

REVIEW

Implementation of Imaging Methods in Evaluation of T2DM-Related Brain Alterations and Cognitive Dysfunction

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ABSTRACT

Introduction: There has been mounting evidence that type 2 diabetes mellitus (T2DM) populations are prone to aberrant brain functionality and cognitive deficits. Hyperglycemic status and insulin resistance, among other factors, have been associated with compromised brain neural congruity, leading to lower cognitive performance. **Aim:** The aim of the present paper is to provide a comprehensive review of imaging techniques and their applicability in detection of brain changes in the setting of T2DM. **Method:** A search of PubMed electronic database was followed. Primary search terms included “imaging methods”, “type 2 diabetes” and “cognitive impairment”. **Results:** A range of imaging modalities that can be of value in depiction of diabetes-mediated structural and functional brain aberrations. **Conclusion:** An increasingly body of research points to the adverse effect T2DM exerts on brain integrity and higher cognitive skills. Findings support the role of imaging techniques in delineation of brain divergence in middle-aged and older diabetic populations.

Keywords: Imaging techniques, Type 2 diabetes, Cognitive impairment

1. INTRODUCTION

Diabetes mellitus (DM) represents a chronic metabolic disease characterized by increased blood glucose concentrations due to the following two mechanisms: inherited and/or acquired deficiency in insulin production or ineffective response of body cells to the insulin produced, called insulin resistance (IR) (1). Based on the International Diabetes Federation (IDF) latest suggestion, type 2 diabetes mellitus (T2DM), referred to as the maturity-onset non-insulin-dependent form, accounts for more than 90 % of diabetes cases (2).

Over its course, T2DM entails an increased risk of chronic complications, mainly in the form of macroangiopathy and microangiopathy. Nevertheless, research has recently focused on another T2DM-related long-term complication, which is cognitive impairment. Dysfunction in higher cognitive processes is a concept, covering a wide range of cognitive domains with vari-

ation in quality and severity of symptoms. This emerging condition often remains clinically undiagnosed, without being a recognizable symptom of the disease. A rapidly increasing body of literature is describing the cognitive decline in T2DM context, since the metabolic and vascular disturbances of the disease along with other additive or synergistic factors, seem to exert a negative impact on brain structural and functional integrity.

Brain correlates of T2DM-associated cognitive impairment, both structural and functional, can be detected with a range of imaging techniques. The latter are valuable tools not only as clinical diagnostic means but they can also contribute to quantifying even subtle brain changes.

Overview of imaging techniques applied in T2DM-associated brain changes and cognitive impairment.

Computed tomography (CT) and magnetic resonance imaging (MRI) modalities permit a non-invasive investigation of brain atrophy, global

and regional, its location, and progression rate. Still, these imaging tools are sensitive in the detection of ventricular enlargements and white-matter hyperintensities (WMHs), frequently met in diabetic subjects. T2DM is reported to be contributing to both global and regional brain atrophy in cortical and subcortical regions, according to a systemic review. The process of brain volume loss is potentially affected by the extent of brain infarcts, diabetes duration, glycemic control achieved, and the history of recurrent hypoglycemic episodes (3). The rate of brain atrophy in T2DM is a rather modest process evolving over the years with a standard deviation of 0.2–0.6 units compared to 3–5 years of normal aging (4).

In their work, Wallin et al. (5) point at two basic imaging methods; structural CT and MRI as well as imaging tools pointing to metabolic disturbances, namely positron emission tomography (PET) and single-photon emission computed tomography (SPECT). In particular, MRI is considered the cornerstone of diabetes research according to a recent systematic review. High-resolution MRI images allow for scientifically valid deductions regarding the complex interrelations among brain anatomy changes, functioning, and cognitive impairments in T2DM (6).

Structural MRI illustrates total and regional macrostructural volume changes, indicative of T2DM-mediated cerebral atrophy. Cortical thickness and signs of cerebrovascular disease can also be identified, all ascribed to T2DM-mediated brain cognitive pathology. Since diabetes itself constitutes a risk factor for vascular disturbances, an increased load of cerebrovascular events have been implied. This entails an adverse impact on higher cognitive processes given the fact that cerebrovascular disease has been related to the course of cognitive deterioration in the literature (7). Based on a surface-based cortical thickness analysis method, researchers provided evidence of disrupted integrity structure in the T2DM brain. They reported that administering insulin for one year had a positive impact on cortical thickness in terms of both white matter (WM) and gray matter (GM) enlargement (8). Meanwhile, another work (9) attempted to investigate the role of cortical thickness exerts on cognitive abilities. The authors concluded that higher rates of thickness in the cortex were positively linked to better cognitive outcomes.

Insight into primary processes mediating brain damage in diabetes is provided by measures of accelerated ventricular expansion illustrated with structural brain MRI. In a large cohort of older women, diabetes was independently associated with significantly greater ventricular volumes. The latter is considered an index of T2DM-associated brain tissue loss, prominent in WM areas nearby the ventricles or subcortical GM regions. Moreover, women with recorded diabetes were prone to greater mean ischemic lesion loads, in both GM and WM regions during the 4.7 years of follow-up. The aforementioned brain changes were consistently related to deficits in global cognitive performance as well as domain-specific cognitive abilities (10).

Concerning regional brain atrophy, MRI scans reveal

changes in GM and WM volume density alongside hippocampal atrophy in T2DM subjects. Authors claim that long-standing exposure to hyperglycemia is harmful to brain structures, leading to poorer cognitive skills. Hippocampal atrophy emerges as the earliest regional brain loss found in the disease, primarily responsible for memory deterioration. The reduced volume of the hippocampus in T2DM appears the dominant neurodegenerative process (11). A recently reported finding after assessing 120 non-demented subjects with long-lasting T2DM, addresses the notion of hippocampal asymmetric atrophy in association with cognitive dysfunction (12). Based on MRI imaging protocol, Hippocampal Asymmetry Index (HAI) score was measured. Authors claimed that hippocampal atrophy is disproportionate, appearing more pronounced in the right hippocampus. It was showed that this precipitates cognitive dysfunction procedures, as it was associated with deterioration in mental capacities.

Functional MRI (fMRI), an informative neuroimaging method, is increasingly utilized in illustrating brain health and function alterations in T2DM status. It provides valuable information concerning neuronal activity and functional connectivity (FC) at the whole-brain level. Disruptions of FC in the default mode network (DMN), a network of highly connected brain areas, have been implicated in global cognitive processing (13). Resting-state fMRI (rs-fMRI) detects cognitively associated reduced connectivity and hypometabolism at rest whereas task-based fMRI (task-fMRI) investigates affected FC during a task (for example reaction time task informative of the involved brain regions) (14). As a technique, rs-fMRI exemplifies the way whole-brain functional architecture is reorganized in diabetes, quite different from normal aging processes. Previous investigations on functional networks and connectivity conceptualizations in the middle-aged diabetic brain place emphasis on alterations in certain regions, namely modified long and short-range brain functional synchronization, as a compensatory mechanism to hyperglycemia-induced brain inadequacy along with poorer FC strength. All the previously mentioned factors have been related to diabetes-related impaired cognitive performance (15).

By employing functional connectivity density (FCD) analyses with rs-fMRI in T2DM populations aged 45–70 years, aberrant brain functional connections were proposed. More specifically, diabetics appeared to have more short-range connections whereas long-range ones were fewer compared to healthy controls (HC). These findings were further interrelated with lower scores in cognitive tasks in diabetics. The authors attributed these results in the diabetic brain to a potential compromise of brain network coherence to the detriment of losing cognitive functioning (16).

The notion of abnormal functional topological reorganization in the diabetic brain has further been exemplified in another study with the use of rs-fMRI modality (17). Authors considered properties of the functional whole-brain network (including cerebellum) in middle-aged T2DM subjects and HC concerning performance

in several cognitive tasks. Advanced cognitive processes, such as episodic and working memory besides language are pertinent to cerebellum function. Their investigation led to the conclusion that diabetics showed evidence of altered nodal brain dynamics with interrelations among different regions compared to controls. This deduction was further correlated with worse cognitive scores and HbA_{1c} ratio, as a clinical variable. Respectively, the cerebellum was characterized by increased functional engagement in an attempt to counterbalance the accelerated cognitive deterioration procedure (18).

By using rs-fMRI analysis and a whole-brain correlation method, it was detected that the posterior cingulate cortex (PCC), one of the DMN hubs, exhibited a reduction in FC in T2DM participants in comparison to HC. An association between abnormal regional activity in terms of decreased FC in the PCC and worse performance in several neurocognitive tests were established in T2DM subjects. This impairment has been related to brain IR along with a decreased spontaneous brain activity (19).

Still, a task-fMRI neuroimaging study (20) pointed to an interconnection between measures of glucose metabolism (blood fasting glucose) and DMN disruptions among others. Decrements in DMN regions in the T2DM context were hypothesized to lead to a decreased activation of task-associated regions and consequently to a default recognition network and poor information encoding. These, in turn, are considered prerequisites for the brain's response to cognitive tasks and optimal cognitive performance.

Brain graph theory method has been proposed as an increasingly prominent way of investigating the human brain connectome. It is perceived as a relatively simple way of illustrating structural or functional connections related to cognitive processes. Human brain graph analyses are valuable tools in the demonstration of key topological properties in the central nervous system (CNS) (21). Graph theory functional connectivity density mapping (FCDM) with rs-fMRI is being increasingly utilized in neuroscientific research. It is a prominent voxelwise data-driven graph modality that analyzes the complex brain networks and it delineates dynamic temporal FC changes at high spatiotemporal resolution. It quantifies the efficacy of the local FC hubs by exploring the way the regional network cluster is functionally related to a brain network node. The FC abnormalities detected are corresponding to the potency of brain connectivity hubs and the amplitude of fluctuations in rs-fMRI signal (22).

Regarding functional brain mapping with fMRI, most studies in diabetes are based on the blood-oxygen-level-dependent (BOLD) contrast technique. This modality uses deoxyhemoglobin (dHb) as an endogenous contrast agent since its local content is largely mediated by metabolic parameters. Reduced glucose metabolism in the T2DM brain is coupled with regional increases in BOLD contrast occurring in response to changes in neural activity (23). BOLD signal change in fMRI represents an index of change in blood flow and cerebrovascular reactivity (CVR). By using hypercapnia (increased blood CO₂ concentration) as a vasodilatory stimulus to pro-

voke increased blood flow, this method illustrates CVR abnormalities in terms of the way cerebral blood vessels respond to vasoactive prompts (24). Since the brain is considered a heavily perfused tissue, decrements in cerebrovascular functioning lead to inhibition of oxygen and glucose supply to the brain. Cerebral hypoperfusion and impaired CVR seem to pertain to the T2DM-associated trajectory of cognitive impairment (25). However, in cases of cerebrovascular disease accompanied by impaired vascular reactivity, BOLD contrast can be implemented by other methods. In such an occasion, a breath-holding test or CO₂ inhalation test can be useful in differentiating impaired neuronal activity from aberrant CVR leading to an attenuated BOLD response.

Advanced fMRI modalities permit dynamic cerebral blood flow (CBF) estimates detecting thus irrevocable parenchymal injuries and providing significant information regarding vital delivery of oxygen and nutrients to the brain. Impaired CBF is perceived as a risk factor of T2DM-related deficits in cognition since the insufficient blood supply to corresponding neurons attenuates neurocognitive performance (26). Changes in CBF most commonly develop and pre-exist before volumetric parameters become evident. T2DM-associated regional tissue perfusion deficits have been studied preferably with arterial spin labeling (ASL) (27). The latter is a non-invasive MRI tool having the advantage of quantitatively determining CBF alterations, neural, and vascular damage with relatively brief scan times, high temporal resolution, independently of exogenous tracers (28).

Nevertheless, more direct measurements of brain neuronal activity can be achieved by the implementation of electroencephalography (EEG) or magnetoencephalography (MEG) (4). Notably, quantitative EEG (QEEG) illustrates the structural and functional interplay of brain networks by registering rhythmic activity mainly evoked by the hippocampus (29).

QEEG and MRI volumetric investigation of the hippocampus were recently applied in elderly subjects of 55-85 years old (30). Participants were categorized as T2DM with cognitive impairment, T2DM with intact cognition, and HC. The researchers found that participants with T2DM and mild cognitive impairment (MCI) demonstrated an increased alpha 2 (high alpha)/alpha 1 (low alpha) power ratio compared to the other two groups. This ration was further seen as having a statistically significant positive interrelation with measures of hippocampal atrophy compared to other groups. Peak power frequency of alpha 2 over frontal, temporal, and cortical regions denote the involvement of cortico-thalamic re-entry loops, as several other areas of the cortex are gradually recruited. Alpha 1 prevalence, a marker of good memory performance, was found to be lower in the group of T2DM with MCI concerning the other groups. Additionally, the same body of participants exemplified significantly lower scores in cognitive assessment with the mini-mental state exam (MMSE) in relation to the other two groups. Cognitive deterioration in this group was associated with QEEG and hippocampal volume alterations.

Graph theoretical analysis and diffusion magnetic resonance imaging, applied in nondemented T2DM subjects, can provide valuable information regarding the human brain structure as a complex network. Disruptions in both global and regional connectivity of widespread brain areas in diabetes have been proposed as predictive markers of cognitive deterioration regarding information processing speed. The authors hypothesized that WM network abnormalities in the T2DM setting result as secondary consequences of diabetes-associated vascular damage. The structural network basis of cognitive dysfunction appeared as partly independent of cerebrovascular lesion load (31).

Lately, diffusion tensor imaging (DTI) has been applied in the investigation of microstructural WM changes, not visible on conventional MRI scans. It is an MRI technique sensitive to the quantification of subtle brain WM pathology, unraveling thus the structural and functional basis of diabetes-mediated cognitive decline. Primary DTI-derived metrics are: mean diffusivity (MD) reflecting the magnitude of water diffusion alterations due to damage to GM tissue density and fractional anisotropy (FA) measuring directionality of random water movement within fiber tracts. FA is a marker of WM integrity loss in terms of demyelination, reduced axonal coherence, and axonal membrane damage, secondary to vascular disease. The aforementioned disruptions in GM and WM microstructural integrity have been implicated in cognitive decrements in T2DM cases (32). Studies exploring fiber integrity based on DTI parameters found brain distortions in T2DM participants compared to HC. In diabetics reduced fiber integrity was the case. All tracts in both hemispheres in them displayed significantly increased MD, evidence of microstructural WM injury. More specifically increase in MD in frontal, temporal, and posterior fiber tracts were associated with slowing of information-processing speed whereas disruption of WM connections in the temporal lobe resulted in poorer memory function (32).

Other authors explored abnormalities in hippocampal FC and microstructural WM integrity by using both DTI and rs-fMRI imaging approaches. When compared to HC, participants with T2DM exemplified imaging markers reflecting brain injury and related changes in brain networks in terms of significant decrements in FC of the hippocampus with other brain regions along with pronounced WM disruptions. Hence, cerebral damage in diabetes has been proved as a strong correlate of cognitive performance (33).

In brain structure study, fiber tractography has been introduced as a valuable tool in the diabetes setting. This imaging method allows for the evaluation of WM integrity in isolated tracts, affected by the disease (32). Diffusion tensor tractography measurements in T2DM have revealed findings of impaired FA in all WM tracts, verifying thus widespread cerebral WM damage. The authors claimed that impairment of WM integrity in diabetes may be associated with clinical variables which negatively influence vascular health and metabolic parameters (34).

An extension of the DTI method, diffusion kurtosis imaging allows for a more detailed description of microstructural changes in the CNS. It is a recognizable promising means concerning the early diagnosis of neurodegenerative diseases (35). Based on diffusion kurtosis imaging techniques, microstructural changes in WM and GM integrity have been detected in diabetic patients compared to controls. It has been proposed that reduced microstructural integrity and microvascular lesions in diabetes could be attributed to poor disease control. Thus, stabilization in the rate of brain atrophy could be achieved by optimal glycemic control of diabetes (36).

Brain volume assessment can be achieved with the use of visual rating scales depicting brain atrophy in a qualitative but rather insensitive way (37). Automated segmentation approaches, namely voxel-based morphometry (VBM), probabilistic tissue classification and surface-based parcellation techniques have also been applied in quantitative brain volume assessment. These are considered the methods of choice in relation to diabetes context, as they appear more sensitive in eliciting even subtle brain changes in GM and WM volume at early disease stages (38).

Observations on T2DM-mediated brain atrophy and ischemic white matter lesions (WMLs) concerning cognitive ramifications have been provided by following an MRI-based automated segmentation algorithm (38). In this work, authors tried to elucidate the effects T2DM exerts on cerebral volumes and WMLs severity. By comparing diabetics over 55 years old with control participants, they found significantly greater WML volumes in diabetic subjects. Moreover, lower GM volumes, indicating cortical atrophy and greater lateral ventricle volumes, a marker of subcortical atrophy, were verified in diabetic cases. Authors concluded that lower total brain volume and larger WML volumes were interconnected with worse performance in a wide range of cognitive skills in the T2DM setting.

Magnetization transfer (MT) imaging as a method is based on magnetization transfer from saturated protons bound to macromolecules to free protons in tissue water. This magnetization exchange defined as magnetization transfer ratio (MTR) permits investigation of WM and GM abnormalities. Lower MTR characterizes WM disruptions, such as axonal loss and myelin injury while in GM it points to membrane damage, reduced dendritic density and neuronal size (14).

Even though magnetization transfer imaging has not been widely utilized in the T2DM literature, Yang et al. (14) claimed that diabetics had a significantly lower MTR in node regions of frontal-subcortical circuits, such as bilateral anterior cingulate and head of the right caudate nucleus compared to control subjects. These imaging findings were positively associated with clinical measures (HbA1c level), vascular risk factors, and performance in cognitive tasks. Cognitive correlates referred to the domains of learning, memory, attention, information processing, and executive functioning.

Another valuable magnetic resonance-based technique is magnetic resonance spectroscopy (MRS) per-

mitting non-invasive investigation of the trajectories of metabolite brain changes (6).

Additionally, PET represents a radioligand-mediated flexible technique regarding brain metabolic abnormalities. By using ^{18}F -2-fluoro-deoxy-D-glucose (^{18}F -FDG), a glucose analog, FDG-PET-CT depicts cerebral glucose metabolic rate and the earliest impact of IR on the brain in vivo. Tracer concentration indicates brain tissue metabolic activity, corresponding to regional glucose uptake. Cerebral glucose hypometabolism signifies an index of dysfunction in terms of neuronal and synaptic functioning along with quantification of degenerative changes in the brain (39).

Abnormalities in brain metabolic rate of glucose uptake have been argued in studies depending on ^{18}F -FDG PET-CT methods. A subsidiary maximum standardized uptake value (SUV_{max}) of glucose in the diabetic brain was suggested. In this work, authors proposed that this ramification could be attributed to diabetes poor glycemic management (40). A further study employed ^{18}F -FDG-PET and voxel-based morphometry to assess brain glucose metabolic changes and GM quantity respectively. Decreased glucose metabolic ratio and GM density were reported in a group of middle-aged and well-controlled T2DM compared to controls. To a large extent, these abnormalities were found in the orbital and prefrontal cortex alongside temporal and cerebellum areas. In the diabetic group, lower performance in cognitive tasks was interlinked to the aforementioned brain alterations (41).

A similar imaging process using radiotracers, SPECT is useful in assessing CBF in conjunction with diabetes. Alterations in brain activity and CBF measures serve as indicative imaging markers of cerebral injury interrelated to pathophysiological substrates and clinical parameters (42).

Transcranial Doppler ultrasound (TCD), a modality with high temporal resolution capacity, can also be valuable in evaluating CBF and in detecting possible aberrations in its function (24).

2. CONCLUSION

Cognitive impairment in the T2DM context is nowadays coming under greater scrutiny, as the disease prevalence steadily increases due to population growth and older age relates to neurocognitive difficulties. Imaging modalities have been increasingly utilized in clinical practice since they are valuable tools in the detection and evaluation of T2DM-mediated structural, functional, and metabolic brain abnormalities. Hence, they hold the promise of serving as early diagnostic markers, assessing brain alterations and risk for cognitive dysfunction in diabetic subjects.

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