Journal of Psychiatric Research 162 (2023) 65–70

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Assessment of cognitive impairment and depressive signs in patients with type 2 diabetes treated with metformin from Southeast Mexico: A cross-sectional study

German Alberto Nolasco-Rosales [a], Guillermo Efrén Villar-Juárez [b], Daniel Arturo Pérez-Osorio [a], Juan Daniel Cruz-Castillo [a], Gabriel Molina-Guzmán [c,h], Thelma Beatriz González-Castro [d], Carlos Alfonso Tovilla-Zárate [e], Ester Rodríguez-Sánchez [f], Alma Delia Genis-Mendoza [g], Filiberto Hernández-Palacios [a], Isela Esther Juárez-Rojop [a,*]

[a] Universidad Juarez Autónoma de Tabasco, División Académica de Ciencias de la Salud, Villahermosa, Tabasco, Mexico
[b] Escuela de Medicina. Universidad Anahuac Querétaro. Querétaro, Querétaro, Mexico
[c] Instituto Mexicano del Seguro Social, Hospital General de Zona 46, Villahermosa, Tabasco, Mexico
[d] Universidad Juarez Autónoma de Tabasco, División Académica Multidisciplinaria de Jalpa de Méndez, Jalpa de Méndez, Tabasco, Mexico
[e] Universidad Juarez Autónoma de Tabasco, División Académica Multidisciplinaria de Comalcalco, Comalcalco, Tabasco, Mexico
[f] Hospital Regional de Alta Especialidad "Gustavo A. Rovirosa Perez", Villahermosa, Tabasco, Mexico
[g] Departamento de Genética Psiquiátrica, Instituto Nacional de Medicina Genómica, Ciudad de México, Mexico
[h] Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Hospital General Dr. Daniel Gurría Urgell, Villahermosa, Tabasco, Mexico

ARTICLE INFO

Keywords:
Metformin
Cognitive impairment
Depression
Type 2 diabetes mellitus

ABSTRACT

Multiple factors associate diabetes with cognitive impairment and depression. Antidiabetic drugs have reported antidepressant and pro-cognitive effects in diabetic and non-diabetic subjects. Antidepressant and pro-cognitive effects of metformin are reported in various studies; however, these effects are not consistent among researches. We designed a cross-sectional study. We recruited patients with T2D diagnosis from the Diabetes Clinic of the Regional Hospital of High Specialty "Dr. Gustavo A. Rovirosa Pérez" from January 2019 to May 2022. We included 431 subjects with T2D, 374 patients with metformin treatment and 57 subjects without metformin. These patients were on intensive therapies and had not a previous diagnosis of cognitive impairment or depression. We applied Mini-Mental State Examination (MMSE) to evaluate cognitive impairment, and Hamilton Depression Rating Scale (HAM-D) to assess depressive signs. Our sample had a mean age of 53.77 ± 13.43 years. Metformin users were 374 individuals, and 57 subjects didn't use metformin. MMSE found cognitive impairment in 8.3% (n = 31) of metformin users, and 14.8% (n = 8) of patients without metformin. HAM-D scale showed that 39.5% (n = 147) of patients with metformin had depression signs, subjects without metformin and depressive signs were 44.6% (n = 25). We found no differences between groups for cognitive impairment and depression grades. We did not find associations between metformin treatment, cognitive impairment measures and depression sign measures. However, chronic metformin treatment, insulin use, glycemic control and age could influence our results.

1. Introduction

Diabetes is a chronic disease characterized by the presence of hyperglycemia in the absence of treatment (WHO, 2019). There are 537 million adults living with diabetes worldwide, and it is expected to increase to 783 million by 2045 (IDF, 2021). In this context, diabetes with poor glycemic control is associated with double the risk of cognitive impairment and dementia (Dove et al., 2021; Srikanth et al., 2020).

Multiple factors are involved in the association of diabetes with cognitive impairment, e.g.: diabetic angiopathy, poor glycemic control, accelerated brain aging, and neurodegeneration (Antal et al., 2022; Pignalosa et al., 2021). Disturbed pathways in diabetes and cognitive

* Corresponding author. División Académica de Ciencias de la Salud, Universidad Juárez Autónoma de Tabasco, Av. Gregorio Mendez 2838-A Col, Tamulte, CP 86100, Villahermosa, Tabasco, Mexico.
E-mail address: iselajuarezrojop@hotmail.com (I.E. Juárez-Rojop).

https://doi.org/10.1016/j.jpsychires.2023.04.007
Received 4 November 2022; Received in revised form 21 March 2023; Accepted 5 April 2023
Available online 10 April 2023
0022-3956/© 2023 Published by Elsevier Ltd.

impairment involve dopaminergic and serotonergic systems, insulin signaling, glucotoxicity, and proinflammatory cytokines IL-1β and TNF-α in the Central Nervous System (Pignalosa et al., 2021; Zilliox et al., 2016). Interestingly, the aforementioned mechanisms also associate depression with diabetes (Woo et al., 2020). Almost one in four adults with type 2 diabetes (T2D) experiences depression; also, the risk of depression is increased in diabetes (Khaledi et al., 2019; Pouwer et al., 2020). Moreover, depression in diabetes is associated with suboptimal self-care behaviors, higher glycated hemoglobin, impaired quality of life, incident vascular diseases, and elevated mortality rates (Pouwer et al., 2020).

Antidiabetic drugs have antidepressant and pro-cognitive effects reported in diabetic and non-diabetic subjects; however, these effects are not consistent among studies (Muñoz-Jiménez et al., 2020; Nibber et al., 2022; Woo et al., 2020). One of the studied antidiabetic drugs in cognitive impairment and depression is metformin. Metformin is the first-line treatment for T2D and is commonly used in type 1 diabetes treatment; furthermore, it is inexpensive, without hypoglycemia risk and adverse effects are rare (ADA Professional Practice, 2021a). Although protective effects of metformin are reported in various studies (Campbell et al., 2018; Kessing et al., 2020; Nibber et al., 2022), other research could not associate metformin with antidepressant or pro-cognitive effects (Hartman et al., 2019; Hu et al., 2015; Kashani et al., 2013; Luchsinger et al., 2016). Nonetheless, many studies are done on subjects with cognitive impairment, diagnosed with depression, advanced age, or without diabetes (Chen et al., 2019; Guo et al., 2014; Koenig et al., 2017; Lin et al., 2018; Teng et al., 2021). Meta-analysis shows limited antidepressant effect of metformin, other studies show mixed results (Kessing et al., 2020; Nibber et al., 2022; Yu et al., 2022). Although metformin could help in comorbid depression, it is needed more studies before it can be recommended as depression treatment (Hamal et al., 2022).

In this cross-sectional study, our aim is to assess possible associations between metformin treatment with cognitive impairment and depressive signs in patients with type 2 diabetes from a Diabetes Clinic in Southeast Mexico.

2. Methods

2.1. Study population

We designed a cross-sectional hospital-based single-center study. We recruited patients with T2D diagnosis from the Diabetes Clinic of the Regional Hospital of High Specialty "Dr. Gustavo A. Rovirosa Pérez" from January 2019 to May 2022. The Diabetes Clinic has all patients on intensive therapies, they were referred from other centers because they did not achieve glycemic control. A diabetologist evaluated and diagnosed all patients based on WHO criteria. All admitted subjects are treated with metformin, except if they have eGFR $\leq$30 mL/min/1.73 m^2 or severe gastrointestinal side effects. Inclusion criteria were at least one year of diagnosis of T2D, at least three months of pharmacological treatment against diabetes, agreed to participate and signed informed consent before the interview. These patients had not a previous diagnosis of cognitive impairment or depression. We screened 490 subjects, then, 59 individuals were excluded. Our sample included 431 patients: 374 patients with metformin treatment and 57 subjects without metformin (Fig. 1).

2.2. Sociodemographic and clinical features

Two graduated physicians applied a structured questionnaire to acquire sociodemographic data (age, gender, schooling, marital status, socioeconomic status, occupation), tobacco use, and alcohol use. We measured the weight and height of all subjects, and later we calculated body mass index (BMI). We retrieved pharmacological treatment and diabetes complications data from clinical records. Pharmacological treatment data included drugs consumed, daily doses, and years with metformin. Diabetes complications encompass non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), diabetic kidney disease (DKD), stroke, neuropathy, and cardiovascular complications (enclosing coronary heart disease, cardiomyopathy, and diabetic foot syndrome).

2.3. Biochemical parameters

We collected blood samples in tubes with EDTA and without

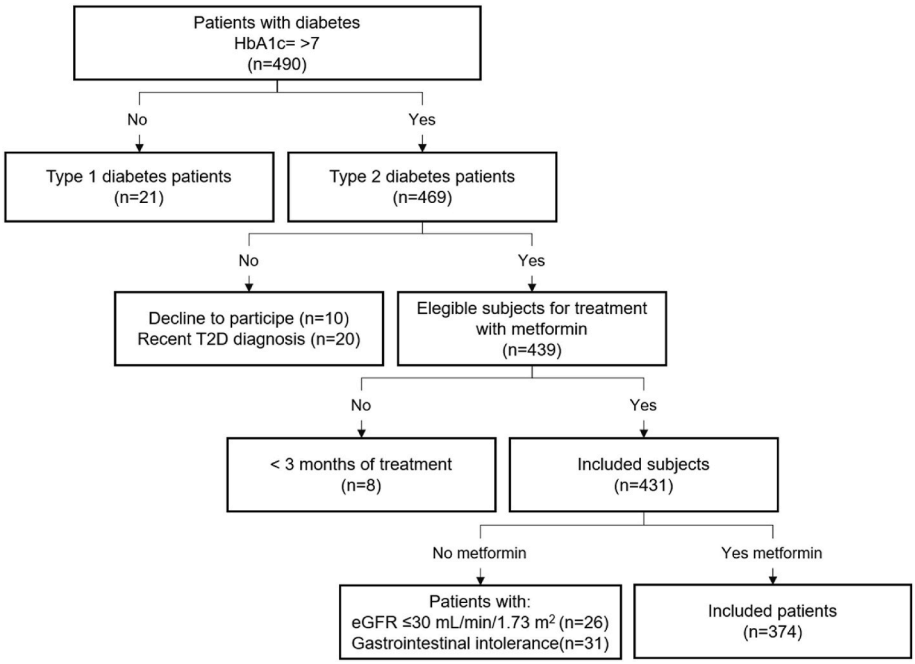

Fig. 1. Flow chart of the patients' selection and classification.T2D, Type 2 Diabetes.

anticoagulants. We determined fasting glucose, total cholesterol, and triglycerides using a Clinical Chemistry System from Random Access Diagnostics; glycated hemoglobin was determined with the enzymatic immunoassay method (Human Glycated Hemoglobin A1c ELISA Kit).

2.4. Mini-Mental State Examination

The interviewers applied the Mini-Mental State Examination (MMSE) to screen all participants for cognitive impairment (Folstein et al., 1975). We employed a validated version of MMSE in Spanish. Final scores were adjusted by schooling following the author's instructions. Scores ≤24 were classified as cognitive impairment, while ≥25 points were considered normal (Beaman et al., 2004). We also evaluated scores by areas of cognitive function: orientation, registration, attention and calculations, recall, language, and complex commands.

2.5. Hamilton Depression Rating Scale

The interviewers screened depression signs in the interviewed patients using the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960); we used a validated version in Spanish of the 17-item reduced version. Scores of 0–7 were considered normal; higher scores were classified by depressive signs severity (mild, 8–16; moderate, 17–23; severe, 19–22; and very severe ≥23) (Zimmerman et al., 2004).

2.6. Statistical analysis

We used frequencies and percentages to express sociodemographic variables, diabetes complications frequencies, pharmacological treatment, MMSE and HAM-D results. We represented biochemical characteristics, pharmacological treatment doses, MMSE, and HAM-D scores as mean ± standard deviation (SD). The Chi-square test (χ^2) was used to compare frequencies between groups, and T-Student test to compare numerical variables. Also, we performed two binary logistic regressions to control confounding variables. One model calculated the probability of having cognitive impairment, while the other estimated the odds of being depressed. The logistic regressions included all subjects of both groups. As covariables, we evaluated age, education, BMI, HbA1c, stroke, alcohol, metformin use, and insulin use. The results of the logistic regressions were the odds ratio (OR) for having a cognitive impairment or showing depressive signs. A p-value <0.05 was considered significant. All statistical analysis were done with SPSS Statistics 26.0 and GraphPad Prism 9.0.

Ethical statement

We followed the Official Mexican Standard NOM-012-SSA3-2012 guidelines and the ethical principles of the Declaration of Helsinki as revised 1989. The study was approved by the Ethics Committee of Regional Hospital of High Specialty "Dr. Gustavo A. Rovirosa Pérez" (No.: PIE-0002-2021; December 3rd, 2021), and informed consent was taken from all individual participants. All patients participated voluntarily without receiving any remuneration. Additionally, participants received verbal and written information about the objectives of this study. Participation in this study was not treatment dependent and did not change the medical care that the hospital provides.

3. Results

From 490 eligible patients, we included 431 subjects with T2D (Fig. 1). Our sample had a mean age of 53.77 ± 13.43 years, low socioeconomic status (n = 233, 53.8%), with female predominance (n = 302, 69.7%), were married (n = 260, 60.0%), and were homemakers (n = 214, 49.4%). Metformin users were 374 individuals, and 57 subjects didn't use metformin as part of their treatment (Table 1).

We found differences between the BMI of metformin users and no users (29.65 ± 6.35 vs. 26.81 ± 6.32). Both groups had no controlled fasting glucose and HbA1c levels. Interestingly, patients with metformin and insulin treatment had increased levels of HbA1c compared with subjects treated only with metformin (8.47 ± 2.17 vs. 7.73 ± 2.04, p=<0.01). Total cholesterol was at near borderline levels, while triglycerides were at high levels. Alcohol and tobacco use were similar between groups. Concerning comorbidities, diabetic kidney disease was less frequent in metformin users (20.6% vs. 44.6%); other comorbidities frequencies were similar among the groups. The mean metformin dose was 1765.29 ± 570.69 mg/day. Pharmacological treatment showed differences between groups. Glibenclamide in treatment was common in the group with metformin (18.7% vs. 7.0%); patients with metformin also consumed higher daily doses (11.08 ± 3.88 vs. 6.88 ± 2.59). Insulin was most frequent in treatment on subjects without metformin (93.0%). Regarding insulin regimens, basal-bolus was more common in people without metformin (52.6%); however, individuals with metformin and basal-bolus regimen used higher insulin doses. Basal insulin regimen was equally frequent with comparable doses in both groups (Table 2). A histogram of years with metformin treatment is in Fig. 2. Patients with less than 15 years of metformin prescription were evenly distributed; nonetheless, 34.5% (n = 131) of subjects have more than 15 years of metformin treatment.

Table 1
Demographic features of patients with T2D and metformin treatment.

Demographics	Treatment with metformin		X2/t, p
	Yes (n = 374)	No (n = 57)	
Age (years)	54.27 ± 12.76	50.20 ± 16.97	1.72, 0.09
Gender			
Female	256 (68.4%)	44 (77.2%)	1.79, 0.12
Male	118 (31.6%)	13 (22.8%)	
Education (years)	**6.78 ± 4.40**	**8.20 ± 4.38**	**−2.25, 0.03**
Marital status (Married)	**234 (62.9%)**	**25 (43.9%)**	**8.45, 0.04**
Socioeconomic status (Low)	207 (55.3%)	26 (46.4%)	2.40, 0.30
Laboral status (Homemaker)	186 (49.7%)	27 (48.2%)	6.89, 0.14

We used the Chi-squared test for categorical variables, and the t-Student test for numerical data. A p-value <0.05 was considered significant.

MMSE found cognitive impairment in 8.3% (n = 31) of metformin users, and 14.8% (n = 8) of patients without metformin. Mean total scores of MMSE did not show cognitive impairment in both groups (28.24 ± 2.50 vs. 28.24 ± 2.50). Metformin dose was similar between normal subjects and patients with cognitive impairment (1760.97 ± 566.72 vs. 1798.39 ± 631.86 mg/day, p = 0.73). We did not observe differences in areas of cognitive function between groups (Table 3).

HAM-D scale showed that 39.5% (n = 147) of patients with metformin had depression signs. We found similar doses of metformin in subjects with depressive signs and without signs (1778.79 ± 596.80 vs. 1756.76 ± 555.49 mg/day, p = 0.72). Subjects without metformin and depressive signs were 44.6% (n = 25). Table 3 summarizes HAM-D classification results; more severe grades are less frequent. Table 4 shows metformin doses by classification of depression symptoms. We found no differences between metformin treatment groups or metformin doses for depression grades.

The logistic regressions evaluated the OR for cognitive impairment or depressive signs, adjusting for metformin use and confounding variables. We found two variables associated with cognitive impairment. An increase of one year of education reduced the probability of cognitive impairment by 27%. In addition, insulin use increased the odds of cognitive impairment three-fold; nonetheless, the inferior 95% CI was close to 1. On the other hand, depressive signs showed an association with age; every year of age decreased OR by 0.98, which could indicate the 10-year accumulated effect of aging decreased 20% the odds of depressive symptoms. Nonetheless, metformin treatment was not significant for OR of cognitive impairment or depressive signs (Table 5).

Table 2
Clinical features of patients with T2D and metformin treatment.

Feature	Treatment with metformin		X2/t, p
	Yes (n = 374)	No (n = 57)	
BMI (kg/m2)	29.65 ± 6.35	26.81 ± 6.32	3.02, <0.01
Fasting glucose (mg/dL)	178.68 ± 73.25	177.71 ± 84.06	0.09, 0.93
HbA1c (%)	8.24 ± 2.15	8.06 ± 2.05	0.58, 0.56
Total cholesterol (mg/dL)	198.19 ± 61.49	192.06 ± 44.69	0.56, 0.58
Triglycerides (mg/dL)	206.45 ± 127.47	184.12 ± 92.17	0.98, 0.33
Alcohol use	62 (16.6%)	7 (12.5%)	0.61, 0.29
Tobacco use	22 (5.9%)	1 (1.8%)	1.63, 0.17
NAFLD/NASH	44 (11.8%)	10 (17.5%)	1.49, 0.16
DKD	**77 (20.6%)**	**26 (45.6%)**	**16.93, <0.01**
Stroke	21 (5.6%)	5 (8.8%)	0.85, 0.25
Neuropathy	162 (43.4%)	25 (43.9%)	0.01, 0.53
Cardiovascular complications	168 (45.0%)	20 (35.1%)	1.99, 0.10
Brain Scales			
MMSE score	28.24 ± 2.50	27.67 ± 3.38	1.19, 0.24
Cognitive impairment, n (%)	31 (8.3%)	8 (12.9%)	1.36, 0.18
HAM-D score	7.51 ± 7.14	8.39 ± 7.87	−0.89, 0.37
Depressive signs, n (%)	147 (39.5%)	28 (43.8%)	0.41, 0.31
Glibenclamide (mg/day)	**70 (18.7%)**	**4 (7.0%)**	**4.76, 0.02**
	11.08 ± 3.88	**6.88 ± 2.59**	**3.03, <0.01**
Linagliptin (mg/day)	113 (30.3%)	17 (29.8%)	0.01, 0.54
	5.36 ± 1.46	5.29 ± 1.21	0.17, 0.86
Insulin use (Any) (UI/day)	**263 (70.3%)**	**53 (93.0%)**	**12.98, <0.01**
	40.34 ± 22.64	33.90 ± 19.03	1.69, 0.09
Basal insulin regimen (UI/day)	138 (36.9%)	23 (40.4%)	0.25, 0.36
	30.36 ± 13.88	27.03 ± 16.31	1.22, 0.22
Basal-bolus insulin regimen (UI/day)	**125 (33.4%)**	**30 (52.6%)**	**7.93, <0.01**
	54.68 ± 22.61	**40.27 ± 18.97**	**2.81, <0.01**

BMI, Body mass index; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; DKD, Diabetic kidney disease. We used the Chi-squared test for categorical variables, and the t-Student test for numerical data. A p-value <0.05 was considered significant.

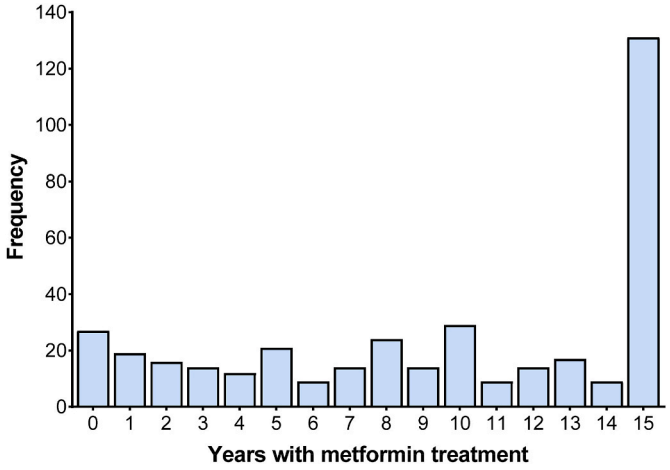

Fig. 2. Histogram of months with metformin treatment in patients with T2D. Patients with more than 15 years of treatment with metformin are group inside the 15 years bar (n = 131). Total of patients with metformin treatment, n = 379.

Table 3
Scores of areas of cognitive function and Hamilton Depression Rating Scale classification in patients with T2D and metformin.

MMSE score (mean ± SD)	Treatment with metformin		t, p
	Yes (n = 374)	No (n = 57)	
Orientation	9.58 ± 1.06	9.31 ± 1.23	1.65, 0.10
Registration	2.95 ± 0.31	2.94 ± 0.30	0.10, 0.92
Attention and calculations	4.60 ± 1.13	4.56 ± 1.16	0.25, 0.80
Recall	2.46 ± 0.96	2.52 ± 0.84	−0.45, 0.65
Language	5.91 ± 0.50	5.70 ± 0.92	1.60, 0.12
Complex commands	2.69 ± 0.65	2.63 ± 0.83	0.47, 0.64
Total	28.24 ± 2.50	27.67 ± 3.38	1.19, 0.24
HAM-D classification (n, %)	**Treatment with metformin**		**X2, p**
	Yes (n = 374)	**No (n = 57)**	
Normal	225 (60.5%)	31 (55.4%)	1.88, 0.76
Mild	65 (17.5%)	10 (17.9%)	
Moderate	46 (12.4%)	9 (16.1%)	
Severe	20 (5.4%)	2 (3.6%)	
Very severe	16 (4.3%)	4 (7.1%)	

We used the Chi-squared test for categorical variables, and the t-Student test for numerical data. A p-value <0.05 was considered significant.

Table 4
Metformin doses of patients with T2D by Hamilton Depression Rating Scale classification.

HAM-D classification	Metformin (mg/day)	F, p
Normal	1756.76 ± 555.49	0.42, 0.80
Mild depression	1729.69 ± 623.40	
Moderate depression	1794.02 ± 588.91	
Severe depression	1913.16 ± 485.01	
Very severe depression	1771.46 ± 571.46	

We used one-way ANOVA test. A p-value <0.05 was considered as significant.

Table 5
Logistic regression of cognitive impairment and depressive signs in patients with type 2 diabetes.

Variable	OR	95% CI	p
Cognitive impairment			
Age (years)	1.03	0.99–1.06	0.147
Education (years)	**0.73**	**0.64–0.83**	**<0.001**
BMI (kg/m2)	0.95	0.88–1.02	0.128
HbA1c (%)	1.12	0.92–1.37	0.252
Stroke (Yes)	2.32	0.52–10.37	0.269
Alcohol (Yes)	0.80	0.21–3.07	0.746
Metformin use (Yes)	0.45	0.15–1.34	0.151
Insulin use (Yes)	**2.98**	**1.02–8.75**	**0.047**
Depressive signs (Yes)	1.85	0.84–4.07	0.128
Depressive signs			
Age (years)	**0.98**	**0.96–0.99**	**0.015**
Education (years)	0.95	0.90–1.01	0.072
BMI (kg/m2)	1.02	0.99–1.05	0.284
HbA1c (%)	1.09	0.99–1.20	0.095
Stroke (Yes)	0.32	0.10–1.00	0.051
Alcohol (Yes)	1.05	0.58–1.89	0.873
Metformin use (Yes)	0.70	0.36–1.35	0.281
Insulin use (Yes)	1.16	0.71–1.90	0.557
Cognitive impairment (Yes)	1.88	0.88–4.00	0.104

Odds ratio of cognitive impairment and depressive signs for each unit increase (or presence) of a given variable. OR, odds ratio; CI, confidence intervals. We used binary logistic regression, a p-value <0.05 was considered as significant.

4. Discussion

In this study, we screened cognitive impairment and depressive signs in patients with T2D, we did not find associations between metformin treatment, cognitive impairment measures and depression sign measures.

One of the proposed mechanisms of the pro-cognitive effects of

metformin is its hypoglycemic effect (Nibber et al., 2022). In this context, chronic hyperglycemia in diabetes produces advanced glycation end-products (AGEs), which have an important role in neurodegenerative diseases and cognitive dysfunction (Jash et al., 2020; Pignalosa et al., 2021). AGEs are related to neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Jiang et al., 2018; König et al., 2018); furthermore, diabetes has a two times higher risk of developing cognitive impairment compared with normal subjects (Jash et al., 2020). Although Guo et al. (2014) associated cognitive function with lower blood glucose, many studies found no differences in glucose levels (Campbell et al., 2018; Lin et al., 2018; Nibber et al., 2022). Another mechanism of metformin is the activation of AMP-activated protein kinase (AMPK) (Madhu et al., 2022; Sharma et al., 2021). AMPK activation promotes glucose consumption and enhances mitochondrial function; in neurons, AMPK also favors synapse formation and memory function (Sharma et al., 2021; Zilliox et al., 2016). Brain insulin resistance and impaired signaling reduce AMPK activation, increases oxidative stress, and impair synaptic plasticity in diabetes (Kellar and Craft, 2020; Zilliox et al., 2016).

There are some reasons for the lack of association of metformin with cognitive impairment in our sample. First is the chronic metformin treatment in our patients. Observational studies report that chronic metformin treatment in patients with T2D is associated with no cognitive impairment (Ng et al., 2014; Teng et al., 2021). Similarly, the neuroprotective effects of chronic metformin treatment are observed in patients with diabetes and stroke (Akhtar et al., 2022; Wu et al., 2016). Remarkably, insulin use was more frequent in our subjects without metformin. Insulin treatment could protect our patients against cognitive impairment as metformin did. Nonetheless, clinical trials studying intranasal insulin as a novel treatment for neurodegenerative diseases show mixed results (Craft et al., 2020; Kellar et al., 2022; Novak et al., 2019). Second, our patients with metformin had similar fasting glucose and HbA1c levels compared to subjects without metformin. In this sense, some studies associated elevated glycemic levels with increased risk of cognitive impairment (Guo et al., 2014; Zilliox et al., 2016). Third, our patients are relatively young (53.17 ± 13.39 years). Mild cognitive impairment prevalence increases with age in the general population (Rajan et al., 2021; Welstead et al., 2021). However, mechanisms of normal brain aging are accelerated in diabetes; structural and functional changes appear earlier (Antal et al., 2022). Nonetheless, studies associating metformin with cognitive improvement in patients with T2D had mean ages above 65 years (Lin et al., 2018; Teng et al., 2021). Likewise, Samaras et al. (2020) excluded younger patients from their samples.

Some studies report a lower risk of depression in subjects with diabetes treated with metformin (Chen et al., 2019; Guo et al., 2014; Kessing et al., 2020; Yu et al., 2022). However, it is not possible to exclude that the antidepressant effects of metformin are secondary to its pro-cognitive effects (Guo et al., 2014; Nibber et al., 2022). Besides, some studies have not observed antidepressant effects of metformin in subjects with diabetes or other comorbidities (Bojanić et al., 2022; Hu et al., 2015; Kashani et al., 2013). Depression, cognitive impairment, and diabetes have shared mechanisms, such as brain insulin resistance, oxidative stress, activated inflammatory pathways, disturbed dopaminergic neurotransmission, and defective neurogenesis and synaptic plasticity (Pignalosa et al., 2021; Woo et al., 2020; Zilliox et al., 2016). Furthermore, regulation of AMPK signaling, also involved in cognitive impairment, is suggested as the antidepressant mechanism of metformin (Woo et al., 2020; Zilliox et al., 2016). Although nearly 40% of our sample had depressive signs, they had similar glycemic values and similar frequencies of cognitive impairment. As demographic, biochemical, and clinical features in both groups are similar, it is expected to find no differences in depressive signs severity or HAM-D scores.

Finally, we found differences in BMI and DKD in our patients. These results were expected because of the differences in metformin treatment indications. Subjects with higher BMI is likely to be treated with metformin because its beneficial effect in weight (ADA Professional Practice, 2021a). On the other hand, metformin is contraindicated in patients with estimated glomerular filtration rate below <30 mL/min/1.73 m2 (ADA Professional Practice, 2021b). As their DKD progress, our patients' first-line treatment changes from metformin to insulin.

One advantage of this study is that we screened patients from a Diabetes Clinic who have not a previous diagnosis of cognitive impairment or depression. Research of protective effects of metformin is made in high-risk populations or individuals with established disorders. Another advantage is that the cross-sectional design of this study shows a population of patients with chronic metformin treatment. Even though we did not find associations, future longitudinal studies could reveal possible associations or show evidence of the lack of association.

Our study has some limitations. First, our group with metformin included subjects treated with other antidiabetic drugs in addition to metformin. Second, as this is a cross-sectional study, we only registered the most recently used treatment regimens. In this sense, a large proportion of our sample has a chronic antidiabetic treatment that has changed over time. The study design could interfere with our results if any protective effects of metformin or other drugs persist over time. Third, the low prevalence of cognitive impairment in the sample could have affected the logistic regression results. Finally, our results should not be generalized to all Mexican populations as we evaluated patients from a single hospital.

In conclusion, our results showed a lack of association between metformin treatment, cognitive impairment, and depression signs in patients with T2D from a hospital in Southeast Mexico. Besides, our subjects did not show cognitive impairment. Similar fasting glucose and HbA1c values, insulin treatment in subjects without metformin, chronic metformin treatment, relative younger age of our patients, and the study design could participate in the lack of association. Future studies should consider these findings.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

G. A. Nolasco-Rosales: Formal analysis, Data Curation, Writing - Original Draft, Visualization. GE Villar-Juárez: Investigation, Data Curation. DA Pérez-Osorio: Investigation, Data Curation. JD Cruz-Castillo: Investigation, Data Curation, Visualization. G Molina-Guzmán: Resources, Writing - Review & Editing. TB González-Castro: Formal analysis, Writing - Review & Editing. CA Tovilla-Zárate: Conceptualization, Methodology, Formal analysis, Writing - Original Draft. E Rodríguez-Sánchez: Resources, Supervision. AD Genis-Mendoza: Formal analysis, Writing - Review & Editing. F Hernández-Palacios: Conceptualization, Writing – Review & Editing. IE Juárez-Rojop: Conceptualization, Methodology, Writing - Original Draft, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Germán Alberto Nolasco-Rosales is a student of Doctor of Biomedical Science degree in Juárez Autonomous University of Tabasco and is supported by CONACYT's scholarship No. 813279. Juan Daniel Cruz-Castillo is a student of Master of Biomedical Science degree in Juárez

Autonomous University of Tabasco and is supported by CONACYT's scholarship No. 812490.

References

ADA Professional Practice, C., 2021a. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. Diabetes Care 45 (Suppl. ment_1), S125–S143.

ADA Professional Practice, C., 2021b. 11. Chronic kidney disease and risk management: standards of medical care in diabetes—2022. Diabetes Care 45 (Suppl. ment_1), S175–S184.

Akhtar, N., Singh, R., Kamran, S., Babu, B., Sivasankaran, S., Joseph, S., Morgan, D., Shuaib, A., 2022. Diabetes: chronic metformin treatment and outcome following acute stroke. Front. Neurol. 13, 849607.

Antal, B., McMahon, L.P., Sultan, S.F., Lithen, A., Wexler, D.J., Dickerson, B., Ratai, E.-M., Mujica-Parodi, L.R., 2022. Type 2 diabetes mellitus accelerates brain aging and cognitive decline: complementary findings from UK Biobank and meta-analyses. Elife 11, e73138.

Beaman, S.R.d., Beaman, P.E., Garcia-Peña, C., Villa, M.A., Heres, J., Córdova, A., Jagger, C., 2004. Validation of a modified version of the mini-mental state examination (MMSE) in Spanish. Aging Neuropsychol. Cognit. 11 (1), 1–11.

Bojanić, I., Bjerkeset, O., Williams, L.J., Berk, M., Sund, E.R., Sletvold, H., 2022. Associations of cardiovascular agents and metformin with depression symptoms: a cross-sectional analysis from the HUNT study, Norway. Drugs - Real World Outcomes 9 (3), 503–516.

Campbell, J.M., Stephenson, M.D., de Courten, B., Chapman, I., Bellman, S.M., Aromataris, E., 2018. Metformin use associated with reduced risk of dementia in patients with diabetes: a systematic review and meta-analysis. J. Alzheim. Dis. 65, 1225–1236.

Chen, F., Wei, G., Wang, Y., Liu, T., Huang, T., Wei, Q., Ma, G., Wang, D., 2019. Risk factors for depression in elderly diabetic patients and the effect of metformin on the condition. BMC Publ. Health 19 (1), 1063.

Craft, S., Raman, R., Chow, T.W., Rafii, M.S., Sun, C.-K., Rissman, R.A., Donohue, M.C., Brewer, J.B., Jenkins, C., Harless, K., Gessert, D., Aisen, P.S., 2020. Safety, efficacy, and feasibility of intranasal insulin for the treatment of mild cognitive impairment and alzheimer disease dementia: a randomized clinical trial. JAMA Neurol. 77 (9), 1099–1109.

Dove, A., Shang, Y., Xu, W., Grande, G., Laukka, E.J., Fratiglioni, L., Marseglia, A., 2021. The impact of diabetes on cognitive impairment and its progression to dementia. Alzheimer's Dementia 17 (11), 1769–1778.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198.

Guo, M., Mi, J., Jiang, Q.-M., Xu, J.-M., Tang, Y.-Y., Tian, G., Wang, B., 2014. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin. Exp. Pharmacol. Physiol. 41 (9), 650–656.

Hamal, C., Velugoti, L., Tabowei, G., Gaddipati, G.N., Mukhtar, M., Alzubaidee, M.J., Dwarampudi, R.S., Mathew, S., Bichenapally, S., Khachatryan, V., Muazzam, A., Mohammed, L., 2022. Metformin for the improvement of comorbid depression symptoms in diabetic patients: a systematic review. Cureus 14 (8), e28609.

Hartman, S.J., Nelson, S.H., Marinac, C.R., Natarajan, L., Parker, B.A., Patterson, R.E., 2019. The effects of weight loss and metformin on cognition among breast cancer survivors: evidence from the Reach for Health study. Psycho Oncol. 28 (8), 1640–1646.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatr. 23 (1), 56.

Hu, Y., Xing, H., Dong, X., Lu, W., Xiao, X., Gao, L., Cui, M., Chen, J., 2015. Pioglitazone is an effective treatment for patients with post-stroke depression combined with type 2 diabetes mellitus. Exp. Ther. Med. 10 (3), 1109–1114.

IDF, 2021. IDF Diabetes Atlas, 2021. https://www.diabetesatlas.org. (Accessed 14 December 2021).

Jash, K., Gondaliya, P., Kirave, P., Kulkarni, B., Sunkaria, A., Kalia, K., 2020. Cognitive dysfunction: a growing link between diabetes and Alzheimer's disease. Drug Dev. Res. 81 (2), 144–164.

Jiang, L., Wang, J., Wang, Z., Huang, W., Yang, Y., Cai, Z., Li, K., 2018. Role of the glyoxalase system in alzheimer's disease. J. Alzheim. Dis. 66, 887–899.

Kashani, L., Omidvar, T., Farazmand, B., Modabbernia, A., Ramzanzadeh, F., Tehraninejad, E.S., Ashrafi, M., Tabrizi, M., Akhondzadeh, S., 2013. Does pioglitazone improve depression through insulin-sensitization? Results of a randomized double-blind metformin-controlled trial in patients with polycystic ovarian syndrome and comorbid depression. Psychoneuroendocrinology 38 (6), 767–776.

Kellar, D., Craft, S., 2020. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol. 19 (9), 758–766.

Kellar, D., Register, T., Lockhart, S.N., Aisen, P., Raman, R., Rissman, R.A., Brewer, J., Craft, S., 2022. Intranasal insulin modulates cerebrospinal fluid markers of neuroinflammation in mild cognitive impairment and Alzheimer's disease: a randomized trial. Sci. Rep. 12 (1), 1346.

Kessing, L.V., Rytgaard, H.C., Ekstrøm, C.T., Knop, F.K., Berk, M., Gerds, T.A., 2020. Antidiabetes agents and incident depression: a nationwide population-based study. Diabetes Care 43 (12), 3050–3060.

Khaledi, M., Haghighatdoost, F., Feizi, A., Aminorroaya, A., 2019. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. Acta Diabetol. 56 (6), 631–650.

Koenig, A.M., Mechanic-Hamilton, D., Xie, S.X., Combs, M.F., Cappola, A.R., Xie, L., Detre, J.A., Wolk, D.A., Arnold, S.E., 2017. Effects of the insulin sensitizer metformin in alzheimer disease: pilot data from a randomized placebo-controlled crossover study. Alzheimer Dis. Assoc. Disord. 31 (2).

König, A., Vicente Miranda, H., Outeiro, T.F., 2018. Alpha-synuclein glycation and the action of anti-diabetic agents in Parkinson's disease. J. Parkinsons Dis. 8, 33–43.

Lin, Y., Wang, K., Ma, C., Wang, X., Gong, Z., Zhang, R., Zang, D., Cheng, Y., 2018. Evaluation of metformin on cognitive improvement in patients with non-dementia vascular cognitive impairment and abnormal glucose metabolism. Front. Aging Neurosci. 10, 227.

Luchsinger, J.A., Perez, T., Chang, H., Mehta, P., Steffener, J., Pradabhan, G., Ichise, M., Manly, J., Devanand, D.P., Bagiella, E., 2016. Metformin in amnestic mild cognitive impairment: results of a pilot randomized placebo controlled clinical trial. J. Alzheimers. Dis. 51 (2), 501–514.

Madhu, L.N., Kodali, M., Shetty, A.K., 2022. Promise of metformin for preventing age-related cognitive dysfunction. Neural Regenerat. Res. 17 (3).

Muñoz-Jiménez, M., Zaarkti, A., García-Arnés, J.A., García-Casares, N., 2020. Antidiabetic drugs in alzheimer's disease and mild cognitive impairment: a systematic review. Dement. Geriatr. Cognit. Disord. 49 (5), 423–434.

Ng, T.P., Feng, L., Yap, K.B., Lee, T.S., Tan, C.H., Winblad, B., 2014. Long-term metformin usage and cognitive function among older adults with diabetes. J. Alzheimers. Dis. 41 (1), 61–68.

Nibber, A., Singh, H., Burnet, P., Lennox, B., Minichino, A., 2022. Investigating the pro-cognitive and anti-depressant efficacy of metformin: a systematic review and meta-analysis of randomised controlled trials. J. Affect. Disord. 310, 52–59.

Novak, P., Pimentel Maldonado, D.A., Novak, V., 2019. Safety and preliminary efficacy of intranasal insulin for cognitive impairment in Parkinson disease and multiple system atrophy: a double-blinded placebo-controlled pilot study. PLoS One 14 (4), e0214364.

Pignalosa, F.C., Desiderio, A., Mirra, P., Nigro, C., Perruolo, G., Ulianich, L., Formisano, P., Beguinot, F., Miele, C., Napoli, R., Fiory, F., 2021. Diabetes and cognitive impairment: a role for glucotoxicity and dopaminergic dysfunction. Int. J. Mol. Sci. 22 (22).

Pouwer, F., Schram, M.T., Iversen, M.M., Nouwen, A., Holt, R.I.G., 2020. How 25 years of psychosocial research has contributed to a better understanding of the links between depression and diabetes. Diabet. Med. 37 (3), 383–392.

Rajan, K.B., Weuve, J., Barnes, L.L., McAninch, E.A., Wilson, R.S., Evans, D.A., 2021. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020-2060). Alzheimers Dement 17 (12), 1966–1975.

Samaras, K., Makkar, S., Crawford, J.D., Kochan, N.A., Wen, W., Draper, B., Trollor, J.N., Brodaty, H., Sachdev, P.S., 2020. Metformin use is associated with slowed cognitive decline and reduced incident dementia in older adults with type 2 diabetes: the sydney memory and ageing study. Diabetes Care 43 (11), 2691–2701.

Sharma, S., Nozohouri, S., Vaidya, B., Abbruscato, T., 2021. Repurposing metformin to treat age-related neurodegenerative disorders and ischemic stroke. Life Sci. 274, 119343.

Srikanth, V., Sinclair, A.J., Hill-Briggs, F., Moran, C., Biessels, G.J., 2020. Type 2 diabetes and cognitive dysfunction-towards effective management of both comorbidities. Lancet Diabetes Endocrinol. 8 (6), 535–545.

Teng, Z., Feng, J., Qi, Q., Dong, Y., Xiao, Y., Xie, X., Meng, N., Chen, H., Zhang, W., Lv, P., 2021. Long-Term use of metformin is associated with reduced risk of cognitive impairment with alleviation of cerebral small vessel disease burden in patients with type 2 diabetes. Front. Aging Neurosci. 13, 773797.

Welstead, M., Luciano, M., Muniz-Terrera, G., Taylor, A.M., Russ, T.C., 2021. Prevalence of mild cognitive impairment in the lothian birth cohort 1936. Alzheimer Dis. Assoc. Disord. 35 (3).

WHO, 2019. Classification of Diabetes Mellitus. World Health Organization, Geneva.

Woo, Y.S., Lim, H.K., Wang, S.-M., Bahk, W.-M., 2020. Clinical evidence of antidepressant effects of insulin and anti-hyperglycemic agents and implications for the pathophysiology of depression—a literature review. Int. J. Mol. Sci. 21 (18), 6969.

Wu, T.Y., Campbell, B.C., Strbian, D., Yassi, N., Putaala, J., Tatlisumak, T., Davis, S.M., Meretoja, A., 2016. Impact of pre-stroke sulphonylurea and metformin use on mortality of intracerebral haemorrhage. Eur Stroke J 1 (4), 302–309.

Yu, H., Yang, R., Wu, J., Wang, S., Qin, X., Wu, T., Hu, Y., Wu, Y., 2022. Association of metformin and depression in patients with type 2 diabetes. J. Affect. Disord. 318, 380–385.

Zilliox, L.A., Chadrasekaran, K., Kwan, J.Y., Russell, J.W., 2016. Diabetes and cognitive impairment. Curr. Diabetes Rep. 16 (9), 87.

Zimmerman, M., Chelminski, I., Posternak, M., 2004. A review of studies of the Hamilton depression rating scale in healthy controls: implications for the definition of remission in treatment studies of depression. J. Nerv. Ment. Dis. 192 (9).