Revista Mexicana de Neurociencia

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REVIEW ARTICLE

COVID-19 and diabetes mellitus in cognitive impairment: an undrawn relationship

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Abstract

Cognitive impairment is a potential short- and long-term disease consequence of COVID-19 virus, the exact mechanism is still in debate. One of their potential linking is with diabetes. Diabetes and COVID-19 infection have possible multiple common mechanisms that could ensue cognitive impairment as pulmonary microthrombi (silent hypoxia); endothelial dysfunction; cerebral vascular injury oxidative stress; renin-angiotensin-aldosterone system; and galectine and interferon responses. In addition, histological markers as amyloid AB plaques and neurofibrillary tangle of Tau protein are common in both pathologies. Despite of this evidence, diabetes mellitus and COVID-19 in cognitive impairment are establishing a bright light in terms of neurological progress. This article describes the relationship between diabetes mellitus and COVID-19 as potential cause of cognitive impairment.

Keywords: *COVID-19. Diabetes mellitus. Cognitive dysfunction. Inflammation. Amyloid.*

COVID-19 y diabetes mellitus *en el deterioro cognitivo: una relación no trazada*

Resumen

El deterioro cognitivo es una probable consecuencia a corto y largo plazo de la enfermedad por COVID-19 cuyo mecanismo preciso aún está en discusión. Una de sus causas factibles es la diabetes. La infección por COVID-19 y la diabetes tienen múltiples posibles mecanismos comunes que podrían precipitar el deterioro cognitivo como son los micro-trombos pulmonares (hipoxia silenciosa); la disfunción endotelial; la lesión vascular cerebral inducida por estrés oxidativo; el sistema renina-angiotensina-aldosterona y la respuesta al interferón y galectina. Además, los marcadores histológicos como son las placas amiloides AB y los ovillos neurofibrilares de la proteína tau que son frecuentes en ambas patologías. A pesar de esta evidencia, la diabetes mellitus *y el COVID-19 en contexto de deterioro cognitivo están dictando futuros caminos en términos de progreso neurológico. Este artículo describe la relación entre la diabetes* mellitus *y el COVID-19 como causa potencial de deterioro cognitivo.*

Palabras clave: *COVID-19. Diabetes* mellitus*. Disfunción cognitiva. Inflamación. Amiloide.*

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Date of reception: 07-06-2022
Date of acceptance: 25-09-2022
DOI: 10.24875/RMN.22000039

Available online: 16-02-2023
Rev Mex Neuroci. 2023;24(1):13-18
www.revmexneurociencia.com

Introduction

Since December 2019, when the first case of COVID-19 pneumonia was reported, the world became aware of a new challenge yet to be completely unfold. In March 11 2020, the World Health Organization (WHO) declared COVID-19 as pandemic[1]. During its evolution, multiple complications have been noted. Importantly, these morbid sequelae appear to affect patients with previous comorbidities, such as diabetes mellitus (DM). Furthermore, cognitive impairment has recently been described as a potential short- and long-term disease consequence of COVID-19 virus. Diabetes and COVID-19 infection have multiple common mechanisms that could ensue cognitive impairment instatement or worsening[2]. Therefore, in this paper, we aim to address the possible and suggested physiopathological mechanisms in a bi-dimensional relationship between COVID-19 and diabetes mellitus that lead to cognitive impairment.

Approximately 10% of patients with COVID-19 infection have DM. A Chinese meta-analysis, which included 1527 patients, observed a DM prevalence of 9.7% on infected cases. Furthermore, those with diabetes and hypertension had a two-fold increase in severity or ICU requirement.[3] Several other detrimental associations between COVID-19 and DM have been noted. A glycated hemoglobin of > 9% increased by 60% the risk of hospitalization and severity progression in pneumonia[4]. On the other hand, mortality increased 3 times in patients with history of DM who developed severe acute respiratory syndrome[5].

On the other hand, brain fog has been recently described in COVID-19 survivors, mainly attributed to endothelial dysfunction and inflammation. Both are mainstays on DM pathophysiology and together may lead to further complications. For example, disturbed function of T-cells and elevated levels of interleukin-6 (IL-6) appear in both. Covid-19 may lead to a cytokine storm, where IL-6 is one of the main inflammatory agents; also, liberation of catecholamine and steroids, higher hyperglycemia, is associated to worse outcomes[6,7]. Novel inflammatory mechanisms in the COVID-diabetes relationship and how they affect cognitive impairment will be described further.

Relationship between diabetes mellitus and cognition. What we know

Regarding the relationship between DM and cognitive impairment, it should be noted that the two main histological markers for this are amyloid AB plaques and neurofibrillary tangle of Tau protein. The amyloid precursor protein (APP) passes through several cuts during its processing. The first is given by the alpha-secretase; the second, by the beta-secretase (BACE); and the third, by gamma-secretase. The latter is encoded by presenilin 1 and 2 associated with hereditary AD. Factors such as oxidative stress and mitochondrial dysfunction overly activate BACE in the amyloid cascade with amyloid AB as the final product. The deposit of amyloid plaques leads to subsequent chronic inflammation and generation of advanced glycosylation products with increased oxidative stress, thus generating a vicious circle by stimulating BACE again.

Theories involve insulin or diabetes mellitus type 3. AB amyloid is enzymatically de-graded by certain enzymes including the insulin-degrading enzyme[8]. The AB peptide that is not removed by the insulin degrading enzyme will form Ab oligomers that later lead to amyloid plaques. Hyperphosphorylation of tau protein and amyloid ab plaques promotes neuroinflammation and the creation of oxygen reactants or peroxides. As previously mentioned, oxidative stress caused by these reactants will promote BACE function[9,10].

There is evidence that insulin can be produced by certain neurons, such as those in the olfactory bulb and the hippocampal gyrus in smaller quantities, than the pancreas. Chronic hyperinsulinemia due to inflammation decreases the insulin receptors in the blood–brain barrier with a consequent decrease in insulin levels in the CNS[9,10]. The pathophysiology occurs as follows: insulin and AB peptide, before the formation of the amyloid AB plaque, compete for the insulin receptor on the neuronal surface. When insulin resistance exists, the affinity for the receptor is lost, and so AB peptide takes its place. The insulin-degrading enzyme, which removes both AB peptide and insulin, consequently acts on the insulin erroneously. The insulin will be degraded and the AB peptide will bind to the insulin receptor[9,10]. Therefore, blocking the insulin receptors will not activate the second messenger system. This leads to hyperphosphorylation of the Tau protein, with instability of the microtubules and aggregation into neurofibrillary tangles[9,10]. These deleterious mechanisms could begin when a glycated hemoglobin (HbA1c) is higher than 8%, an association with cognitive impairment has been drawn[11].

DM generates multiple micro and macrovascular complications. These arise from advanced glycation end-products, oxidative stress, and inflammation. Some abnormalities that will be of interest in this paper are hypercoagulability and endothelial damage. Endothelial and capillary dysfunction is one of the main mechanisms for brain damage in

DM. Endothelial dysfunction could be described as an irregular response to endothelial vasodilators and lower flow response in consequence. The exposition of proteins to high glucose leads to chronic accumulation of advanced glycation end products. These are oxidants that may potentiate oxidative stress and compromise vascular activation[12,13].

The main mechanisms involved in cognitive impairment development in DM and COVID-19 are pulmonary microthrombi (silent hypoxia); endothelial dysfunction; cerebral vascular injury; oxidative stress; renin-angiotensin-aldosterone system; and galectine and interferon responses. Other theories are available such as cerebral hypoperfusion or COVID-19 encephalitis; however, these do not involve DM as a main factor. As we dive into the concepts, first, a relationship between lungs and brain by direct and indirect mechanisms will be established as is important to understand its outcomes (Fig. 1).

Pulmonary microthrombi (silent hypoxia)

Both, DM and COVID-19, predispose to thrombi formation by generating a hypercoagulable environment. Platelet hyper reactivity, inflammation, renin-angiotensin-aldosterone system (RAS) over-activation, and factors related to sepsis are some of the disturbed pathways for induced coagulation[14]. COVID-19 creates clots and shunts all over the lungs, and this has shown to be 9 times more prevalent in COVID-19 than other infections such as Influenza AH1N1[15].

Alveolar capillary microthrombi could form during the acute disease, which could damage gas exchange, and later on, when oxygen is insufficient and required in the brain, it could predispose to cognitive impairment. Normally, gas exchange or oxygen uptake is regulated to meet specific levels by maintaining blood flow and the rate of oxygen exchange in the alveoli. Microthrombi may limit the permeable surface for gas exchange; therefore, the time necessary for this process needs to increase to avoid hypoxia. In other words, with less functional surface, transit time increases to compensate this loss. As we know, the brain is a high-level consumption organ and relatively sensitive to change. This pathophysiological process could be of no acute clinical relevance in infected patients, principally in the young, but, in the future, brain damage could be boosted. This mechanism is called silent hypoxia. However, in the elderly and more commonly in patients with established dementia, it could worsen previous cognitive symptoms. In summary, transit time increases due to high permeability in alveoli causing hypoxia that could cause a "brain fog" either now or in the future[16,17].

Endothelial dysfunction

Very closely related to thrombi formation, endothelial dysfunction completes the full circle in cognitive impairment development. Integrating the basis to maintain blood flow in cerebral strokes, additional mechanisms need to activate when brain oxygen is lacking. When a threshold is reached by hypoxia, vasodilatation occurs to increase blood oxygen availability and maintain flow. This step occurs both in brain and lungs. DM develops microvascular damage over the years and inhibits a full transition to vessel vasodilatation. Other comorbidities such as dyslipidemia or tobacco history also worsen endothelial dysfunction. A partial compensatory mechanism could led to loss of cognitive functions over time, as oxygen blood extraction is impaired[16,17]. In fact, patients with mild cognitive impairment and Alzheimer's disease have shown abnormal cerebral microvascular flows when compared to controls[18].

Brain oxygen uptake is not the only way that endothelial dysfunction could cause decline particular regions and cognitive impairment. Compromised neurotransmission and secondary inflammation go along with acute or chronic hypoxia. Impaired neurotransmission is an important cognitive impairment contributor. Enzymes associated with neurotransmitter synthesis are oxygen dependent. Tyrosine hydroxylase and dopamine-B-hydroylase require oxygen for their catalytic activity to synthetize dopamine, serotonin, and norepinephrine, respectively. As in sleep apneas, hypoxia by COVID-19 may interfere with rate-limit enzymes and impair cognition[19].

Cerebrovascular injury

COVID-19 infection has shown neurotropic characteristics. Brain vasculature damage and thrombi formation are due to multiple causes. As for now, virus direct brain damage or endothelial brain cell targeting is suspected; however, other mechanisms proposed seem to also contribute to cognitive impairment[20]. SARS-COV-2 virus binds by its spike protein to the angiotensin converting enzyme receptor (ACE2) located at endothelial and glial cells. Furthermore, there is evidence that supports olfactory bulb nerve invasion[21].

Brain damage is caused by numerous interrelated and connected effects. Similarly, as alveoli capillary microthrombi, subcortical white matter microcirculation is subject to vascular lesions characterized by small subcortical ischemic and hemorrhagic injury[22]. Brain inflammation caused by multiple paths such as hypoxia, oxidative stress, vascular injury, infection, innate immune response or microglial response, and amyloid aggregates,

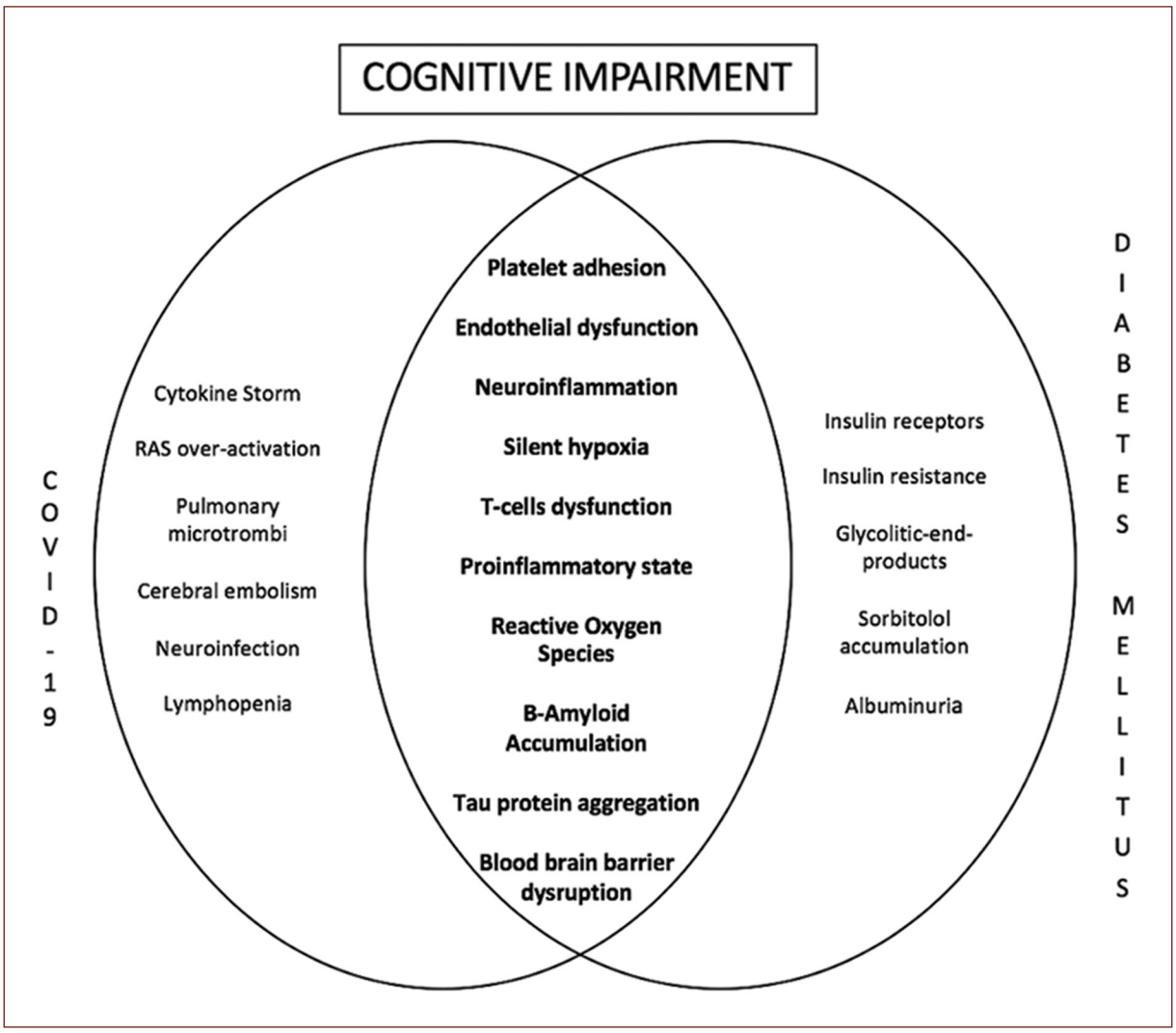

Figure 1. Cognitive impairment mechanisms in COVID-19 and diabetes mellitus.

among others, compromise the blood–brain barrier (BBB) structure. As a vicious circle, BBB leakage increases hypoxia and inflammation, with neuronal death as consequence[17]. Hippocampal structures are one of the main areas affected by inflammation, hypoxia, and neurotropic virus. CA-1 and CA-3 areas present neuronal loss after COVID infection in animal models[23].

Diabetes mellitus-COVID-19-cognition

Some interesting specificities support a relationship between DM, COVID-19, and cognition. Related to the already mentioned injury routes, RAS is dysregulated. DM increases angiotensin II levels. Remarkably, COVID-19 infection also increases angiotensin II levels. Although angiotension II is increased, SARS-COV-2 virus blocks its activity by binding to its receptor first; leading to deleterious effects. RAS disruption leads not only to vasoconstriction but also to inflammation, snowballing endothelial dysfunction, oxidative stress, and cerebral injury[24]. Of note, ACE2 in Alzheimer's disease patients is overexpressed, but its activity is reduced[25,26]. This theorizes a higher brain entry for SARS-COV-2, as more receptors are available, but with serious deleterious effects as vasoconstriction is highly reasonable.

Another synergic compromised activity is immune response in specific proteins such as galectine, interferon, and amyloid. Chronic inflammation in diabetes stimulates the expression of immune modulators such as IL-6 and galectine-9, a β-galactoside binding protein with polarizing effects. Considered as a damage-associated molecular pattern, it has shown to improve chemotaxis, cell adhesion, and

apoptosis in T-helper cells among others[27]. In the brain, it facilitated myelin repair and oligodendrocyte activity[28]. However; recently in COVID-19, galectin has been described as a therapy target, as its "beneficial" effects could prompt cytokine storm and enhance immune reaction[29]. Galectins are also considered inducers of amyloid oligomerization[30].

β-Amyloid-42 (Aβ42), one of the main proteins involve in AD pathology, has shown antipathogenic properties, as Aβ42 oligomers form fibrils to enclose microbes and activate microglial cells[31]. This response has been demonstrated for diverse viruses such as hepatitis, herpes, and zoster virus[32]. Aβ42 mediates the expression of interferon genes, in particular the amyloid-stimulated type I interferon (A-IFN). These cytokines increase the inflammatory response to virus and induce complement cascade activation[33]. On the other hand; DM and hyperglycemia accelerate the expression of interferon regulatory factor 5 (IRF5), as it is glucose sensitive. IRF5 was investigated in the influenza A infection. DM, COVID-19, and amyloid may synergize by stimulating a highly inflammatory environment[34].

In relationship with cognitive impairment, multiple mechanisms have already been shown to increase its risk[35]. IL-6 is inversely correlated to cognitive performance in such as the Mini-mental test, and hippocampal volumes[36]. Interferon levels are higher accordingly to a greater Braak score in patients with AD[37]. At last, it is also important to remember the association between DM, insulin, and amyloid, previously described. The olfactory bulb has the highest concentration of insulin and insulin receptors in the brain. The study of ACE2 expression in insulin sensitive tissues began as a search for an explanation of smell loss, a characteristic COVID-19 symptom. Now, as SARS-COV-2 invades the olfactory bulb, a dysregulation of insulin signaling begins[38]. The previously proposed connection between DM and cognition exacerbates. Therefore, secondary to insulin resistance due to DM, insulin-degrading enzyme is unable to remove increased Aβ42 aggregates as innate pathogen response. This promotes greater neuroinflammation, higher oxidative stress, increased BACE function, and most importantly tau protein aggregation into neurofibrillary tangles[9].

At last, a vicious cycle has been suggested. A newly described hypothesis between SARS-COV-2 and DM proposes the expression of ACE2 receptor on pancreatic islets. ACE2 is an important mechanism in the homeostasis of pancreatic B-cell survival and also maintains insulin resistance at its minimum. Therefore, COVID-19 infection leads to an inflammatory state, where persistent hyperglycemia and elevated insulin resistance due to downregulation of ACE2 receptors are created[39,40]. These hypotheses could add another step into the predisposition of developing dementia.

From clinical perspective, severe COVID-19 cases are at higher risk of developing cognitive decline according to 1 year follow-up in Wuhan, China population, intriguingly this population reported higher number of comorbidities compare to non-severe cases, such as diabetes, hypertension, stroke, coronary heart disease, and chronic obstructive pulmonary disease[41]. In addition, from electronic health records in US population, individuals with COVID-19 were in increased risk for new diagnosis of Alzheimer's disease in 12 months after infection[42]. These suggest that comorbidities such as diabetes mellitus may synergize with COVID-19, predispose to cognitive impairment and later to dementia.

In neurocognitive studies, some authors have described executive function, attention, and memory impaired by COVID-19[43-45], which is most likely a vascular dementia pattern, this correlates with silent hypoxia, endothelial dysfunction, and cerebrovascular injury mechanisms; nevertheless, anatomical hippocampal changes are reported in COVID-19 patients and hippocampal and Aβ42 inflammation play a major role in Alzheimer's disease as we described in the previous sections[46].

We suggest that COVID-19 predispose cognitive impairment specially in severe cases and studies show Alzheimer's disease and/or Vascular dementia progression. We hypothesize that infection itself through neuroinflammation, endothelial dysfunction, silent hypoxia, pro-inflammatory state, and reactive oxygen species, predisposes a vascular dementia at the beginning, in case of diabetes mellitus, these pathways could be precipitated, thereafter β-amyloid accumulation and tau protein aggregation begins making patients susceptible to develop Alzheimer's disease, or according to infectious hypothesis of Alzheimer disease COVID-19 triggers this process[47].

Conclusion

The silent access of SARS-COV-2 into the brain could predispose to neurodegenerative disease in many ways. Many questions are still unsolved. Although, many answers, such as the inflammatory response, are currently being elucidated, some like the synergistic effect of diabetes mellitus and COVID-19 in cognitive impairment are establishing a bright light in terms of neurological progress.

Acknowledgment

Ninive Vargas De la Peña for assistance with reviewing and revising the manuscript for grammar and syntax.

Funding

None.

Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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