseload and includes maturity-onset diabetes of the young and neonatal diabetes (occurring in babies under nine months). Other rare types include drug- or chemical-induced diabetes (vacor, pentamidine, diazoxide, thiazides, diethanols, interferon, etc.), immune-mediated diabetes (‘Stiff-man’ syndrome), endocrinopathies (acromegaly, Cushings syndrome, phaeochromocytoma, hyperthyroidism, aldosteronoma), Pancreaticogenetic diabetes (often referred to as type-3e diabetes), diabetes caused due to genetic defects in insulin action (Rabson–Mendenhall syndrome, Lipoatrophic diabetes, leprechaunism), diabetes caused due to diseases of the exocrine pancreas (pancreatitis, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculus pancreatopathy), infection-induced diabetes (congenital rubella, cytomegalovirus) and Alstrom syndrome, to name a few.

Apart from these forms of diabetes, another type has been lurking in the background, slowly making its way and marking its territory, thereby emerging as a true form of diabetes. Recent epidemiological evidence has correlated a high possibility of development of dementia-like symptoms in some T2D patients when compared to healthy individuals. Some prospective longitudinal studies have indicated that T2D and hyperinsulinaemic conditions are the driving forces for the development of dementia and Alzheimer’s disease (AD)-like symptoms. In addition to these epidemiological evidence, mounting statistical and biological data support a direct association between T2D and dementia, as they share multiple similar cellular and underlying molecular mechanisms leading to the development of the disease. Hyperinsulinaemic conditions caused due to T2D contribute significantly to abnormal amyloid-beta (Aβ) metabolism (a major component of the amyloid plaques found in the AD brains), endothelial dysfunction and an overall increase in arterial stiffness. Dysfunction in regular insulin signalling has a tremendous contribution to the pathogenesis of AD. This is because insulin signalling regulates glucose metabolism in the brain, thereby playing a significant role in neuronal development, learning and memory. Disruption in the insulin signalling cascade results in abnormal glucose metabolism that correlates to mitochondrial dysfunction, cognitive decline and inflammation, common factors resulting in the development of both T2D and AD. Reduced neuronal levels of glucose transporter-3 have also been identified in patients with T2D. AD is a neurodegenerative disease that is characterized by a stealthy onset and has a progressive course. A recent report from the World Health Organization (WHO), Geneva, mentions that approximately 50
million people worldwide suffer from dementia. Although there are various kinds of diabetes, the most well-known form among them is AD, which accounts for nearly 50–75% of the entire case burden worldwide. As an irreversible, progressive and neurodegenerative disorder, AD is typically characterized by neuronal loss, the formation of senile Aβ plaques and the presence of neurofibrillary tangles in the neuronal microtubules11. All these common pathophysiologicals associated with mounting evidence have led to categorizing of AD as a form of T3D (ref. 3).

Several clinical studies have proved the association between T2D and AD, thereby providing solid evidence for categorizing AD as the third form of diabetes. In the Washington Heights-Inwood Columbia Aging Project, 683 subjects aged 65 years and above without prevalent dementia were studied; 149 persons developed dementia, including 137 developing AD. The risk of developing AD was double in 39% of individuals with hyperinsulinemia/diabetic conditions. Hyperinsulinemia was also related to a substantial decline in memory-related cognitive scores in diseased individuals12. In the Kungsholmen study, 1301 dementia-free subjects aged 75 years and above in Stockholm, Sweden were longitudinally examined twice over six years. Three hundred and fifty subjects developed dementia, including 260 diagnosed with AD. T2D was associated with both dementia (HR 1.5) and AD (HR 1.3)13. In a longitudinal study, a Swedish community-based cohort of 1173 dementia- and diabetes-free subjects aged 75 years and above was considered. During the nine-year follow-up period, 397 individuals developed dementia, of which 307 were diagnosed with AD. Borderline diabetes was found to be associated with both dementia (HR 1.67) and AD (HR 1.77) relative to the control population14. In the Interdisciplinary Longitudinal Study on Adult Development and Aging, a representative birth cohort of 381 individuals born in Germany from 1930 to 1932 was evaluated. When compared to the healthy subjects (n = 159), patients with mild cognitive impairment (MCI; n = 108) or AD (n = 26) showed similar tendencies in the prevalence rates for T2D (P = 0.18)15. A case-control analysis using the Swedish Twin Registry included 13,693 twin individuals aged 65 years and above. Of all the subjects, 1396 were diagnosed with diabetes and 467 with dementia, including 292 with AD. Individuals suffering from diabetes showed an increased adjusted odds ratio (ORs) for dementia (OR 1.89) and AD (OR 1.69) when compared to those without diabetes. Correlating the onset of diabetes and dementia, the risk associated with mid-life diabetes (onset age <65 years) on dementia was found to be much stronger when compared to late-life diabetes (onset age ≥65 years)16. In a prospective community-based study, 103 subjects aged 65 years and above diagnosed with MCI were considered from primary-care practices in South London, United Kingdom. T2D was associated with increased cognitive impairment and progression of dementia, post adjustment for socio-demographic factors and other health conditions17.

With mounting evidence pointing to a direct association between T2D and AD, with T2D being the root cause of cognitive decline, thereby increasing the risk of AD through hyperinsulinemia and its contribution to Aβ plaque formation and cerebrovascular dysregulation, it is high time we acknowledge AD as being one of the predominant types of diabetes – T3D or ‘brain diabetes’ to be precise18. With advancements in neuroendocrinology, we can unravel further insights into the intertwining interactions between T2D and T3D, thereby allowing us to have an in-depth understanding of AD pathophysiology in T2D. This can assist in developing new preventive measures and/or practical therapeutic approaches, thereby decreasing the morbidity associated with the two diseases.

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