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# Perspectives on Effect of Ketogenic Diet on Type 3 Diabetes Induced Alzheimer's Disease

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## Abstract

Type 3 diabetes is a term used when Alzheimer's disease is generated by insulin resistance in the brain. This disorder is most often used to define people who have type 2 diabetes and are also detected with Alzheimer's or dementia. This term is proposed by researchers because of the common molecular and cellular aspects among Type-1-Diabetes, Type-2-Diabetes and insulin defiance linked with memory loss and cognitive failure in old people. These investigations are supported by numerous vital biological studies that translate the impact of insulin in the pathology of AD through convinced mechanisms. The aim of this review article is to confer the cellular and molecular influences between diabetes and AD for labelling Type-3-Diabetes and also this review sheds light on the benefits of natural remedies such as lifestyle changes including ketogenic and low carb diets for treating type 3 diabetes and Alzheimer's disease.

**Keywords:** Diet; Diabetes; Alzheimer's Disease

## Introduction

Alzheimer's disease (AD) is an advanced neurodegenerative ailment considered by the intensifying decline of memory, cognitive functions, and fluctuations in behaviour and personality. AD is the 6$^{th}$ foremost cause of death in the United States and the 5th leading reason of death for those aged 65 and older. Presently, 5.4 million Americans grieve from AD, with a predictable 200,000 under the age of 65 and these numbers are anticipated to increase up to 20 million by 2020. Approximately two-thirds of those with AD are women (3.3 million). AD dementia has a vast financial impact on medical possessions, with the total assessed healthcare cost at about $818 billion in 2015, which is estimated to increase to 2 trillion by 2020 [1-3].

Immunological examination of AD post-mortem brain exposed the existence of extracellular neurotic plaques, intracellular neurofibrillary tangles and neuronal loss. AD is also linked with the loss of synapses, oxidative stress and mitochondrial structural and functional irregularities, inflammatory responses, fluctuations in cholinergic neurotransmission, hormonal disbalance and cell cycle deviations [3-7].

AD is multifactorial, with both genetic and environmental features occupied in its pathogenesis. A small part of AD cases show an autosomal dominant transmission of the disease, and currently mutations in the genes encoding APP, presenilin 1 and presenilin 2 have been considered in early-onset familial AD cases. The finest defined risk factors for AD are age and a positive family history of dementia Other risk factors that may be allied with the progress of AD include severe head trauma, low levels of education, female gender, previous depression, and vascular factors [3,4].

The proliferated occurrence in AD would be due to one of the developing obstacle of type 2 diabetes mellitus (T2DM).In the United States there are more than 23 million T2DM patients extant. Presently, 366 million people have diabetes mellitus world-wide, and this number is expected to reach 552 million by 2030 according to IDF, Diabetes atlas [8].

T2DM is depicted by high blood sugar (hyperglycaemia), insulin resistance, and relative deficiency of insulin. This ascends due to a diminished sensitivity of muscle, liver and fat cells to insulin. In general, instantly after the meal there is increase in production of insulin by pancreas [2].

The affected organ for insulin is adipose tissue, skeletal muscle, liver, and fat. This stimulates the uptake of glucose from the blood and elevates glycogenesis by impeding glucose production. Another feature of diabetes is the development of human islet amyloid polypeptide (hIAPP, amylin) that directs to pancreatic β-cell dysfunction. The subsequent metabolic disruption leads to chronic hyperglycaemia, which is the instant cause of many of the indications of diabetes such as retinopathy, peripheral neuropathy and nephropathy [9].

An epidemiological evidence advises that T2DM are strongly connected with cognitive loss due to failure in the action of glucose absorption in the neurons for energy production. The correlation between T2DM and AD is complex; both are intertwined with insulin resistance, insulin growth factor (IGF) signalling, inflammatory response, oxidative stress, glycogen synthase kinase 3β (GSK3β) signalling mechanism, amyloid beta (Aβ) formation from amyloid precursor protein (APP), neurofibrillary tangle formation, and acetylcholine esterase activity regulation. Because of shared mechanisms among Type-1-Diabetes (T1DM), T2DM and AD; researchers named "Type-3-Diabetes" [10-14].

The aim of the review article is to confer the cellular and molecular influences between diabetes and AD for labelling Type-3-Diabetes.

## Relationship between type 3 Diabetes and Alzheimer's

Physio-pathological connections between AD and insulin :AD is attributed with low insulin levels and insulin resistance within CNS insulin resistance and hyperinsulinemia cause decrease in brain insulin level. Some mechanisms shows why it facilitate membrane. In brain insulin receptors are present in area responsible for discernment. Insulin is responsible for pathways like energy production neuronal survival and energy metabolism. Thus, it activates signaling pathways responsible for learning and memory, therefore insulin insensitivity affects cognition. Insulin is responsible for growth of cell including neurons. Thus, insulin resistance causes neurodegeneration [15]. Alzheimer's Disease Is Type 3 Diabetes Experimental Animal Model Results: The human postmortem brain studies associated with many of the attribution of molecular and pathological features of AD to the reduced expression of the insulin and IGF1 and IGF2 genes and their corresponding receptors. However, without direct experimentation that generates cause–effect data, conclusions drawn from human studies would remain correlative rather than mechanistic. Consequently, we use experimental models to exhibit that diabetes mellitus-type molecular and biochemical deformity could be produced in CNS neurons and brain by exposure to streptozotocin (STZ) [16].

## Clinical and preclinical evidence for obesity/diabetes contributing to Type 3 Diabetes

Lately, several studies on T2DM, obesity, IR, and hyperinsulinemia have shown relations with cognitive impairment and AD [15-17]. A current meta-analysis on obesity (BMI > 30 kg/m$^2$) has informed as obesity an enlarged risk factor for AD[18]; in alternative study it has shown that cardiovascular disease is also a risk factor for memory loss [19]. Whitmer [20] has shown 'mid-life obesity' as independent association with an increased risk of dementia and AD [20].

This study has specified that both obesity and overweight, as measured by body mass index in middle-age are strongly connected with an increased risk of all cause of dementia, AD and vascular dementia (VaD), autonomous of the development of diabetes and cardiovascular-related diseases There is also a value in evaluating regional body shape distributions of adiposity especially the role of abdominal obesity. Mechanistic pathways such as adipocyte secreted proteins and hormones, and inflammatory cytokines could clarify the recommendation between obesity and increased risk of dementia [20].

While midlife and late-life obesity and the risk of dementia cardiovascular health study has revealed that an increased risk of dementia was found for obese (BMI > 30) vs normal-weight (BMI 20–25) persons, familiar for demographics (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.03–1.87) and for cardiovascular risk factors (1.36; 0.94–1.95).

The risk evaluations were inverted in calculations of late-life BMI. Underweight persons (BMI < 20) had an increased risk of dementia (1.62; 1.02–2.64), whereas being overweight (BMI > 25–30) was not linked (0.92; 0.72–1.18) and being obese decreased the risk of dementia (0.63; 0.44–0.91) as compared to those with normal BMI [21].

Luchsinger., *et al*. [22] results have minute paradox with the above study results which revealed reduce risk of dementia with increasing BMI, but the subjects are ≥ 76 years of age, but a U-shaped association in subjects < 76 years of age [22] These results recommended that change in body size and composition with age caused BMI thereby having a poor measure of obesity in older subjects as well as weight loss thus stating preclinical condition of AD [20,23,26].

Up till now the literature articulates that the pathology of AD may progress in the advanced stage of AD so the recent risk factors such as obesity and IR in mid-life may be more essential than they are in later life to cure insignificant cognitive loss. Afterward it is also possible that insulin sensitivity may facilitate the effects of obesity on dementia, VaD and AD risk. Remarkably, several studies shown rise in insulin concentrations in AD patients compared to controls [15,16,24-26].

All these clinical and preclinical studies have revealed that obesity, and insulin resistance/hyperinsulinemia would be the risk factors for AD, but whether adiposity and peripheral insulin sensitivity facilitate incidence of AD remains unidentified. However Baker., *et al*. [27] have revealed little suggestion on the function of peripheral insulin sensitivity on cognition [27]. In particular, superior IR was associated with an AD-like pattern of condensed cerebral glucose metabolic rate (CMRglu) in frontal, parieto-temporal, and cingulate regions in adults with PD/T2D. The relationship between CMRglu and homeostasis model assessment insulin resistance (HOMA-IR) was independent of age, 2-hour OGTT glucose concentration, or apolipoprotein E ε4 allele carriage.

Throughout the memory encoding task, healthy adults displayed activation in right anterior and inferior prefrontal cortices, right inferior temporal cortex and medial and posterior cingulate regions. Adults with PD/T2D showed a qualitatively dissimilar outline during the memory encoding task, categorized by more prolix and extensive activation, and recollected fewer items on the delayed memory test [27]. All these deviations recommend that IR may be a marker of AD risk that is linked with reduced CMRglu and subtle cognitive impairments at the initial stage of disease, even before the commencement of mild cognitive impairment [27].

Alternative study has revealed that greater levels of HOMA-IR along with hyperinsulinemia have also been connected to an amplified burden of amyloid plaques over 10 years later in autopsy samples [28].

Therefore, obesity/diabetes and Type 3 Diabetes are directly and indirectly connected with AD. Additional research is still required to better comprehend the specific molecular relations among obesity/diabetes, Type 3 Diabetes and AD.

## Type 3 diabetes and Alzheimer's treatment

There are some specific treatments for the people who suffer from type 3 diabetes. Lifestyle changes such as eating a low sugar clean diet with high fibre intake and exercise can contribute towards the treatment of the disease.

High sugar levels that can lead to organ damage can be prevented by losing about 5-7% of body mass [29]. A diet low in fat and rich in fruits and vegetables can also improve symptoms. Foods containing refined carbs, sugar, alcohol, caffeine, processed foods, dairy, and inflammatory, omega-6 rich oils are to be avoided and should be replaced with foods containing healthy fats like avocados, walnuts, almonds and cashews, grass-fed meats, pastured chicken and eggs, olive and coconut oil [30]. Smoking and drinking is not advisory.

For a person suffering from both type 2 and type 3 diabetes, treatment of type 2 diabetes is essential to prevent type 3 diabetes [31]. Metformin is common drug used by diabetic patients that can help with the symptoms of dementia. A study at Tulane university included 6000 veterans with diabetes and concluded that risk factors of developing Alzheimer's were a quarter lesser with people who were on medications that included metformin.

Prescription medications are available to treat cognitive symptoms of Alzheimer's and dementia. Cholinesterase inhibitors like donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon) can be prescribed to improve the way that your body's cells communicate with one another. Memantine (Namenda) may slow the progression of Alzheimer's disease [32].

A newer class of drugs known as GLP-1 receptor antagonists have been found to improve memory and prevent Alzheimer's in mice and preliminary human studies.

Other symptoms of Alzheimer's and dementia, like mood swings and depression, may be treated with psychotropic drugs. Antidepressants and anti-anxiety medications are part of treatment in some cases.

## Alzheimer's disease and ketogenic diet

Alzheimer's disease (AD) is the most extensive neurodegenerative disease and the major cause of dementia among the aged population. AD symptoms are in common a cognitive impairment with progressive memory slippage and personality changes. The section of such cognitive decline can be allocate to a progressive synaptic dysfunction and the subsequent loss of neurons; this loss seems to be located in many unprotected regions of the brain: mainly neocortex, limbic system, and the subcortical regions. In deliberation of the strong link between aging process and AD and of the positive effects of KD in ageing brains, the multifaceted nature of AD that includes mitochondrial and metabolic dysfunctions suggests that there could be a reasoning for the use of KD in these patients. For example, an *in vitro* study has revealed that addition of KB (beta-hydroxybutyrate) prevent the hippocampal neurons from A$\beta$ toxicity; this suggests possible therapeutic roles for KD on mitochondrial defects related to AD. Preclinical studies though showed differing results: Van der Auwera., *et al*. revealed that decrease of A$\beta$ in the brain of young transgenic AD mice overexpressing the London APP mutation fed with KD for 1.5 months whilst on aged canines the effect of KD on A$\beta$ seemed to be limited to the parietal lobe of the brain. It was also revealed that long-term (8 months) feeding of a ketone ester in middle-aged mice (8.5 months old) upgrade cognition and ameliorated A$\beta$ and tau pathology. Beckett., *et al*. demonstrated that AD mice model fed with a high-fat, low-carbohydrate ketogenic diet showed an enhance motor function without changes in A$\beta$. Many researchers have demonstrated that KD could significantly enhance glucose homeostasis, reducing metabolic dysregulation and insulin resistance. Considering the shift in the brain's metabolism from glucose to ketones, during a KD, shift that is useful in glucose transporter type I deficiency syndrome KD be a therapy for neuronal degeneration related to GLUT deficiency in AD. nutritional approach appears favourable and so deserves further clinical study extensive trials. Even though there are no direct or strong evidence of the efficacy of KD in humans [33,34].

## Research gap and conflicts of interest

Evidence from Human Studies A Supposition was directly examined on postmortem cases of advanced Alzheimer's diseases and it was determined that if neurodegeneration is linked with deviation of expression of gene encoding insulin IGF1 and IGF2 peptides, their receptors and downstream signaling mechanism. All signaling pathways that mediate insulin and IGF1 stimulated neuronal survival, expression, energy production and energy metabolism were fretful in AD [35].

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**Volume 3 Issue 5 May 2019**