REVIEW ARTICLE

POST-COVID COGNITIVE IMPAIRMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

DOI: 10.36740/WLek202208113

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ABSTRACT

The aim: The revealing of the consequences of the long-term postcovid effects on the particular cognitive domains in patients with diabetes mellitus type 2 (DM 2) by comparing the characteristics of patients with DM 2 without postcovid disorders and the characteristics of cognitive impairment in patients with long-therm postcovid without DM 2 by forming the research hypothesis to improve the adherence to treatment of patients.

Materials and methods: Literature search was performed using PubMed search criteria "covid AND cognitive AND domain" 217 articles, as a result, and separately "diabetes mellitus 2 type AND cognitive impairment AND domain" with the result of 164 articles. There were 26 remaining studies included in this review. The hypothesis about the relationships between the particular cause factors and the defeating of specific cognitive domains in patients with DM 2 in the long-term postcovid period has been formed.

Conclusions: This is important in the terms of the influence of cognitive impairment on the concordance to treatment process and quality of life level in patients with DM 2 in general. So, involving specialists of different profiles in a multidisciplinary approach is the solution to this issue.

KEY WORDS: COVID-19, medication compliance, treatment adherence

Wiad Lek. 2022;75(8 p1):1895-1899

INTRODUCTION

The consequences of the SARS-CoV-2 pandemic is still a significant problem for the health care system in the world. This issue is even more relevant for groups of patients with the permanent diseases, especially, diabetes mellitus type 2 (DM 2). Manifestations of postcovid syndrome include symptoms that persist for more than three weeks after diagnosis of COVID-19. The incidence of postcovid syndrome in general – is nearly from 10% to 35%, however, among the patients with the history of hospitalisation for COVID-19 reported about 85% [1]. Cognitive impairment and affective disorders – are the most common mental components of postcovid syndrome. It has been shown that among COVID-19 survivors – the incidence of the affective disorders in the remote postcovid period was about 23% between 1 to 180 days and 16% between 90 and 180 days after COVID-19 transfer and the proportion of cognitive impairment was about 8% and 4%, respectively [2]. Significant damage supporting the central nervous system (CNS) due to the SARS-CoV-2 infectious disease and the cognitive deficit is often the leading symptom of this. The pathogenesis of postcovid syndrome is multifactorial, and more than one mechanism may be involved in several clinical manifestations and may include, for example – immune-mediated vascular dysfunction with CNS damage. Prolonged inflammation plays the key role in the pathogenesis of postcovid syndrome and can cause some neurological complications, such as cognitive dysfunction and other symptoms [3-5]. Although, the significant damage to CNS occurs due to this infectious process. Brain damage occurs through the olfactory bulb by the retrograde transport of neurons from the olfactory epithelium and through the hematoencephalic barrier. Symptoms of postcovid syndrome can occur not only by the result of CNS damage, but also after the process of treatment of this infectious disease. Neurological signs and symptoms should inform physicians not only about the current worst consequences, but also about the development of degenerative brain disorders in the future. Neurological signs and symptoms may signal the possibility of developing degenerative brain lesions in the future, which can cause the significant negative consequences for psychoneurological status and, consequently – the quality of life level and effectiveness of treatment in DM 2 patients. Consequently, DM 2 is the major risk factor for the long-term sequelae and complications due to COVID-19 and postcovid syndrome due to the certain pathophysiological mechanisms of DM 2 [6-10].

THE AIM

The revealing of the consequences of the long-term postcovid effects on the particular cognitive domains in patients with diabetes mellitus type 2 (DM 2) by comparing the

characteristics of patients with DM 2 without postcovid disorders and the characteristics of cognitive impairment in patients with long-therm postcovid without DM 2 by forming the research hypothesis to improve the adherence to treatment of patients.

MATERIALS AND METHODS

STUDY SELECTION

Research papers have been found by searching the PubMed database using the keywords. Literature search was performed using PubMed search criteria "post covid AND cognition AND diabetes 2 type" according to the results – only 4 articles were received that did not meet our inclusion criteria. Then we searched separately for the criteria of "post covid AND cognition AND diabetes" and found 25 articles that also did not meet our criteria, as none of them described the issues that interested us, particularly about the patients with DM 2. Finally, literature search was performed using PubMed search criteria "covid AND cognitive AND domain" 217 articles, as a result, and separately "diabetes mellitus 2 type AND cognitive impairment AND domain" with the result of 164 articles.

STUDY METHOD

We have used the scoping review research methodology to provide the overview of the available research evidence. There have been 26 studies included in this review. In the review part of this article, we cited all of the studies, which have been included in the study.

CASE STUDY

Therefore, the study was conducted by comparing the characteristics of patients with DM 2 without postcovid disorders and the characteristics of cognitive impairment in patients with long-therm postcovid without DM 2 by forming the research hypothesis. Based on the results of the literature review – it has been formed the hypothesis about the relationships between the particular cause factors and the defeating of specific cognitive domains in patients with DM 2 in the long-term postcovid period [11].

REVIEW AND DISCUSSION

The question about which cognitive domains are affected and in which cases in different groups of patients with permanent diseases is relevant for the study. However, cognitive impairment could also be the result of complications, which are pathophysiologically associated with DM 2, such as metabolic and vascular disorders which affect brain functions. For example, cerebral perfusion in DM 2 patients have been significantly reduced in different brain areas, including the occipital lobe and cerebellum. In addition, biochemical parameters such as glycosylated haemoglobin and insulin resistance have been negatively correlated with regional circulatory parameters in the brain. The prevalence of cognitive dysfunction also increases with age in DM 2 patients, from mild cognitive decline up to dementia. Decreased regional cerebral circulation has been associated with the wide range of cognitive impairment in patients with DM 2, including learning, memory, attention, and executive processing, as well as visual function [12]. The permanent hyperglycemia and insulin resistance are still the main risk factors for the development of Alzheimer's disease and other cognitive disorders. The functioning of the brain requires the constant supply of glucose and oxygen as well as the regulation of metabolic processes. It is important to evaluate the interaction between oxidative stress, insulin resistance and dyscirculatory processes in the brain which can result in the neurodegeneration processes [13]. Changes also occur in neuroplasticity and brain metabolism. Structural and functional MRIs have shown that abnormal connections and synchronisation occured in brain circuits and related networks as the major effector systems that may be associated with beta-amyloid deposition [14]. In addition, the specific type of dementia which can occur in DM 2 patients, and manifested by the high levels of glycosylated haemoglobin, disease duration, insulin resistance, increased levels of the inflammatory cytokines, oxidative stress, the final products of glycosylation level and low circulation in the medial temporal lobe [15]. Therefore, the impaired insulin signalling promotes the accumulation of amyloid-β, neurofibrillary tangles, tau proteins and α-synuclein in the brain. While the improvement of the insulin signalling slows the progression of cognitive decline. It has also been found that DM 2 patients have cognitive impairments that lead to learning and memory deficits, while patients with type 1 diabetes have less severe levels of these disorders [16]. So, the presence of DM 2 increases the risk of cerebrovascular diseases and stroke. Cerebrovascular dysfunction and endothelial integrity disorders lead to decreased cerebral blood flow and iron deposition in the brain, which can be identified as the targets for intervention to prevent mixed forms of cerebrovascular disorders in patients [17]. Affective disorders can be manifested by the cognitive decline, which could be the characteristic of depressive syndrome, particularly. Among the other causes and additional risk factors of the cognitive impairment in DM 2 patients could be the comorbid psychoneurological and metabolic disorders and complications of DM 2 which could be also accompanied by the cognitive decline [18]. For example, the intermittent hypoxia, particularly as a result of the obstructive sleep apnea in DM 2 patients. The activation of chemoreflex suppress the baroreflex, which thereby stimulating the sympathetic nervous system and causing the arterial hypertension. As well as the level of HIF-1α proteins increases and HIF-2α proteins – decreases. Disturbed HIFs increase reactive oxygen species (ROS) through the HIF-1-dependent activation of prooxidant enzyme genes in addition to reduced the transcription of antioxidant HIF-2 genes. Increased ROS generation contributes to insulin resistance as well as impaired NMDA receptors signalling in the hippocampus, leading to decreased cognitive function [19].

DM 2 is closely associated with lower performance in many domains of cognitive functioning and with structural abnormalities of the brain. It is important for the future studies to research the pathophysiology and factors associated with cognitive decline and various metabolic and neuroradiological markers that indicate this pathological condition is crucial for the proper treatment of this potentially debilitating complication of DM 2 [20]. Patients with DM 2 are the risk group for the impairment of cognitive functioning because of metabolic and vascular disorders affecting brain anatomy and functioning and completed by ageing. Neurocognitive impairment includes decreased performance in cognitive domains such as verbal and nonverbal, immediate and delayed memory, executive function, attention, visual-spatial and psychomotor performance, information processing speed, semantic skills, and language skills, which is observed in DM 2 patients [21]. The small and moderate effects for five of the six domains, such as: motor function, executive function, processing speed, verbal and visual memory have been obtained. However, the size of the effect for the attention and concentration has been the smallest [22]. Particularly, cognitive dysfunction, especially executive function disorders — negatively affects patients' self-care skills. Therefore, it is important for investigating, including the effect of hypoglycemic therapy on cognitive function in DM 2 patients [23].

However, the reliable data on the specificity of CNS lesions in the long-term postcovid period have not been found enough yet. Anyway, the neurological complications significantly complement the comorbidity of DM 2. Inflammatory stimuli and associated pro-inflammatory immune responses may promote neurodegeneration and threaten survival after infection. As a result, the imbalance between pro- and anti-inflammatory processes can alter the immune activity of brains` microglia, astrocytes, perivascular macrophages, oligodendrocytes and dendritic cells, leading to neuronal damage. Vagus nerve mediates the peripheral cholinergic anti-inflammatory reflex and emphasises the consistent control of inflammation of the body and brain with proinflammatory cytokines that affect cholinergic functions; therefore, impaired this reflex may exacerbate cognitive impairments [24]. As well as the nonspecific neuroinflammation with microglial activation and lymphoid infiltrations, ischemic or hypoxic encephalopathy, acute cerebrovascular disease, and microthrombi or whether the other infectious, toxic, vascular, or metabolic mechanisms also can cause the cognitive impairment [25]. For example, clinical observations, biomarkers of neuroimaging and biofluids, and pathological studies have suggested an association between the severity of acute neuroinflammation, subsequent neurodegeneration, and disease-related morbidity [26-27]. Persistent psychiatric symptoms among COVID-19 victims, such as depression, anxiety, post-traumatic symptoms, and cognitive impairment, may be associated with psychological factors and neurobiological trauma [28]. For example, the syndrome which consists of the combination of cognitive dysfunction, depression, anxiety and post-traumatic stress disorder (PTSD) symptoms combined with physical weakness in the post-intensive care period is called the post-intensive care syndrome [29-32]. Postcovid syndrome may include debilitating symptoms of reduced aerobic tolerance, anxiety, PTSD, and cognitive dysfunction [33].

However, it has been insufficiently studied the problem of which cognitive domains are affected in DM 2 patients in the remote postcovid period. But it has been researched the domains of lesions in patients who have suffered from COVID in general. For example, by comparing COVID and postcovid groups of patients has been found by the results of psychometric scales: that deficits of MMSE in COVID compared to the postcovid group, while most of both groups reported cognitive impairment in total MoCA results. The postcovid group reported significantly higher scores in the MMSE subtests for language and in the MoCA subtests for executive functions, language and abstraction in comparison with COVID-19 group [34]. By the results of studies it has been shown the widespread effect on the ability to pay attention, both in the individual affected area (19 % of single-domain disorders) and in combination with the reduced productivity of executive functions, learning and long-term memory. However, attention deficit and associated executive deficits were largely unrelated to clinical factors [35-36]. Rehabilitation programs must be aimed to provide the holistic and multifaceted approach to the treatment of postcovid symptoms. Clinicians should try to individualise programs and control for advertising events and symptoms, given the limited evidence in this area. Finally, the rehabilitation programs for supporting people with symptoms of long-term COVID-19 must be safely and demonstrate the improved symptoms and condition [37]. It is important to investigate this in the future in the aspects of multicomponentity, for example, for metabolic syndrome, which implies its complex and heterogeneous pathogenesis, knowledge of which is constantly replenished with new details as the results of scientific research [38].

Therefore, by the review of studies – the decline in cognitive function due to postcovid disorders in patients with DM 2 may occur with the reduced productivity of: abstraction, attention, executive functions, language, learning and long-term memory. This is important in the terms of the influence of cognitive impairment on the concordance to treatment process and quality of life level in DM 2 patients in general.

CONCLUSIONS

According to the results of the study – it could be concluded that it is necessary and important for finding and developing ways to correctly diagnose, prevent and treat cognitive impairment in patients, particularly in the period of postcovid rehabilitation. The studying of the features of psychoneurological and psychosocial status of patients with DM 2 and comorbid postcovid disorders is important in the context of studying the features of the postcovid syndrome. Comorbid postcovid disorders cause cognitive deficits and

decrease compliance and adherence to treatment level, which can manifest itself in the inability to follow the doctor's recommendations and disrupt treatment process. It is important to address this in the multidisciplinary collaboration and to create multidisciplinary teams that include representatives from different fields of medicine: endocrinology, internal and family medicine, psychiatry, neurology and medical psychology. It would improve the effectiveness of treatment and increase the quality of life level of DM 2 patients.

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Conflict of interest:
The Authors declare no conflict of interest

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Received: 02.04.2022
Accepted: 27.07.2022

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article