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Editorial Board Member of *World Journal of Diabetes*, Maja Cigrovski Berkovic, MD, PhD, Associate Professor, Department of Sport and Exercise Medicine, University of Zagreb Faculty of Kinesiology, Zagreb 10000, Croatia. maja.cigrovskiberkovic@gmail.com

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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MINIREVIEWS

Diabetes mellitus and glymphatic dysfunction: Roles for oxidative stress, mitochondria, circadian rhythm, artificial intelligence, and imaging

Kenneth Maiese

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Kenneth Maiese, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20810, United States

Corresponding author: Kenneth Maiese, MD, National Heart, Lung, and Blood Institute, National Institutes of Health, Cellular and Molecular Signaling, Bethesda, MD 20810, United States. wntin75@yahoo.com

Abstract

Diabetes mellitus (DM) is a debilitating disorder that impacts all systems of the body and has been increasing in prevalence throughout the globe. DM represents a significant clinical challenge to care for individuals and prevent the onset of chronic disability and ultimately death. Underlying cellular mechanisms for the onset and development of DM are multi-factorial in origin and involve pathways associated with the production of reactive oxygen species and the generation of oxidative stress as well as the dysfunction of mitochondrial cellular organelles, programmed cell death, and circadian rhythm impairments. These pathways can ultimately involve failure in the glymphatic pathway of the brain that is linked to circadian rhythms disorders during the loss of metabolic homeostasis. New studies incorporate a number of promising techniques to examine patients with metabolic disorders that can include machine learning and artificial intelligence pathways to potentially predict the onset of metabolic dysfunction.

Key Words: Artificial intelligence; Circadian rhythm; Clock genes; Diabetes mellitus; magnetic resonance imaging; Glymphatic pathway; Mitochondria; Oxidative stress; Programmed cell death; Sleep fragmentation

Core Tip: Diabetes mellitus (DM) is a significant disorder across the globe affecting almost five hundred million individuals with significant disability that can involve musculoskeletal disease as well as cognitive loss. Multiple pathways can lead to DM that can affect the critical function of the brain's glymphatic function, but the targeting of novel mechanisms tied to oxidative stress, mitochondrial dysfunction, circadian rhythm impairment, and new techniques such as artificial intelligence and imaging protocols offer exciting prospects for clinical care and treatment.

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INTRODUCTION

A recent paper by the authors Tian *et al*[1] presents a new process for the assessment of glymphatic function in patients with diabetes mellitus (DM) that employs diffusion tensor imaging along the perivascular space. The employment of a number of different avenues to assess metabolic disorders and the effects on the glymphatic system may offer new directions for the clinical treatment of DM and the devastating effects of this disease. DM affects individuals of all income levels but those individuals in low and middle income countries are more severely impacted than individuals residing in high income nations[2,3]. A number of factors can lead to DM affecting lower income individuals that involve not only education level and socioeconomic status[4,5], but also comorbidities that involve infections. Although at least ten percent of the population in countries such as the United States are believed to suffer with DM, additional individuals remain without the diagnosis and also have metabolic disorders and heightened risk for the eventual development of DM[6,7]. Of further concern is that DM is a progressive and chronic disease that impairs all organs of the body with liver disease, retinal neuron loss, kidney failure, peripheral neuropathies, cardiovascular disease, and cognitive loss[8-11].

UNDERLYING PATHWAYS FOR DM: OXIDATIVE STRESS, MITOCHONDRIAL IMPAIRMENT, AND CIRCADIAN RHYTHM

Several important underlying pathways can contribute to metabolic disorders and DM. Oxidative stress can play a significant role in the pathology of DM and lead to programmed cell death with apoptosis, autophagy, ferroptosis, pyroptosis, and mitophagy[12,13]. Oxidative stress results from the generation of reactive oxygen species (ROS) that can involve nitric oxide, peroxynitrite, singlet oxygen, hydrogen peroxide, and superoxide free radicals. These ROS with the generation of oxidative stress can lead to cell senescence[14,15], vascular disease[16,17], loss of stem cell development[18-20], and neurodegeneration[21-23].

Oxidative stress also can control the fate of mitochondria and impair the function of these cellular organelles with the release of cytochrome c and caspase activation that leads to programmed cell death. For example, during DM, pyroptosis programmed cell death can promote mitochondrial injury and endoplasmic reticulum stress[9,17,24]. In addition, pathways of programmed cell death can also result in mitochondrial dysfunction and the elimination of these organelles from the cellular structure. During mitoptosis, mitochondria that are damaged are removed from cells in an attempt to offer cellular protection during oxidative injury[25-27]. Cell death that involves autophagy and mitochondria can also assist with cell survival to remove injured mitochondria in the presence of oxidative stress[21,23].

Within this scenario of cell injury during DM, oxidative stress, and mitochondrial dysfunction, circadian clock genes play a central role. Circadian clock genes can oversee a number of processes during DM that involve cellular metabolism [28,29], energy control of mitochondria[30,31], and oxidative stress[32,33]. Circadian rhythm pathways also control comorbidities tied to DM that involve infections and viral diseases[34,35]. Circadian clock gene dysfunction through the involvement in metabolic pathways also may lead to neurodegeneration and cognitive impairment. Alterations of circadian rhythm during extend space flight may result in cognitive decline[36] as well as the onset and progression of Alzheimer's disease[36].

DM, ARTIFICIAL INTELLIGENCE, THE GLYMPHATIC PATHWAY, AND NEW AVENUES FOR ANALYSIS

Given that DM affects all organs of the body including the nervous system, it becomes essential to assess pathways that can affect the function of the brain (Figure 1). In this regard, the glymphatic pathway is recognized as a vital component for the maintenance of the central nervous system. Cerebrospinal fluid bathes the brain through a perivascular network known as the glymphatic pathway that removes toxins of the brain to include b-amyloid (Ab), tau, and a-synuclein[37]. The glymphatic pathway is affected by sleep fragmentation and sleep deprivation[38,39] that impairs circadian rhythm and the removal of brain toxins that can lead to cognitive loss[37,40,41]. Of further concern is that sleep loss can promote metabolic disease in patients with DM and lead to oxidative stress and mitochondrial injury. Dysfunction in circadian

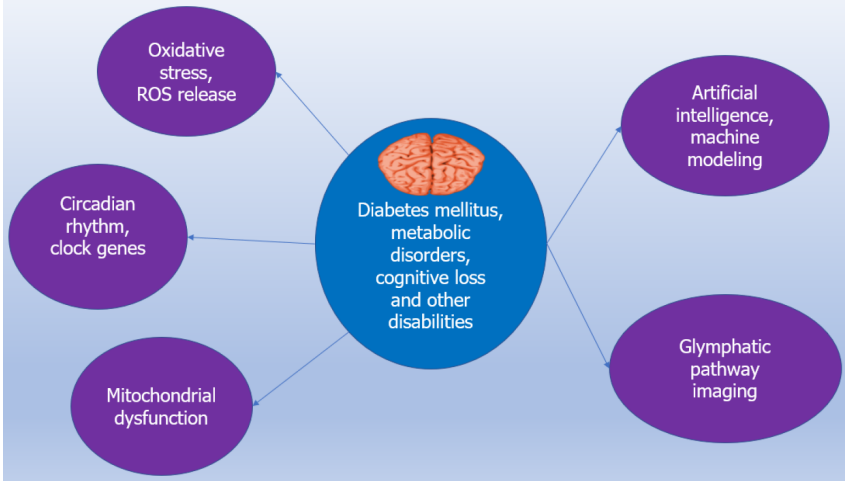

Figure 1 Diabetes mellitus and metabolic disorders lead to multiple disorders including cognitive loss. Diabetes mellitus (DM) affects critical pathways of oxidative stress, reactive oxygen species release, circadian rhythm with clock genes, and mitochondrial function. New avenues of investigation offer promise to assess the onset and progression of DM that involve artificial intelligence with machine learning and innovative imaging of the glymphatic pathway. ROS: Reactive oxygen species.

clock genes can alter mitochondria dynamics, the production and secretion of endocrine hormones that control motor function and cognition, skeletal muscle function, programmed cell death pathways with apoptosis and autophagy, cellular metabolism, and pathways of inflammation[12,28,30,31,42-44]. The glymphatic system may be necessary to remove ROS during oxidative stress and if the glymphatic system is impaired, this may lead to ROS accumulation, inflammation, and cellular injury that has been tied to major depression and cognitive impairment[39,45].

New technologies are now being applied to assess metabolic disease and the underling pathways that contribute to this disorder. One method involves artificial intelligence (AI) and machine learning. AI can be used for the diagnosis and clinical care of multiple disorders that include pulmonary fibrosis, obstructive pulmonary disease, and cancer[46-48]. Disorders of metabolism, such as DM, and cognitive loss are also coming into play for the application of AI such that AI may be able to predict the onset and progression of metabolic disorders. Machine learning methods have been used to assess the risk for development of metabolic disease or aging-related disorders in conjunction with circadian rhythm impairment[49,50]. The use of AI also has relied upon specific circadian rhythm clock gene assessment to identify patients with cancer into low-risk or high risk groups for improved prognosis[48]. Pathways involving Wnt proteins have come under evaluation with machine learning assessments. Wnt proteins are cysteine-rich glycosylated proteins that can control multiple processes throughout the body that involve both development and aging[3,19,51-55]. Using AI, Wnt pathways are being assessed that can involve oxidative stress o explore therapeutic strategies for vascular complications that can involve retinopathy, neuropathy, coronary artery disease, cerebrovascular disease, cancer, and cellular microglia [46-48,56,57].

In regard to complementary evaluations, assessments with magnetic resonance imaging (MRI) is now being proposed to monitor glymphatic function. Interestingly, prior work has reported the effects of biological magnetic fields on cellular metabolism, circadian clock pathways, neurogenesis, and microtubule assembly[58,59]. Diffusion tensor imaging, also known as diffusion-weighted MRI that employs the use of magnetic fields and generates images from data that uses the diffusion of water molecules to develop contrast in imaging, was used to assess the perivascular network of the glymphatic system of the brain in individuals with reported pre-DM, type 2 DM, and those without DM[1]. The study was noted to illustrate that those individuals only with type 2 DM had a decreased mass in regions of the brain such as the basal ganglia and changes in perivascular space (DTI-ALPS) in imaging when compared to those individuals with pre-DM and no DM and a potential tend in decline of cognitive function with type 2 DM individuals. The work is interesting and suggestive that metabolic disease in a clinical setting may impair the function of the glymphatic system. Prior work using diffusion tensor imaging and MRI that assessed the perivascular space (DTI-ALPS) found impairment in glymphatic function in patients with restless leg syndrome, a sleep and circadian rhythm disorder disease[37]. Yet, further studies are warranted since this work has several limitations that include a very small sample size, participants appeared to be from a single clinical site, some inclusion criteria may have introduced bias, standardization for imaging protocols is necessary, and the cognitive assessments are limited in nature.

CONCLUSION

DM is a devastating disease that is increasing in prevalence and leads to disability and death through the impact of the disease on multiple organs of the body, especially the nervous system. Multiple cellular pathways affect the onset and progression of DM that include oxidative stress, energy pathways, altered cellular metabolism, mitochondrial dysfunction, programmed cell death, Wnt proteins, inflammation, and circadian rhythm impairment that can ultimately affect a number of toxins in the body, such as through the glymphatic pathway. New processes and technologies are

necessary to assess the onset and progression of DM and the underlying pathological mechanisms that include the use of AI and MRI. These processes offer highly innovative tools to assist with basic science investigations and clinical care but at present are considered at an early stage in development and require further study and validation to blossom into robust resources for the care of patients.

FOOTNOTES

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Country of origin: United States

ORCID number: Kenneth Maiese 0000-0002-5049-9116.

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