Influence of Covid 19 on cognition impairment with Type II diabetes

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Abstract

Background: Due to the increase in life expectancy and population growth over 65 years, cognitive impairment (CI) is gradually increasing. Because of many changes in the human brain that occur with aging, cognitive decline usually worsens with age. The number of neurons, dendrites, synapses, receptors, glial components, and critical neurotransmitters (norepinephrine, dopamine, acetylcholine) diminishes every year after age 50 (by 0.1–0.2 percent). As a result, the brain's volume, metabolism, and perfusion decrease, and an average age-related cognitive decline emerge. **Objective:** This review will elucidate the underlying factors mediating the interaction of COVID-19, diabetes, and mental health, which may provide essential clues for tailored intervention for this vulnerable population. **Result:** As per the World Alzheimer Report, 46.8 million individuals worldwide suffered from dementia in 2015, a figure that's still expected to quadruple every 20 years. During the COVID-19 epidemic, researchers and practitioners are becoming increasingly concerned about the emergence of neurological symptoms, particularly the development of cognitive impairment. Learning, memory, flexible thinking, concentration, and executive function are all cognitive functions. Examples of executive functions include understanding a specific problem, solving problems, judging, halting, or modifying old behaviors, and initiating new ones. When patients are required to complete complex tasks, such as changing their insulin dose, predicting the effects of physical exercise on blood glucose, or even diagnosing and treating appropriate hypoglycemia, all these behavioral reactions are critical. **Conclusion:** Cognitive problems impair a patient's capacity to carry out several treatment measures, such as adhering to a medical regimen and recognizing signs of deterioration, all of which compromise the patient's treatment compliance. The current review focuses on the state of cognitive functioning in patients with metabolic syndrome and diabetes mellitus at the time of diagnosis and following COVID-19.

Keywords: Cognitive impairment, type II diabetes, COVID-19, hypoglycemia, mental health, mini-mental state examination

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Introduction

The coronavirus infection in 2019 was caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARCoV2). COVID-19 is a virus that can be transmitted from one person to another. The number of positive cases and mortality rate began to rise after that, and on March 11, 2020, the World Health Organization (WHO) proclaimed a pandemic (1). As of 17th June 2022, WHO claimed about 535 million people had been affected. It also confirmed 6,314,972 deaths worldwide, with the United

States accounting for 2.75 million deaths, followed by Europe with 2 million deaths (2).

Because of the increase in life expectancy ad population growth over 65 years, the urgency of the problem of cognitive impairment (CI) is gradually increasing (3). Cognitive impairment usually worsens with age because of many changes in the human brain that occur as we age. After 50, the number of neurons, dendrites, synapses, receptors, glial elements, and critical neurotransmitters (norepinephrine, dopamine, and acetylcholine) drops by 0.1–0.2 percent per year. The result is a decrease in brain volume, metabolism, perfusion, and the onset of typical age-related cognitive decline (4).

As older adults are not only more likely to become seriously ill with COVID19, but they are also more vulnerable to potentially long-lasting health consequences. Long-term complications in surviving patients are currently unknown. However, as has been observed in similar viral infections and survivors of serious illness, some of these patients may experience neurological sequelae in the form of cognitive and psychomotor impairment in the coming months and years. Neurological lengthening (5-8). Therefore, in this study, we review the evidence on the neuropsychiatric and cognitive manifestations of COVID 19 and its direct and indirect consequences in survivors, especially in older adults with dementia (9).

Diabetes and Cognitive impairment

The detrimental consequences of diabetes on the retina, renal, cardiovascular, and peripheral neurological systems are well known, but its implications on cognitive function and neurodevelopment have gotten less attention. Diabetes is linked to poor performance in a variety of cognitive domains.

Figure 1. Factors that lead to the development of cognitive impairment in diabetes individuals

Although the specific pathogenesis of cognitive impairment in diabetes individuals is unknown, vascular disease, hyper or hypoglycemia, and insulin resistance appear to play essential roles. People with diabetes are more likely to suffer microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (heart, cerebrovascular, and peripheral artery disorders) issues, which can lead to cognitive impairment. Figure 1 shows the various factors that lead to the development of cognitive impairment in diabetic populations.

Because of inconsistent reports, studies on cognitive impairment and diabetes mellitus are inconclusive. The inconsistency in findings could be attributed to differences in study design, study subject sources, and variations in diabetes mellitus or cognitive impairment criteria. It could also be due to differences in the duration or severity of diabetes mellitus among study participants. For this study, great care was taken to include subjects from the community, use definite case criteria for diabetes mellitus (fasting and postprandial investigations), and assess cognitive impairment by trained clinical psychologists and physicians for diagnostic formulation and table 1 reveals the prevalence of cognitive impairment in the diabetic population from various studies; these studies also show that diabetic patients have reduced performance in information processing speed and impaired memory, attention, and executive function.

Table 1. Prevalence of Cognitive impairment in the Diabetic population

Sr. No.	Number patients studied	Prevalence	Reference
1	516	33.73%	Khullar S *et al* 2017 (20)
2	250	22.8%	Gupta A *et al* 2021(21)
3	240	30.0%	Subramanian *et al* 2021(22)
4	70	54.29%	Lalithambika *et al* 2019 (23)
5	54	63%	Verma *et al* 2021 (24)
6	1545	18.4%	Feinkohl *et al* 2018 (25)
7	3938	26.9%	*Anjana RM et al* 2017 (26)
8	705	10.1%	Callisaya *et al 2018* (27)
9	6865	55.4%	Pelimanni *et al* 2018 (28)

Cognitive dysfunction related to COVID-19

Through the ACE2 receptor, SARS-CoV-2 infects lung tissue. The expression of ACE2 receptors is higher in people with diabetes. Insulin resistance, hyperglycemia, and an increase in angiotensin-converting enzyme 2 (a cellular "receptor" for the virus) all contribute to increased inflammation in T2DM (29). Angiotensin-converting enzyme 2 (ACE2) is a plasma membrane protein found primarily in the lungs, and also in the heart, kidneys, and insulin-producing cells (30). SARS-CoV-2 has a high affinity for ACE2, and the complex is internalized after binding the virus, allowing the virus to replicate intracellularly (31). The primary route by which SARS-CoV-2 enters the lungs and other cells in the body is through ACE2, which acts as a "receptor" for the virus (30, 32).

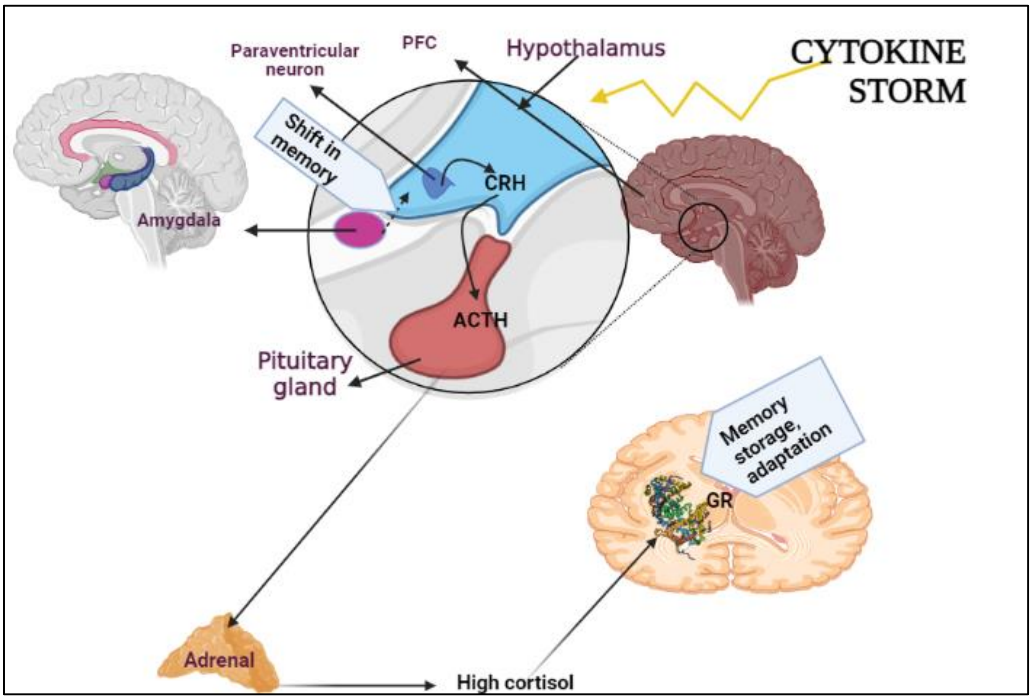

Figure 2. Detailed Illustration of HPA axis on Cognition

Hypothalamic-Pituitary-Adrenal Axis, or HPA axis as commonly called, describes the interaction between the hypothalamus, pituitary gland, and adrenal glands. HPA AXIS is activated during a stress or cytokine storm. Hypothalamic neurons produce the corticotropin-releasing hormone in the HPA axis, which causes the pituitary to release ACTH, which causes the adrenal gland to release cortisol. The Thymus and Spleen produce corticosteroids, which are released into the bloodstream when the HPA axis is activated. Because type 2 diabetes causes an upregulation of the hypothalamic-pituitary-adrenal axis and hypercortisolemia can cause cognitive dysfunction, the rise in cortisol levels seen in type 2 diabetes patients may contribute to cognitive dysfunction (33).

Corticosteroid exposure is one possible mechanism for hippocampal injury. Excess corticosteroids cause reversible and irreversible changes in the structure and cognition of the hippocampus, according to animal studies, a topic that has been discussed previously (34). On the HPA axis, the hippocampus provides negative feedback and is involved in key declarative and spatial memory aspects. As a result, hippocampus dysfunction could explain both memory problems and neuroendocrine abnormalities in mood disorders. In animal and human studies, the hippocampus has been shown to play a critical role in declarative memory, emotional processing, and stress susceptibility. Long-term potentiation, neurogenesis, and dendritic remodeling are just a few cellular processes currently being studied in the hippocampus. Human studies have found cognitive deficits in depression, bipolar disorder, Cushing's disease, and those taking exogenous corticosteroids that are consistent with hippocampal dysfunction (35).

The sympathetic-adrenal system and the HPA axis are involved in an organism's ability to adapt to stressors, and the interaction between these two systems is crucial in adaptation. Patients with stress-related disorders may be more vulnerable to mental illness for years after being exposed to stress. Stressors activate the sympathetic arm of the autonomic nervous system, followed by the HPA axis, on a systemic level. The adrenal medulla's chromaffin cells release catecholamines, epinephrine, and norepinephrine in response to activating the splanchnic nerve, promoting a rapid response. When the HPA axis is turned on, the ventricular nucleus of the hypothalamus secretes corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). The anterior pituitary is then stimulated to secrete adrenocorticotropic hormone (ACTH), which enables the adrenal cortex to produce corticosteroids in response to CRH and AVP (34).

The hypothalamus, pituitary gland, hippocampus, and amygdala are all involved in glucocorticoid feedback and have glucocorticoid receptors. A proper response to acute stress is critical for survival, but frequent or prolonged activation can change the functional tone of stress systems, resulting in negative consequences later. Excessive or chronic activation of the endocrine stress axis, which also results in a disrupted feedback loop, causes and contributes to various human diseases and stress states, such as anxiety, PTSD, major depressive disorder, and occupational burnout. Furthermore, gonadal steroids can have multiple effects on the HPA axis, resulting in gender variations in stress response (36). Men appear to be at higher risk in adolescence and adulthood, especially if they experience stress-related adversity or trauma early in life, according to animal models and human studies. On the other hand, women appear to be at higher risk in adolescence and adulthood, particularly if they experience stress-related adversity or trauma early in life to have a childhood Women are more vulnerable to mood disorders including depression and schizophrenia throughout perimenopause and menopause (37).

COVID-19: Diabetes Mellitus

Pathophysiology & Mechanism

Diabetes is one of the comorbidities that people with COVID-19 report having the most commonly. However, diabetes is more common in these individuals than in the general population (8–10%), suggesting that diabetes is not a risk factor for developing COVID19 but is linked to higher mortality and more severe illness in COVID-19 pneumonia. This suggests that people with diabetes are more susceptible to a cytokine storm, metabolic dysregulation, and immunological dysfunction (38).

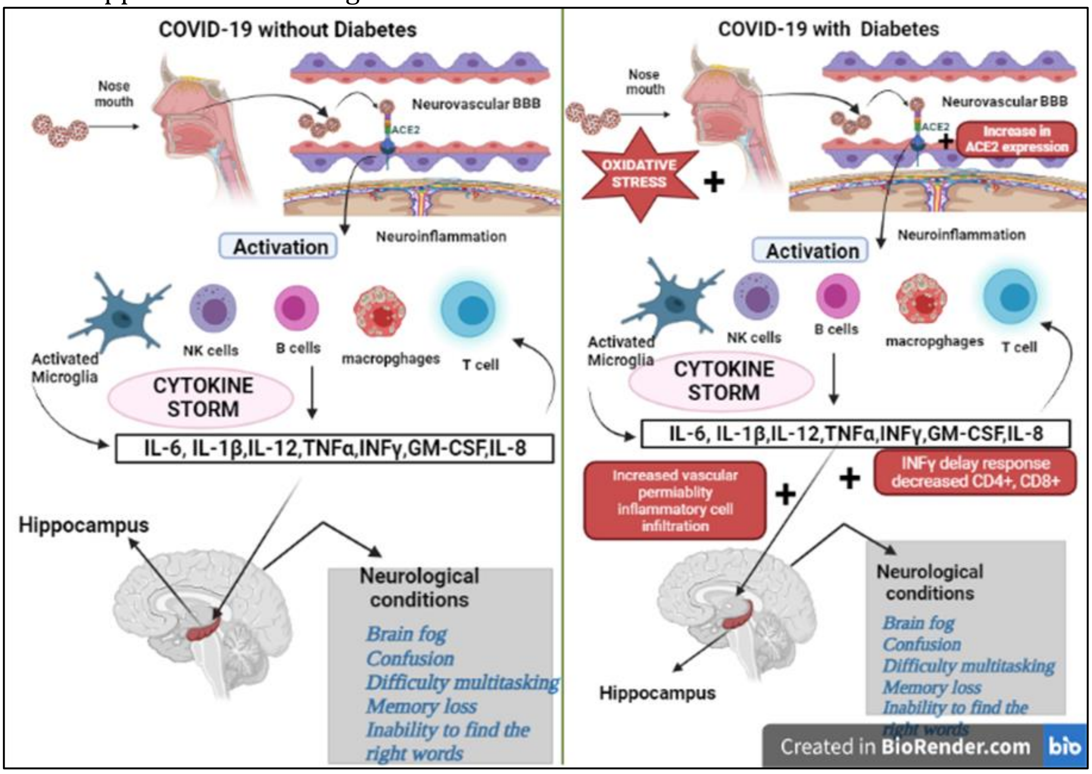

Figure 3. Comparision of Cognitive impairment with and without diabetes during COVID-19

COVID-19 and diabetes mellitus are both linked to acute and chronic inflammation, and both have the potential to influence clinical progression and prognosis. Two phases of the virus's immunological response can be distinguished clinically. The first stage is the non-severe stage, where the virus is eliminated, and the sickness is prevented from progressing to the more severe second stage. We'll show that it's far more complicated from an immunological standpoint and that the body's reaction to a viral challenge depends on the immune fitness of the individual exposed to the virus. The intensity, appropriateness, and size of the response and the pace of recovery will be determined by behavior, adaptiveness, and responsiveness. These immune fitness measures can identify whether the immune system is functioning normally or abnormally. When a person's systemic resilience, dependent on regulatory subsystems and organ functional reserves, deteriorates, the risk of morbidity and death rises (39).

SARS CoV-2 can infect endothelial cells and produce edema by increasing BBB permeability and causing endothelial cell injury. ACE2 is expressed in neurons and glial cells in the CNS under physiological settings, rendering the brain more sensitive to COVID-19 infection (40). Cell death is a result of viral infection and replication. Neurological problems may influence the morbidity and mortality of COVID-19 patients. The coronavirus's spike protein (S1) interacts with neuronal ACE2 (41). S protein and is made up of two subunits: S1 (for attachment) and S2 (for membrane fusion) (42). Membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins are the SARS-CoV-2 proteins responsible for viral entrance and replication (43). Infected neurons can emit inflammatory chemicals that stimulate immune cells in the surrounding area, such as mast cells, endothelial cells, pericytes, neurons, microglia, and astrocytes. SARS-CoV-2 infection can cause intracerebral hemorrhage and BBB disruption because cerebral endothelial cells produce ACE2 (26). Endothelial cell destruction, cerebral edema, neuronal death, and cognitive loss can all result from this. Even though all COVID-19 patients have cytokine storms, high-risk individuals with diabetes, obesity, hypertension, smoking, and lung illness experience a severe type of cytokine storm (43).

Additionally, this low-grade inflammation may cause the number of proinflammatory memory B cells to rise in COVID-19 diabetic patients and the percentage of anti-inflammatory B cells to fall, resulting in early maturation of the antibody response. Accordingly, Secchi M et al. found that SARS-CoV-2 antigens, such as the SARS-CoV-2 spike Receptor Binding Domain, cause a quicker development of humoral response and superimposable antibody response in diabetic individuals compared to non-diabetic patients, regardless of blood glucose levels (38).

Covid 19: Oxidative Stress: Cognitive Impairment

During oxidative phosphorylation, mitochondria produce free radicals (Oxygen and Nitrogen species). Their high reactivity, caused by unengaged electrons, increases oxidative stress. This illness primarily affects the brain, which requires a lot of oxygen and has a high chance of accumulating "Reacting Species." Antioxidant molecules are critical in minimizing free-radical damage, particularly in the central nervous system: in fact, oxidative stress appears to accelerate the progression of neurodegenerative illnesses (44).

The brain's high oxygen demand causes the creation of reactive oxygen species (ROS). Their high reactivity causes an increase in oxidative stress, which promotes: I glycosylation and oxidation of proteins, resulting in the formation of advanced glycation products (AGE) or loss of protein function; (ii) DNA damage via guanine base oxidation or nitration; and (iii) lipid peroxidation, which causes a decrease in membrane fluidity and an increase in cell permeability, altering cellular homeostasis All of these variables have the potential to contribute to the development of neurodegenerative diseases (45).

Multiple studies have found considerably higher levels of lipid peroxidation and protein, DNA, and RNA oxidation in sensitive brain areas of individuals with late-stage Alzheimer's disease (AD). Recent research on people with amnestic moderate cognitive impairment (MCI), the first clinical indication of Alzheimer's disease, has revealed comparable patterns of oxidative damage. These findings imply that oxidative damage to critical biomolecules begins early in the development of Alzheimer's disease and precedes severe neuropathologic changes. Because oxidative damage occurs early in the evolution of Alzheimer's disease, it is a possible therapeutic target for decreasing the onset and progression of the illness (46).

Covid 19: ACE2 increase expression: Cognitive Impairment

The effect of SARSCoV2 on cognition may be related to the virus's sensitivity to specific CNS cells and its direct invasion of the CNS. The binding of the S1 subunit of the S protein, one of four structural proteins of the SARSCoV2 virion, to the angiotensin-converting enzyme 2 (ACE2) receptor on cell surfaces results in viral attachment to host cells, with the subsequent subcellular entry of the viral genome occurring after fusion of viral and host living cells. As a result, SARSCoV2's cellular tropism is related to the expression of the ACE2 receptor (47).

Alveoli, the stomach, the kidney, the epidermis, and vascular endothelial cells express the receptor outside the central nervous system. It is expressed in endothelial cells, neurons, oligodendrocytes, and astrocytes inside the CNS. Regionally, the posterior cingulate gyrus, middle temporal gyrus, substantia nigra, and olfactory bulb all contain high amounts of the ACE2 receptor (48).

Covid 19: Inflammatory Process (cytokine storm)

The "cytokine storm" that generates high levels of proinflammatory cytokines and chemokines such as interleukin-6 (IL-6), IL-1, tumor necrosis factor-alpha (TNF-), chemokine (C-C-motif) ligand 2 (CCL2), and granulocyte-colony stimulating factor is now a characteristic of COVID-19 pathophysiology (G-CSF) (49). Delirium was the most reported impairment, and numerous reports of increased inflammatory markers imply an etiology. Other studies have shown that the condition causes significant increases in IL-6, TNF, and IL-1, cytokines known to have a substantial influence on working memory and attention. Impairment of these cognitive skills is a defining feature of delirium, suggesting that these cytokines are essential mediators in the pathogenesis of COVID-19-induced cognitive deficits. Researchers are urged to test inflammatory markers to investigate the potential involvement of inflammation in mediating cognitive dysfunction in COVID-19 patients (50).

Discussion

In diabetes-associated COVID 19, there may be abnormalities in cognitive function, which may be more severe in T2DM with associated metabolic syndrome. Diabetic cognitive impairment has a complicated etiology that entails altered insulin signaling, increased inflammation and oxidative stress pathways, and problems in metabolism and regulation. Identifying essential pathophysiological components is critical for creating novel therapeutic methods. According to various studies, TNF (42) and IL-1 can both influence attention and working memory deficits because they can both inhibit regular neuronal firing. Additionally, these consequences would be more pronounced in the case of neurotropism with clinical manifestations. In such cases, it is fair to suppose that more toll-like receptor 3/7/8-stimulated microglial and astrocytic populations would be activated, and lower levels of BDNF would exacerbate this inflammation.

Conclusion

As a result, we assume that uncontrolled hyperglycemia may be a pivotal contributor to the development of COVID-19 in the diabetic population and significant increases in IL-6, TNF, and IL-1, cytokines known to have a substantial influence on working memory and attention and leads to cognitive impairment. Such individuals may be suitable candidates for early intervention with colchicine, anti-IL1a, anti-IL1b, or anti-IL6 biological agents to avoid cytokine storm, lung, and cardiovascular consequences from COVID-19 infection. Further study is needed to understand the association between Cognition, Covid 19 & diabetes, and the prevalence of these three conditions to yield better patient management.

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Conflict of Interest

The author(s) declared no potential conflict of interest concerning this article’s research, authorship, and /or publication.

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