



Mini Review

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Impact of Diabetes, Depression in Dementia

Priyanka Rawat and Arubala P Reddy*

Department of Nutritional Sciences, College of Human Sciences, Texas Tech University, Texas

*Corresponding author: Arubala P Reddy, Department of Nutritional Sciences, College of Human Sciences, Texas Tech University, 1301 Akron Avenue Lubbock, TX 79409, USA.

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Abstract

With increasing aging population, dementia is a major healthy concern in US and worldwide. Increasing evidence also suggests that coexistence of diabetes and depression exacerbate the high prevalence of dementia in elderly. Recent advanced medical care, diagnostic features, timely provided medicines and caregiving facilities, lifespan is increased in elderly individuals with diabetes and depression. Our mini-review discusses the latest developments in depression, diabetes, and dementia research. We also covered interlinks between depression, diabetes, and dementia in relation to gender, age, and lifestyle risk factors. We also briefly discussed, pharmacological and lifestyle intervention to reduce diabetes, depression, and dementia.

Keywords: Diabetes, Depression, Dementia, Lifestyle Factors, Aging Population, Lifespan

Abbreviations: 5-HT: Serotonin; AD: Alzheimer's disease; ADRD: Alzheimer's Disease-Related Dementias; A β : Amyloid- β ; DM: Diabetes Mellitus; MDD: Major Depressive Disorder; P-Tau: Phosphorylated tau; T2D : Type 2 Diabetes

Introduction

Dementia is a growing concern in modern society. Dementia does not represent a distinct pathological entity; it serves as a comprehensive designation for cognitive decline. Alzheimer's Disease (AD) stands out as the predominant manifestation within the spectrum of dementia [1]. Dementia is also linked to Alzheimer's Disease-Related Dementias (ADRD) in elderly population. While dementia predominantly affects the elderly population [2], it is crucial to emphasize that it does not form an integral aspect of the usual aging trajectory. Dementia is the result of various alterations at the cellular level, including synaptic depletion, dysfunctional mitochondria, the emergence of amyloid- β (A β) plaques, and the presence of actively phosphorylated tau in the brain [3]. Amyloid beta and Phosphorylated Tau (P-Tau) accumulation are hallmarks of AD. In conjunction with the interaction of these proteins, numerous other factors, including age, gender, genetics, comorbidities such as depression, diabetes, hypertension, race/ethnicity, lifestyle, and environmental factors, contribute to the onset of dementia [4].

According to the Alzheimer's Association (2023), AD affects over 6 million individuals across various age groups in the United

States. In 2023, approximately 6.7 million Americans aged 65 and above were struggling with AD. Comorbidities such as chronic diabetes, depression, hypertension, and obesity are closely associated with dementia. Diabetes is a prolonged health condition characterized by a protracted impairment in the utilization of blood glucose within the body; the regulation of blood glucose is governed by insulin, a hypoglycemic hormone [5]. Historically, the emphasis in diabetes management has centered on addressing conventional complications such as diabetic retinopathy, peripheral neuropathy, nephropathy, and cardiovascular diseases [6]. Nevertheless, recent reports have increasingly indicated that prolonged diabetes may impact cognitive functions [6]. Considerable epidemiological evidence suggests a robust correlation between T2DM and cognitive impairment, attributed to the inadequacy of glucose absorption in neurons for energy production [7-9].

Depression, specifically Major Depressive Disorder (MDD), is a prevalent and significant medical condition that adversely impacts one's emotional state, cognitive processes, and behavioral patterns. Depression is one of the causative factors of dementia. The manifestations of depression vary among individuals, and

there exist different degrees of severity in depressive states. Studies, both retrospective and prospective, have demonstrated that depression, whether accompanied by cognitive features or presenting as depressive symptoms without explicit depression, is associated with an increased susceptibility to dementia [10-12]. Increasing evidence indicates the complexity of the association, as

epidemiological studies suggest that depression may function as an independent risk factor for dementia. Crucially, the timing of depression is noteworthy, with earlier-life depression or depressive symptoms being linked to a more than twofold increase in the risk of dementia (Figure 1).

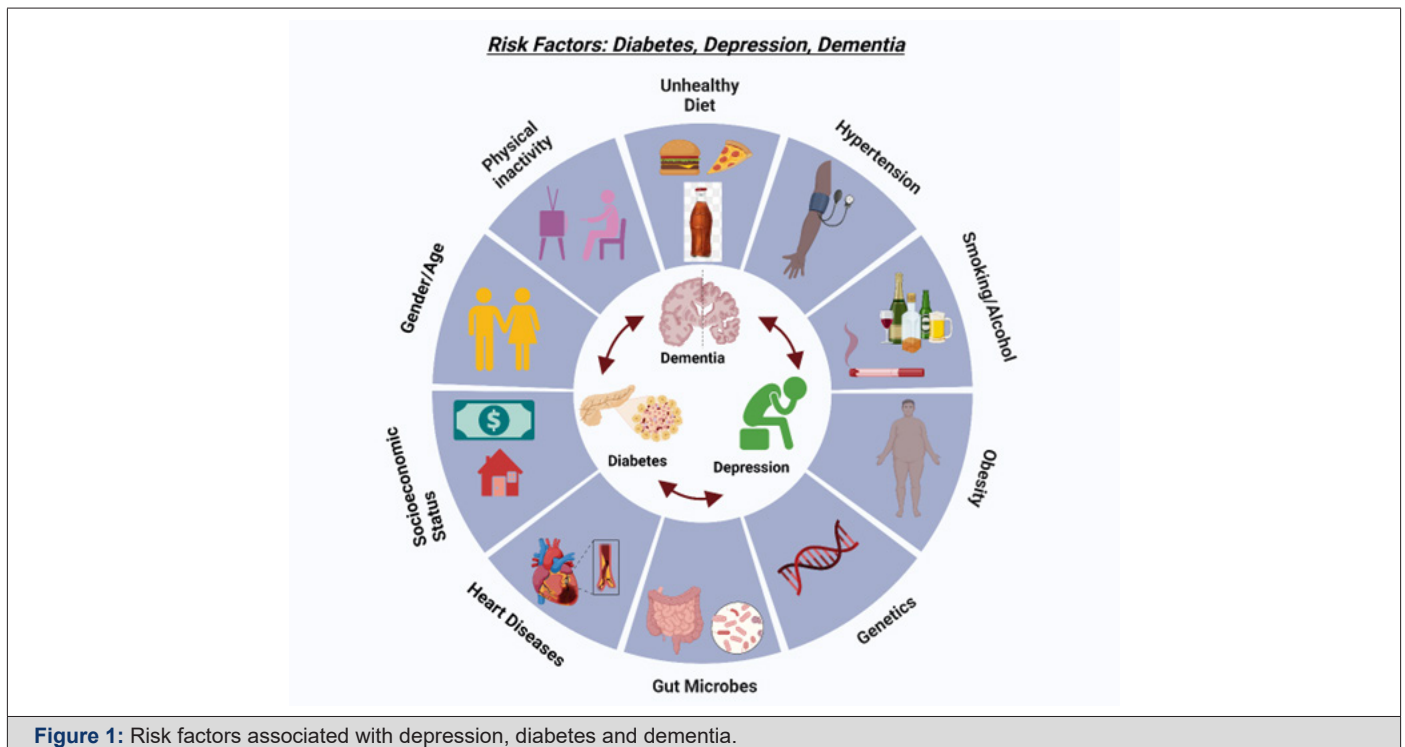


Figure 1: Risk factors associated with depression, diabetes and dementia.

Gender Differences in Diabetes, Depression, and Dementia Risk

Gender differences are increasingly recognized as a critical factor in clinical variation, potentially influencing the transition from diabetes and depression to dementia and/or AD/ABRD. Females are statistically twice as prone to developing overweight or obesity conditions compared to males [13]. Which might increase the risk of diabetes in women. Females have approximately a two-fold higher incidence of being diagnosed with depression and dementia compared to males. A suggested theory for the increased risk of ABRD in women is changes in internal estrogen production related to menopause [14]. Additionally, the average life expectancy is higher in females than in males. Hormonal influences are significant in the development of these chronic conditions.

Diabetes and Dementia

Because of the heightened risk of late-onset AD associated with diabetes mellitus, impaired mitochondrial energy metabolism and oxidative stress, researchers referred AD as Type 3 diabetes mellitus [15-17]. The link between prolonged T2DM can contribute to various factors. Diabetes Mellitus (DM) is linked to notable cognitive deficits and an elevated risk of dementia, specifically vascular dementia, and AD, with respective elevations in risk

estimated at 100%-150% and 50%-100% [18]. Amyloid beta and phosphorylated tau are identified as the primary pathogenic factor in the development of AD [1]. Advanced glycation end products contribute to its elimination, while an insulin-degrading enzyme, with which it competes with insulin, facilitates its deterioration.

The secretion of A β and the promotion of brain inflammation are triggered by insulin [19]. Another factor involves the impact of diabetes on heart health, which is interconnected with brain health. Heart disease and high blood pressure, (in other words hypertension), often associated with diabetes, can contribute to strokes, a known precursor to dementia. Research has demonstrated impaired insulin signaling in the brain, leading to the tau protein's heightened phosphorylation (hyperphosphorylation). This hyperphosphorylation is ultimately causing the accumulation of neurofibrillary tangles [20]. Insulin depletion in both T1DM and T2DM influences brain health, particularly impacting memory functions [20]. Beyond its metabolic role, insulin appears to play a crucial role in cognitive processes, and its deficiency may contribute to cognitive impairments, affecting memory functions in individuals with diabetes.

Depression and Dementia

When considering depression as either a cause or a risk factor

for dementia, it is essential to recognize the substantial overlap in symptoms. Individuals experiencing depression often report memory issues and exhibit measurable cognitive deficits on tests [21]. Common indicators of major depression include a predominantly low mood. However, it may manifest as irritability, anger, or anxiety, and disruptions in biological rhythms, affecting sleep, appetite, and energy levels, are frequently observed. Additionally, individuals experiencing major depression may exhibit negativity, feelings of hopelessness, or even nihilistic perspectives [22]. These alterations in lifestyle can lead to dementia. Research findings indicate that when depression occurs in individuals already experiencing pre-existing dementia, it contributes to an expedited cognitive decline [23]. Neurotransmitter alterations might potentially be underlying mechanisms that could be linked to both dementia and depression. Depression is commonly characterized by decreased levels of brain Serotonin (5-HT) and norepinephrine, forming the foundation for the neuropharmacological treatment of depression [24]. Increasing evidence also suggests that serotonin levels are reduced in women compared to men further supporting high prevalence of depression and dementia/AD in women [23,24].

Conclusion

Current evidence suggests a complex and significant association between diabetes and depression are strongly linked to in the pathogenesis of AD and ADRD. The coexistence of both diabetes and depression may exacerbate the vulnerability to developing dementia. Additional research is essential to elucidate the intricate mechanisms driving the interconnection between diabetes, depression, and dementia. This understanding will be crucial in creating specific interventions aimed at reducing the dementia risk in individuals affected by both diabetes and depression. The adoption of lifestyle modifications is vital for disease prevention. Diabetes and depression are a precursor to chronic health conditions, significantly reducing both life expectancy and quality of life. Therefore, this triad of conditions necessitates an integrated clinical approach for early detection and intervention, aiming to attenuate the compounded risk and progression of dementia in individuals with diabetes and depression.

Conflict of Interest statement

Authors declare that they do not have any conflict of interest.

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