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Metformin use and brain atrophy in nondemented elderly individuals with diabetes☆

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ABSTRACT

Objective: There is a shred of growing evidence demonstrating that diabetic patients are at higher risk of developing Alzheimer's disease compared to the general population. The previous investigation showed the protective effect of metformin for delaying dementia in diabetic patients. However, there are limited data on the effect of metformin on structural changes. This study aims to investigate the effect of metformin on hippocampal and cortical volumes in non-demented diabetic individuals.

Method: We entered 157 non-demented diabetic subjects including 89 mild cognitive impairment (MCI), and 68 cognitively healthy individuals from Alzheimer's disease Neuroimaging Initiative (ADNI) which were then categorized as metformin users and non-users. We used the ANCOVA model for measuring the association between metformin use and hippocampal and cortical volumes.

Results: Among 157 subjects with a mean age of 71.8 (±7.7) included in this study, 76 individuals were stratified as metformin users. Results of the univariate model indicate that metformin users had a higher right ($p = 0.003$) and left parietal lobe volume ($p = 0.004$). Moreover, the volume of left cingulate was higher in those who used metformin compared to those not used it ($p = 0.027$). Our results were also significant for the right frontal lobe and indicated that metformin users had higher volume ($p = 0.035$). There were no significant differences in the hippocampus, occipital, and temporal regions.

Conclusion: Our findings showed the protective effects of metformin on brain volumes in non-demented elderly individuals with diabetes. Comparing the groups show strong enough results regarding the lower atrophy in metformin users.

1. Introduction

Due to population aging growth, the increased risk of neurodegenerative diseases related to aging such as Alzheimer's disease (AD) is expected (Ping et al., 2020). AD is the most common cause of dementia with rising incidence, which corresponds to about 50 % to 75 % of cases of dementia (Hodson, 2018).

Over time, numerous epidemiological and clinical studies, demonstrate that diabetic patients are at higher risk of developing AD compared to the general population (Gudala et al., 2013). The pathophysiological mechanism behind this association is multifactorial. As insulin plays an important role in the brain including neuroinflammatory response, synapsis, glial cells, and neuron metabolism, there is a growing interest in the link between insulin resistance and AD (Arnold et al., 2018). Also, several studies have shown the potential role of insulin resistance in Amyloid βeta (Aβ) deposition and tau phosphorylation which are pathophysiological hallmarks of AD (Sato and Morishita, 2015; Kellar and Craft, 2020).

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Metformin is the most common oral anti-diabetic drug which positively affects serum lipid profiles, inflammatory process, and antioxidative mechanism (Markowicz-Piasecka et al., 2017). A systematic review and meta-analysis conducted in 2018 showed the protective effect of metformin in delaying dementia among diabetic patients, but there is not enough evidence to support the use of metformin to treat AD in non-diabetic patients (Campbell et al., 2018). Another systematic review revealed that metformin may improve cognition, AD biomarkers including plasma and cerebrospinal fluid Aβ40 and Aβ42, cerebral blood flow (CBF), and imaging parameters in AD patients (Muñoz-Jiménez et al., 2020).

Magnetic resonance imaging (MRI) is a crucial tool for understanding the pathophysiology and also clinical identification of AD and mild cognitive impairment (MCI) (Chandra et al., 2019). MRI can show the AD-related changes several years before the onset of disease symptoms. Studies have shown atrophy in the medial temporal lobe including a reduction in entorhinal, amygdala, parahippocampal and hippocampal volumes as a consequence of AD (Ledig et al., 2018). Moreover, MRI can be used for monitoring the disease progression and predicting future clinical manifestations (Chandra et al., 2019).

Although the previous studies are promising regarding the use of metformin in AD and MCI patients, there is a need for further studies to investigate the therapeutic effect of metformin in MCI and AD or its role in delaying the onset of disease. There are also limited data on the effect of metformin on structural changes (Muñoz-Jiménez et al., 2020; Koenig et al., 2017). Thus, further research is warranted to find out if there is an association between metformin use and positive structural changes in AD and MCI patients. This study aims to investigate the effect of metformin on hippocampal and cortical volumes in non-demented diabetic individuals.

2. Materials and methods

2.1. Data acquisition

The participants' information was collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI, which was led by the principal investigator, Michael W. Weiner (MD), was launched in 2003 as a public-private partnership. The primary goal of ADNI was to determine whether serial MRI, positron emission tomography (PET), biological marker examinations, and clinical/neuropsychological assessments can be combined to measure the progression of MCI and early AD. We enrolled 157 non-demented diabetic subjects including 89 MCI and 68 cognitively healthy (CH) individuals. Participants were stratified as metformin users if they had drug use for at least two years and the other subjects were considered as metformin non-users. We entered subjects whose all required variables such as the diagnostic status, Mini-Mental State Examination (MMSE) score, and the result of apolipoprotein E gene (APOE) genotyping were available at ADNI. All MCI subjects were diagnosed as amnestic MCI based on the following criteria: this diagnostic classification required Mini-Mental State Examination (MMSE) scores between 24 and 30, a memory complaint, objective memory loss measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, absence of significant impairment in other cognitive domains, essentially preserved activities of daily living and absence of dementia.

2.2. Image analysis and MRI processing

The FreeSurfer image analysis suite was used for Cortical reconstruction and volumetric segmentation, which is freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Briefly, the processing can be summarized in motion correction and averaging of multiple T1-weighted images, removal of non-brain tissues, automated Talairach transformation, segmentation of subcortical white matter and gray matter structures, automated topology correction, and intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction. We used the ADNI date run with FreeSurfer version 5.1. In ADNI, two T1 weighted images are acquired for each subject—an accelerated and a non-accelerated acquisition. Mayo Clinic pre-processed both of these images. The overview of processing has three steps: in the first step, the "autorecon-1" command initiates these tasks: 1) Motion correction and registration 2) Non-Uniform intensity normalization (NU) 3) Talairach transform computation 4) Intensity Normalization 1Skull Strip. In the second step, Autorecon-2, the creation of the White-Matter and Pial surfaces as well as segmentation of the gray and white matter, and the subcortical structures are performed. In the third step, the –autorecon3 command creates the cortical parcellation. To reduce type I error due to multiple comparisons we identified six regions of interest including temporal, frontal, parietal, occipital lobe, hippocampus, and cingulate.

2.3. Cognitive measurements

Mini-Mental State Examination (MMSE) was used to assess cognitive function and thinking ability. This test measured skills like memory, language use, comprehension, and basic motor. Each subject's MMSE score was acquired from ADNI. Scores more than 24 in MMSE indicate normal cognition but, scores below 9 points can show severe cognitive impairment. We also obtained the Montreal Cognitive Assessment (MoCA) score of participants which included 30 questions and was used to assess dementia. Also, the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) to evaluate the level of cognitive dysfunction.

2.4. APOE genotyping

The participant's status of APOE ε4 genotyping was available at ADNI. Subjects with at least one ε4 allele considered carriers. More details about the procedure are described: http://adni.loni.usc.edu/methods/documents/.

2.5. Statistical analysis

The SPSS statistics version 16 (IBM Corp., Armonk, NY) was used for statistical analyses. The clinical and demographical comparison between groups stratified by metformin exposure was done using the *t*-test for continuous variables and X^2 for categorical variables. Before the statistical analyses, the neuroimaging variables log-transformed to ensure of meeting normal distribution criteria. The association between metformin exposure and neuroimaging parameters was assessed using the ANCOVA model adjusted for age, sex, APOE ε4 genotype, cardiovascular conditions (hypertension, diabetes, hypercholesterolemia, coronary artery disease, and dyslipidemia), and cholinesterase inhibitor use. For addressing type I error due to multiple comparisons the Benjamini Hochberg correction was used.

3. Results

Among 157 subjects with a mean age of 71.8 (±7.7) included in this study, 76 individuals were stratified as metformin users. The clinical and demographical characteristics of the subjects were detailed in Table 1. There are also no differences in demographic characteristics except age ($p = 0.006$) between metformin users and non-users (Table 1). Comparing the cognitive function between groups showed that metformin users had better performance in ADAS-cog 11 ($p = 0.001$) and ADAS-cog 13 ($p = 0.007$) but there was no difference in MMSE and MoCA scores.

We conducted a univariate linear model to compare hippocampal and cortical volume between metformin users and non-users. The analyses were adjusted for age, sex, APOE ε4 genotype, cardiovascular

Table 1
Summary characteristics classified by metformin use.

Demographics	Metformin non-users ($n = 81$)	Metformin users ($n = 76$)	p value
Age, years, mean (SD)[a]	70.2 (6.8)	73.6 (8.2)	0.006
Sex (male/female)[b]	44/37	36/4	0.385
MMSE score[a]	27.9 (2.1)	28.4 (1.5)	0.117
ADAS-cog 11 item score, mean (SD)[a]	9.9 (5.4)	7.4 (3.5)	0.001
ADAS-cog 13 item score, mean (SD)[a]	15.3 (7.6)	2.0 (5.8)	0.007
MoCA score, mean (SD)[a]	23.4 (4.0)	24.3 (2.8)	0.217
Education, years, mean (SD)[a]	16.1 (2.5)	16.5 (2.6)	0.292
APOE ε4 genotype (carriers/non-carriers)[b]	25.47	25.5	0.862

MMSE: Mini-Mental State Exam, ADAS-cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale, MoCA: Montreal Cognitive Assessment.
[a] Continues variables.
[b] Categorical variables.

conditions, and cholinesterase inhibitor use.

Results of the univariate model indicate that metformin users had a higher right ($p = 0.003$) and left parietal lobe volume ($p = 0.004$), (Table 2). Moreover, the volume of left cingulate was higher in those who used metformin compared to those not used it ($p = 0.027$). Our results were also significant for the right frontal lobe and indicated that metformin users had higher volume ($p = 0.035$). There were no significant differences in the hippocampus, occipital, and temporal regions. The significant results are visualized in Fig. 1.

4. Discussion

In the present study, we investigated the effect of metformin on the volume of the hippocampus and cortical regions. Analyses were performed on non-demented diabetic patients. Overall, the metformin users had higher volume in different regions which shows its protective effect on atrophy.

Recent evidence showed type 2 diabetes mellitus as a major risk factor for neurodegenerative diseases such as AD (Akimoto et al., 2020; Picone et al., 2016; Chen et al., 2009; Cardoso and Moreira, 2020; Kuan et al., 2017). This has prompted many studies to investigate the therapeutic effect of anti-diabetic agents in the course of AD (Muñoz-Jiménez et al., 2020; Koenig et al., 2017). Insulin resistance, impaired glucose metabolism, and mitochondrial dysfunction were suggested as an explanation for the direct link between AD and type 2 diabetes mellitus (Picone et al., 2016; Cardoso and Moreira, 2020; Bendlin, 2019). Increased insulin resistance in brain regions such as the hippocampus, and cerebellar has been also reported in AD patients (Akimoto et al., 2020).

Table 2
Neuroimaging markers in metformin users and non-users within ANCOVA models.

Variable	Metformin non-users ($n = 81$)	Metformin users ($n = 76$)	p value
Right hippocampus, mm^3, mean (SD)	3632.0 (505.0)	3670.5 (572.9)	0.263
Left hippocampus, mm^3, mean (SD)	3586.0 (500.4)	3619.2 (539.4)	0.405
Right temporal, mm^3, mean (SD)	39,090.7 (6502.5)	39,968.9 (4759.4)	0.149
Left temporal, mm^3, mean (SD)	39,292.4 (6444.3)	40,090.1 (4717.1)	0.185
Right cingulate, mm^3, mean (SD)	9058.0 (1278.3)	9373.7 (1217.5)	0.1
Left cingulate, mm^3, mean (SD)	9453.5 (1465.7)	9860.4 (1355.3)	0.027
Right parietal, mm^3, mean (SD)	53,572.3 (7267.7)	56,022.8 (5886.0)	0.003
Left parietal, mm^3, mean (SD)	51,766.4 (6883.3)	53,973.4 (5631.8)	0.004
Right frontal, mm^3, mean (SD)	70,439.4 (7776.4)	72,223.7 (6920.8)	0.035
Left frontal, mm^3, mean (SD)	71,392.9 (7922.4)	72,826.7 (6952.4)	0.068
Right occipital, mm^3, mean (SD)	21,680.7 (4151.3)	21,889.2 (2861.4)	0.422
Left occipital, mm^3, mean (SD)	20,826.3 (3802.5)	21,159.0 (2830.4)	0.291

p value as defined using ANCOVA models adjusted for age, sex, APOE e4, cardiovascular condition, and cholinesterase drugs use.

Metformin (1, 2-dimethyl biguanide hydrochloride) is an anti-diabetic agent of the biguanides class that is a small chemical compound (129 Da) with high water solubility. It is used as a first-line anti-diabetic drug in patients with type 2 diabetes mellitus in patients with the glomerular filtration rate (GFR) higher than 30 ml/min/1.73$m^{2.}$ (Campbell et al., 2018). Metformin regulates blood glucose levels by reducing glucose production in the liver, increasing peripheral glucose uptake, and improving insulin sensitivity (Bendlin, 2019). There are many contradictory results on metformin administration and its effect on neurodegenerative disease. While some investigations revealed that metformin use has a neuroprotective effect and thereby may result in a significant improvement in cognition or at least a delay in cognitive decline in elderly patients with diabetes (Ng et al., 2014), other studies demonstrated that long-term use of high-dose metformin was correlated with a greater risk of AD development (Kuan et al., 2017; Imfeld et al., 2012). According to our findings, we observed that at least two years of metformin use is associated with overall lower atrophy in non-demented diabetic subjects (Table 2).

The MRI, computed tomographic (CT) scans and PET scan data of patients are the main tools to study the pattern of disease progression in AD (Petersen et al., 2010). The quantified level of atrophy in brain regions can be measured by MRI in the early stages of AD (Petrella et al., 2003) and it is used to assess the atrophy to predict future clinical manifestation of AD (Petrella et al., 2003; Kantarci and Jack, 2003). Jack et al. used serial MRI to compare the level of brain atrophy among three groups, including controls, and AD. Their finding suggested that controls with a higher risk of converting to MCI or AD, MCI group who converted to AD, and patients with AD with fast clinical progression showed the highest level of brain atrophy. They then concluded that serial MRI studies in addition to clinical measures can be considered as a precise marker for AD progression (Jack et al., 2004). Recently, a study by Ponirakis et al. revealed that the diagnostic capability of corneal confocal microscopy compared to brain volumetry is higher for identifying MCI and comparable for dementia. However, abnormalities in both brain volumetry and corneal confocal microscopy are associated with cognitive impairment (Ponirakis et al., 2022).

Our analysis showed that there was no association between metformin use and the volume of the hippocampus and temporal which are the specific regions in AD. However, they are not the only regions affected by AD pathology and as previous studies demonstrated, cognitive impairment may occur due to atrophy and loss of connectivity in widespread brain regions (Torso et al., 2021; Weintraub et al., 2012). However, further studies with longitudinal design are needed to investigate the effect of metformin use on hippocampus and temporal volumes.

Previous studies indicated that metformin activates AMP-activated protein kinase (AMPK) resulting in a significant increase in the generation of Aβ species (Campbell et al., 2018; Picone et al., 2016). Furthermore, a transcriptional up-regulation of β- secretase (BACE1), generates elevated protein levels and increased enzymatic activity (Chen et al., 2009). Besides, metformin induces mitochondrial dysfunction by impairing MPT pores and membrane channels. These neuropathological mechanisms lead to the onset and progression of neurodegeneration and along with normal aging cause a rapid decline in cognition in patients with dementia (Cardoso and Moreira, 2020). On the other hand,

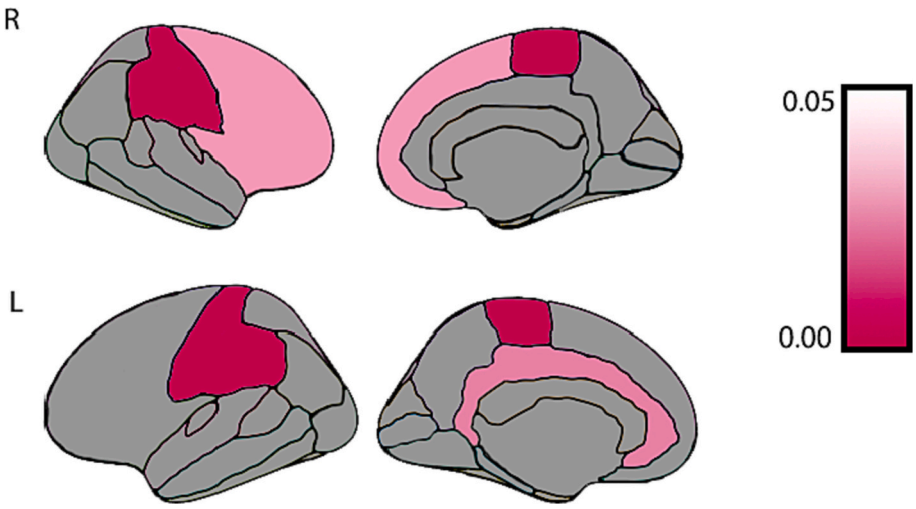

Fig. 1. Regions of interest are shown for significant results. *P* values are presented.

metformin use has been reported to associate with a lower risk of developing dementia (Hsu et al., 2011; Cao et al., 2018). However, Chen and colleagues in their series revealed that metformin use as a monotherapy in the elderly patient with AD disease and diabetes may lead to potentially harmful consequences (Picone et al., 2016; Chen et al., 2009). While, insulin and rosiglitazone use showed improvement in cognition and memory in patients with mild to moderate AD (Chen et al., 2009; Watson et al., 2005; Reger et al., 2008). Furthermore, the administration of glucagon-like peptide I receptor agonist and rosiglitazone showed a significant decrease in AD risk in patients with type 2 diabetes (Akimoto et al., 2020). In the present study, subjects who did not use metformin had lower volumes in the cingulate, parietal, and frontal lobes (Table 2). Cortical changes in AD progression have been extensively studied (Janke et al., 2001; Eskildsen et al., 2013; Du et al., 2004; Duning et al., 2009; Landin-Romero et al., 2017), however very less is known about subcortical changes and AD progression. Ishino et al. observed common subcortical regions subjected to neurofibrillary tangles accumulation including nucleus mamillo-infundibularis, nucleus basilaris, nucleus dorsalis raphe, nucleus centralis superior (Ishino and Otsuki, 1975).

Although metformin can penetrate the blood-brain barrier, protect neurons through an anti-inflammatory mechanism and improve brain energy metabolism (Lin et al., 2018), it can increase the production of Aβ and subsequent abnormal cleavage of precursor proteins lead to amyloid plaques formation, accumulation in neurons, and disintegration of the neuron transport system as a result of neurotoxicity (Tarasoff-Conway et al., 2015). Long-term metformin treatment stimulates amyloid precursor protein processing in the brain cortex regions. Immunohistochemically studies revealed that the majority of the intraneuronal Aβ deposits lead to neuronal apoptosis via a JNK activation (Shoji et al., 2000) and over a long period results in severe brain atrophy. In contrast with these experimental studies, Ou et al. demonstrated that metformin use decreased Aβ plaque formation and chronic inflammation in the hippocampus and cortical regions. Metformin was observed to enhance cerebral AMPK, although suppressed the activation of the enzymatic proteins responsible for protein expression (Ou et al., 2018). Activation of AMPK correlated with gender divergence when cognition was examined in murine models. According to their findings, another study demonstrated that activation of AMPK results in an equivalent increase in memory dysfunction in males, however, was protective in females (DiTacchio et al., 2015).

Our findings showed the protective effects of metformin on brain volumes in a pooled sample of MCI and CH diabetic individuals. Comparing the groups show strong enough results regarding the lower atrophy in metformin users. The many controversial results on the effect of metformin on AD development necessitate more studies, especially on the pharmacological mechanism of how metformin results in mediating significant effects on brain metabolism.

There are several limitations in our studies such as a lack of longitudinal design and small sample size. Moreover, we entered patients with at least two years of metformin use which may not be enough to draw a conclusive result. Further longitudinal investigations with a large sample size are needed to examine the effect of metformin use on structural changes in MCI and AD.

Declaration of competing interest

We have no conflicts of interest to disclose.

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Compliance with ethical standards

None.

Data availability statement

The data used in this manuscript is openly available.

Critically revised the paper: All authors - All authors approved the final version of the manuscript and are accountable for all aspects of the work.

Ethical approval

Since the data in this paper were obtained from the ADNI database (adni.loni.usc.edu), it does not include any research involving human or animal subjects.

Consent for publication

This manuscript has been approved for publication by all authors.

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