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REVIEW ARTICLE

MRI brain findings in patients with depression and type 2 diabetes – a scoping review

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Background: The incidence of depression is increased by 200–300% in patients living with diabetes mellitus (DM), with both conditions overlapping in about 10–15% of patients.
Methods: A scoping review was conducted through reputable medical search engines to find articles that mentioned an association between magnetic resonance imaging (MRI) brain findings in patients with concurrent depression and type 2 diabetes mellitus (T2DM).
Results: There were 12 studies found (with 8 790 patients) with publication dates ranging from 2007 until 2020. Most studies utilised a cross-sectional study design with the mean age ranging between 53.8 and 74.5 years. The associations between depression and T2DM varied across the studies, with both comorbidities independently shown to decrease brain size. Two studies suggested that DM decreased the size of the brain (independent of depression), while two other studies suggested that comorbid DM and depression decreased the size of the brain. In addition, decreased myo-inositol concentrations, cerebral hypoperfusion, and abnormal electrical activity of the brain were also observed in those patients with comorbid DM and depression, which differs from patients without these comorbidities.
Conclusion: We recommend that future prospective studies be conducted to establish a consensus on how these comorbidities affect the brain.

Keywords: diabetes, depression, MRI, neuro-imaging

Background

According to the World Health Organization (WHO), there are approximately 422 million patients living with diabetes (PLWD) worldwide.[1] Approximately 90% of the PLWD have type 2 DM (T2DM).[2] According to the Centers for Disease Control and Prevention (CDC), PLWD have a 200–300% higher incidence of depression compared with those without diabetes, and only 25–50% of these patients receive treatment.[3] Furthermore, the WHO estimates that there are approximately 280 million patients who currently have depression.[1] According to Sartorius, around 10–15% of patients experience an overlap between depressive disorders and diabetes mellitus (DM).[4] In addition, poor glycaemic control has been found to increase the odds of depression,[5] highlighting the importance of good glycaemic control and avoidance of the risk of depression.

Depression is strongly linked to suicidal ideation and attempts.[6] Orsolini *et al*. suggest that patients diagnosed with major depressive disorder (MDD) have an incidence of suicidality of around 15%.[7] Additionally, this can impact family members who may have poorer overall health and experience more pain,[8] demonstrating the disease burden associated with caring for a loved one with depression.

Age-related brain changes are important to consider. Certain regions of the brain shrink, especially those required for learning and performing complex mental activities.[9] Depression has been found to have a lower prevalence in older adults as compared with younger adults.[10] Compared with younger patients, elderly individuals are less likely to exhibit affective symptoms, but more likely to display cognitive changes, somatic symptoms, and loss of interest.[10] Research has demonstrated that the impact of depression on the brain is more significantly affected by its duration rather than the patient's age.[11]

The impact of medication on the brain cannot be ignored. A longitudinal study published in 2021 evaluated the effects of antipsychotic medication and illness on brain volumes and concluded that both psychotic illness and antipsychotic medication have distinct and spatially distributed effects on brain volume.[12] Regarding diabetes, some patients with T2DM have shown improvement in cognitive or mood functions when treated with metformin.[13] Metformin has also been found to have positive effects on various neurological conditions, including major depressive disorder, but the underlying mechanism is not yet completely understood.[13] Additionally, insulin contributes to brain function by regulating nutrient homeostasis, cognitive processes, and memory and by exerting neurotrophic, neuromodulatory, and neuroprotective effects.[14]

Magnetic resonance imaging (MRI) studies have demonstrated reduced brain activity in the hippocampus among patients with depression.[15] Furthermore, other changes have been observed, including reduced brain volume in depression, as demonstrated by Trifu *et al*. when comparing patients with and without depression,[16] as well as vascular-related depression, which was emphasised by George *et al*.[17] Changes in cognitive function and brain structure have been linked to DM, with patients experiencing a decrease in both.[18] Additionally, DM is a known risk factor for the development of vascular disease, which can lead to strokes.[19] Post-stroke depression, which affects approximately one-third of patients, is another mechanism by which depression is linked to DM,

and can result in poorer recovery, decreased quality of life, recurrent vascular events and even mortality.[20] In a previous PubMed summary article from 2010, McIntyre *et al*. examined the association between mood disorders and diabetes.[21] While that article is similar to the present scoping review in some respects, McIntyre *et al*. focused on mood disorders and discussed various types of diabetes while the current article concentrates on depression and T2DM, given its higher prevalence.

Aim

The aim of this scoping review was to provide a summary of articles that focused on the MRI brain findings of patients with comorbid depression and T2DM.

Methods

Scoping reviews aim to synthesise data on a specific topic,[22] with Mak and Thomas outlining five main steps (and one optional step) for conducting a scoping review. These steps include identifying the research question (Step 1) and selecting relevant studies (Steps 2 and 3), charting the data (Step 4) and collating, summarising, and reporting the results (Step 5).[22] The optional sixth step involves discussing the results with stakeholders.[22] The current scoping review was conducted following this methodology. If an article was identified in multiple sources during the search process, it was excluded from consideration to avoid duplication in the review.

The responsibility of data extraction, which involved screening of titles, abstracts, and full-text articles, was divided between two authors. A third author (SP) participated in the synthesis and analysis of the data to ensure its accuracy.

Search terms and data sources

For this scoping review, data were collected using online search engines, which found research articles from medical journals. The search engines Cochrane, PubMed and Scopus were utilised to search for articles. The following terms were used to conduct the search: ('MRI' OR 'Magnetic Resonance Imaging') AND ('depression' OR 'major depressive disorder' OR 'MDD') AND ('Diabetes' OR 'type 2 diabetes'). Variations of diabetes, e.g. 'Diabetes Mellitus' or 'adult-onset diabetes' or 'insulin-dependent diabetes', were not used in searches as a keyword because the root word 'diabetes' was still present in alternatives that picked up other articles. Searches were refined using the 'intext' function which excluded articles where keywords were present in the articles' references.

Articles that presented an association between MRI findings in patients diagnosed with 'depression', 'depressive disorder', or 'depressive symptoms' and T2DM were included and the observed associations were reviewed. Case studies were excluded from the scoping review. Any studies not containing T2DM were excluded, e.g. type 1 diabetes, gestational diabetes, diabetes insipidus, etc. A brief Google search was also conducted for completeness to detect other potential articles that met the inclusion criteria.

Data synthesis

As of 30 January 2023, 482 articles were identified using the aforementioned search terms on the medical search engines (Scopus = 284; PubMed = 124; Cochrane = 74). An additional 20 articles were screened through a Google search. The articles were screened via their title; any articles that did not meet our criteria were eliminated. Thereafter, screening was done through the article's abstract. If the abstract suggested that the article met our inclusion criteria, the full article was read. Articles that contained a cohort of patients living with type 2 diabetes and had MRI findings which showed a relationship with depression were kept aside. The articles were then read in full to establish the relationship that was utilised in this study (Figure 1).

A total of 12 articles were obtained that met our inclusion criteria and these are summarised in Table 1.

Results

Demographics of the different studies

There was a total of 12 studies that met our inclusion criteria and included 8 790 participants from the various studies. These studies were published between 2007 and 2020. One

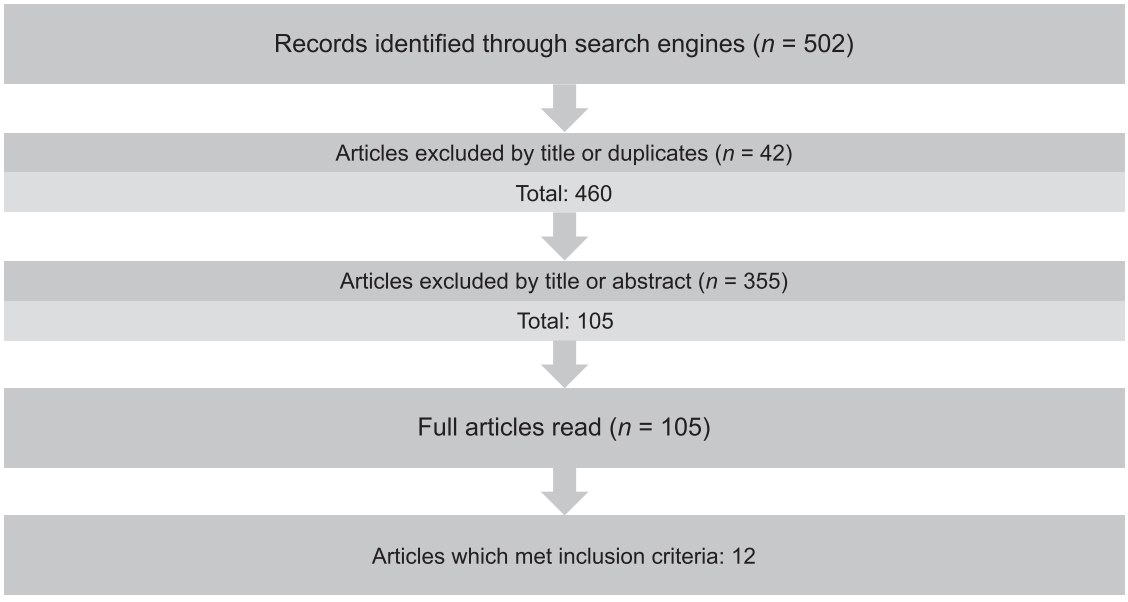

Figure 1: Flow diagram showing how articles were obtained for the study

Table 1: Articles included in the scoping review

Article no.	Author	Year of publication	Country	No. of participants	Mean age in years (SD)	On DM treatment	On antidepressants	Comorbidities	Gender	Type of study	Associations found relevant in this scoping review
1	Bands et al.[23]	2007	Netherlands	174	65.9 (5.7)	Yes	Not recorded	Vascular comorbidities and mood disorders included but other neurological and psychiatric conditions excluded	49.4% male	Cross-sectional	Patients with T2DM had higher Beck Depression Inventory and 'worse MRI ratings than controls'
2	Ajilore et al.[24]	2007	USA	65	56.6 (10.2)	Yes	Free of antidepressants > 2 weeks	Patients were excluded if they had other pre-determined comorbidities	26.2% male	Not stated	Myo-inositol concentrations were decreased in depressed diabetic patients in the frontal white matter
3	R Kumar et al.[25]	2008	Australia	478	60–64*	Yes	Not recorded	Not excluded	51.8% male	Cross-sectional	DM has increased brain atrophy and larger CSF volumes in 60–64-year-old patients, independent of depression
4	A Kumar et al.[26]	2008	USA	77	55.5 (9.6)	Yes	Free of antidepressants > 2 weeks	Other medical/ neurological and psychiatric conditions excluded	Not stated	Cross-sectional	PLWD had smaller total brain grey matter volumes regardless of whether they had depression, compared with controls
5	McIntyre et al.[21]	2010	Various countries	4858	Varied between studies	Varied between studies	Varied between studies	Varied between studies	Not stated	Summary article	'The pattern of volumetric and neurocognitive deficits in diabetic populations are highly similar to that reported in populations of individuals with major depressive disorder'
6	Ajilore et al.[27]	2010	USA	72	55.5 (9.7)	Yes	Free of antidepressants > 2 weeks	Excluded unstable medical patients and neurological conditions	26.4% male	Not stated	DM and depression are associated with cortical grey matter thinning in the medial prefrontal area
7	Cui et al.[28]	2014	Israel	69	65.5 (8.7)	Yes	Not mentioned	No exclusion criteria	49.3% male	Cross-sectional	T2DM was associated with greater variability, more depression and less grey matter in the limbic and temporal-parietal lobes (e.g. cingulum, insular, hippocampus)
8	Hsu et al.[29]	2016	USA	604	57.7 (9.3)	Yes	Not mentioned	No exclusion criteria	40.1% male	Not stated	In T2DM, adiposity is inversely associated with brain volumes and positively associated with depression in European Americans

(*Continued*)

Table 1: Continued.

Article no.	Author	Year of publication	Country	No. of participants	Mean age in years (SD)	On DM treatment	On antidepressants	Comorbidities	Gender	Type of study	Associations found relevant in this scoping review
9	Jansen et al.[30]	2016	Netherlands	80	61.1 (9.5)	Yes	Not mentioned	Non-dementia patients	56.3% male	Cross-sectional	The effect of T2DM on cerebral blood flow (CBF) is small (independent of cerebral atrophy) Subcortical CBF is positively associated with depression
10	Zhang et el.[31]	2019	China	56	53.8 (8.1)	Not stated	Not mentioned	Other psychiatric and vascular conditions excluded	60.1% male	Cross-sectional	Increased depression and abnormal spontaneous activities in regions of the brain were found in patients with T2DM with neuropathy
11	Roy et al.[32]	2020	USA	122	56.8 (7.1)	Yes	Not mentioned	Other medical, psychiatric and neurological conditions were excluded	50.0% male	Not recorded	Decreased grey matter volumes (in prefrontal, hippocampus, amygdala, insular, cingulate, cerebellum, caudate, basal forebrain, and thalamus areas) were seen in DM Decreased grey matter was significantly associated with depression
12	Rensma et al.[33]	2020	Iceland	2135	74.5 (4.6)	Not stated	On treatment	Patients with dementia were excluded	41.7% male	Longitudinal	T2DM is associated with increased depressive symptoms and cerebral small vessel disease

*Age range, not standard deviation.

Table 2: Summary of countries and number of articles published.

No.	Country	Number of studies
1	USA	5
2	Netherlands	2
3	China	1
4	Iceland	1
5	Australia	1
6	Israel	1

article was a summary article published in 2010[21] while the other 11 articles were original research publications. Most of the articles were published in developed countries, with all (except Israel) being from upper-income countries. The USA and Netherlands both published more than one article on this topic with five and three articles, respectively.

Most articles published had cross-sectional study designs (57.1%) while only one article (7.1%) was a longitudinal study. The other articles did not comment on the study design utilised in their study (Table 2).

Other relationships between depression and T2DM

Varying relationships existed between T2DM and depression. Some studies assessed the size of the brain while others assessed electrolyte concentrations, blood flow, or electrical activity in the brain.

The volume of the brain varied across the different studies conducted. Two studies suggested that DM decreased the size of the brain, independent of depression[25,26] while two other studies suggested that comorbid DM and depression decreased the size of the brain.[27,32] One study suggested that DM decreased the size of the brain and was associated with depression; however, it did not mention the combined effect of DM and depression on the size of the brain.[28]

Other associations suggested that decreased blood flow to the brain in the sub-cortical regions was positively associated with depression[30] and that T2DM led to cerebral small vessel disease.[33] Moreover, alterations of neurochemistry also occurred, with studies finding decreased myo-inositol concentrations and other biomarkers in different regions in patients with both DM and depression.[24]

The patients who were on medication varied among studies. Regarding DM treatment, 75% of the studies had patients on treatment; the other 25% either did not comment on this association (or comprised the summary article). With regard to antidepressant medication, 25% of studies had patients free of antidepressants for greater than two weeks while the other studies did not comment on this association.

Discussion

Several previous studies have been conducted that identified MRI associations between depression and T2DM. Varying associations highlighted the lack of consensus that occurred in this cohort of patients.

The variations in brain size observed in patients with comorbid T2DM and depression raise questions concerning the individual impact of each condition, as well as their combined effect. Esplelend *et al*. discovered that T2DM was associated with smaller grey matter and increased ischemic lesions in the brain, but not white matter.[34] A meta-analysis of patients with T2DM further found that it could accelerate cognitive decline and brain ageing.[35] Similarly, decreased brain volumes have been reported in depression, with studies identifying reduced volumes in the rostral and dorsal anterior cingulate gyrus.[36] A 2021 quantitative meta-analysis also demonstrated reduced brain volumes in the grey matter of individuals with first-episode major depressive disorder.[37] This suggests that decreased brain matter may be a shared feature of both depression and DM. However, these findings do not explain why depression did not reduce brain size in the studies conducted by Kumar *et al*.[25] and Kumar *et al*.[26] It has been suggested that depression may lead to variations in brain size that affect patients with different comorbidities differently, with larger brain volumes found in patients with comorbid anxiety, according to a meta-analysis.[38] Given that normal brain ageing is associated with various structural changes, which can be visualised using MRI, it is possible that the participants' age (mean age greater than 50 years) may have contributed to the changes observed in this review.[39] While the additive effects of the structural changes that occur in the ageing brain have been acknowledged, there is still a significant gap in our understanding of the interaction and implications of these changes.[40]

Abnormal cerebral blood flow changes have been observed in patients with depression, which is thought to result in a dysfunctional state due to decreased blood flow rates that can limit the delivery of oxygen and nutrients to the brain.[41] This has led to the development of the 'vascular depression hypothesis' which is associated with late-life depression.[42] The findings from the study conducted by Jansen *et al*. could potentially be explained by this hypothesis.[30] Furthermore, DM is a well-known risk factor for vascular disease[43] and has been found to increase the incidence of depression,[44] further supporting the idea of the 'vascular depression' hypothesis.

The studies reviewed also revealed neurochemical alterations. Myo-inositol, an abundant brain metabolite that functions as an osmolyte, was found to be decreased in the prefrontal region of individuals with depression.[45] DM exacerbates this reduction by causing an increase in myo-inositol breakdown and elimination, as well as a decrease in tissue levels due to elevated glucose levels.[46] These findings may help explain the results reported by Ajilore *et al*.[24]

Assessing other comorbidities and variables in patients was challenging. However, most of the studies excluded other conditions that could have had a confounding effect on the results. In some articles, patients were required to be free of antidepressants for at least two weeks before the study to ensure that the true nature of the brain was examined. Discontinuing antidepressants too quickly can increase the risk of withdrawal symptoms and potentially lead to a relapse or worsening of depression.[47] This highlights some of the risks associated with non-adherence. Fortunately, this was not an issue for patients with DM who were generally on treatment during the studies.

The main limitation of using imaging is that neurological disorders are multifaceted and can be influenced by various other factors, such as concurrent disease and artefacts. There have been varying opinions on the use of MRI in depression. A 2019 review article found that some studies suggest MRI can help exclude structural causes while other studies explore

functional uses of MRI, such as the use of biochemical markers to predict the prognosis of depression and monitor treatment efficacy.[48] Although research in this area is still emerging, further studies to understand MRI changes in depression, particularly in the context of DM, could help establish more practical applications for imaging in these conditions.

In the above studies, all were done in countries outside of Africa, with the majority conducted in the USA. This is likely due to limited resources in Africa where many hospitals are unable to perform MRI scans. With this paucity of data and backgrounds different from Western societies, it would be useful to attempt to find additional associations in these lower-to-middle-income countries to increase our knowledge on this topic and see if any additional associations are found.

Conclusion

The associations found between brain findings in patients with depression, and T2DM varied across studies, with most studies utilising cross-sectional designs. We suggest that further prospective studies be conducted to establish a consensus on how these comorbidities affect the brain.

Limitations

- Difficult to establish causal relationships due to some studies having patients with multiple comorbidities.
- Articles are still being added on a daily basis, so newer evidence is likely to be available in the foreseeable future.
- Search engines were limited to those mentioned previously.

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