

# Depression scores correlate with glycosylated hemoglobin a levels in type 2 diabetics from a mayan community

Los puntajes de depresión se correlacionan con los niveles de hemoglobina glucosilada en diabéticos tipo 2 de una comunidad maya

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## Abstract

**Objective:** To assess whether depression and quality of life scores correlate with glycosylated hemoglobin A (HbA1c) levels in type 2 diabetes mellitus (T2DM) patients of predominant Mayan ethnicity, from a rural community in the state of Yucatán, Mexico.

**Materials and methods:** Instruments: for depression, CES-D (cutoff  $\geq 16$ ); for quality of life, D-39; criterion for poor glycemic control, HbA1c  $\geq 8\%$ .

**Results:** Depression was detected in 36.3% of 33 diabetic subjects (10 men, 23 women), and their HbA1c levels (mean  $\pm$  SD) were higher ( $10.7 \pm 2.5\%$ ) than for those without depression ( $8.6 \pm 2.2\%$ ,  $p = 0.015$ ; unpaired Student's t-test, two-tailed). Depression occurred in 33.3% of diabetics with HbA1c  $\geq 8\%$ , but only in 3.0% of those with HbA1c  $< 8\%$  ( $p = 0.027$ , Fisher's exact test). HbA1c levels positively correlated with CES-D scores ( $r^2 = 0.135$ ;  $p = 0.035$ ; Pearson). D-39 “Anxiety-Worry” (AW) dimension scores were higher in diabetics with depression ( $43.3 \pm 22.2$ ) than in those without depression ( $17.7 \pm 17.8$ ;  $p = 0.005$ , Mann-Whitney U-test). A positive correlation was found between CES-D and AW scores ( $r^2 = 0.304$ ;  $p = 0.001$ ; Pearson).

**Conclusions:** Considering that depression and anxiety have been related to poor self-care for achieving a good glycemic control, we propose the concomitant use of CES-D and D-39, which are validated and easy-to-apply instruments, as screening tests to detect depression and anxiety in T2DM patients residing in rural communities. Therefore, if patients test positive on one or both instruments, they can be referred to a psychiatrist to confirm the diagnosis and provide appropriate therapy. This would help to promote adherence to diabetes control measures and improve their quality of life.

**Key words:** Diabetes Mellitus, Type 2; Depression; Anxiety; Glycosylated hemoglobin A

## Resumen

**Objetivo.** Evaluar si las puntuaciones de depresión y calidad de vida se correlacionan con los niveles de hemoglobina glucosilada (HbA1c) en pacientes con diabetes mellitus tipo 2 (DM2) de etnia maya predominante, de una comunidad rural en el estado de Yucatán, México.

**Materiales y Métodos.** Instrumentos: para depresión, CES-D (punto de corte  $\geq 16$ ); para calidad de vida, D-39; criterio de mal control glucémico, HbA1c  $\geq 8\%$ .

**Resultados.** Se detectó depresión en el 36.3% de 33 sujetos diabéticos (10 hombres, 23 mujeres), y sus niveles de HbA1c (media  $\pm$  DE) fueron más altos ( $10.7 \pm 2.5\%$ ) que para los que no tenían depresión ( $8.6 \pm 2.2\%$ ,  $p = 0.015$ ; prueba t de Student, no pareada). La depresión se presentó en el 33.3% de los diabéticos con HbA1c  $\geq 8\%$ , pero solo en el 3.0% de aquellos con HbA1c  $< 8\%$  ( $p = 0.027$ , prueba exacta de Fisher). Los niveles de HbA1c se correlacionaron positivamente con las puntuaciones CES-D ( $r^2 = 0.135$ ;  $p = 0.035$ ; Pearson). Los puntajes de la dimensión “Ansiedad-Preocupación” (AW) del D-39 fueron más altos en diabéticos con depresión ( $43.3 \pm 22.2$ ) que en aquellos sin depresión ( $17.7 \pm 17.8$ ;  $p = 0.005$ , prueba U de Mann-Whitney). Se encontró una correlación positiva entre las puntuaciones CES-D y AW ( $r^2 = 0.304$ ;  $p = 0.001$ ; Pearson).

**Conclusiones.** Considerando que la depresión y la ansiedad han sido asociadas a autocuidados inadecuados para alcanzar un buen control glicémico, proponemos el uso concomitante de CES-D y D-39, que son instrumentos validados y de fácil aplicación, como pruebas de cribado para detectar depresión y ansiedad en pacientes con DM2 residentes en comunidades rurales. Por lo tanto, si los pacientes dan positivo en uno o ambos instrumentos, se les puede derivar a un psiquiatra para confirmar el diagnóstico y proporcionar la terapia adecuada. Esto ayudaría a promover el cumplimiento de las medidas de control de la diabetes y a mejorar su calidad de vida.

**Palabras clave:** Diabetes mellitus tipo 2; Depresión; Ansiedad; Hemoglobina A glucosilada.

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## Introduction

Depressive disorders have a negative impact on the mental health of many people around the world. According to the systematic analysis and update of The Global Burden of Diseases, Injuries and Risk Factors Study 2017 (GBD 2017)<sup>1</sup>, since 2007 depressive disorders became the third leading cause of non-fatal health loss, measured in years lived with disability (YLD), which in 2017 amounted to 14.3% (13.1 - 15.6%). Based on data from GBD 2002, Mathers and Loncar projected that by 2030, in the baseline scenario, unipolar depressive disorders will rank second in disability-adjusted life years (DALYs), defined as the sum of years of potential life lost due to mortality plus the years of productive life lost due to disability<sup>2</sup>.

Several studies have estimated the prevalence of depression in México. In the National Survey of Psychiatric Epidemiology (2001-2002), the WHO World Mental Health Survey Initiative version of the Composite International Diagnostic Interview was applied to 5826 adults (54% women) aged 18-65, living in communities with >2500 inhabitants. It was found that major depressive disorder had a lifetime prevalence of 3.3%, and 1.5% in the previous year<sup>3</sup>. In another study performed during 1999 and 2001, 2509 adults (63.9% women) aged 18-92, residing in four major cities in different regions of México were interviewed, and major depression had a 12.8% lifetime prevalence, 6.1% of them in the previous year<sup>4</sup>. In the 2002-2003 National Performance Evaluation Survey based on the DSM-IV diagnostic criteria for depression, an adult aged  $\geq 18$  years was interviewed in each of 38700 households sampled in cities classified as rural, urban or metropolitan (with <2500, 2500-100000, or >100000 inhabitants, respectively). A total prevalence of depression of 4.5% (95% CI=4.1-4.9) was estimated<sup>5</sup>.

Projections of global mortality and burden of disease predict that, by 2030, unipolar depressive disorder will represent 6.7% of all DALYs in middle-income countries<sup>2</sup>, which currently includes México. To avoid this increase and the excessive burden on health systems, preventive measures are necessary, such as identifying and reducing modifiable factors that increase the risk of depression.

Strong evidence indicates that suffering type 2 diabetes mellitus (T2DM) increases the risk of developing depression<sup>6,7,8,9,10</sup>. A systematic review with meta-analysis of 24 high quality longitudinal cohort studies showed that people with T2DM had a greater risk of developing depression (pooled odds ratio 1.33; 95% CI, 1.18-1.51)<sup>10</sup>. The comorbidity of diabetes and depression acts in synergy to further reduce the quality of life (QoL) of afflicted persons, increasing the loss of productivity and health-care expenditure<sup>6,8,9</sup>. This interaction of both maladies is

bidirectional, since depression in diabetic patients favors negligence in treatment adherence<sup>6,8</sup>. Thus, many studies have documented that depression in patients with T2DM is associated with poor glycemic control, evidenced by higher levels of fasting blood glucose<sup>11,12,13,14</sup>, or glycated hemoglobin A (HbA1c) levels<sup>15,16</sup>. In a meta-analysis it was estimated that reducing the burden of T2DM by 10-25% could likely prevent between 0.93 and 2.34 x 10<sup>6</sup> cases of depression globally<sup>10</sup>. The above effect would be of utmost importance since in the GBD 2017, T2DM emerged as the fourth leading cause of age-standardized YLD worldwide, and the leading cause of YLD in Mexico<sup>1</sup>. Another reason for implementing measures to reduce the incidence of diabetes is that its comorbidity with depression multiplies the risk of mortality<sup>6,8,10</sup>.

In a study carried out in Mexicans over 40 years old, it was found that the prevalence of depression (DSM-IV) in diabetics with at least 5 years of evolution was 52%, while in non-diabetics it was 18% ( $\chi^2 = 12.7$ ;  $p < 0.05$ )<sup>7</sup>. Moreover, many studies have shown a high prevalence of depression in Mexican patients with T2DM, ranging from 27 to 73%, depending on the geographical area, and the type of instrument used<sup>7,11,12,13,14,17,18,19</sup>. These values are higher than the reported prevalence among the general population (3.3-6.1%)<sup>3,4,5</sup>.

The prevalence of depression in Mexican patients with T2DM has been mainly based on subjects from urban populations<sup>7,11,12,13,17,18,19</sup>, rather than from rural communities. In one study, comprising 4555 outpatients who attended 6 rural clinics in the state of Chiapas during 2014, a 7.9% global annual prevalence of depression was found (10.1% in women, 3.9% in men), but the association with T2DM was not significant ( $p = 0.06$ )<sup>20</sup>. In another study, carried out between 2017 and 2018, the Beck Depression Inventory (BDI) was applied to 112 patients with T2DM attending a rural clinic in the state of Yucatán. The prevalence of depressive symptoms was 62%, and the capillary blood glucose level was directly proportional to depression severity<sup>14</sup>.

Since in Mexico there is a great diversity of ethnic groups that live in rural communities, it is important to assess the relationship between depressive symptoms and diabetes control in these populations. Here we report the results of a cross-sectional study in a small sample of T2DM outpatients treated only with oral antidiabetic drugs and living in a rural community of predominantly Mayan ethnicity. The aim was to evaluate the possible correlation between the glycemic control assessed by HbA1c levels during the previous three months, and the depressive symptoms measured with the CES-D questionnaire, as well as with the QoL assessed with the D-39 instrument.

## Materials and methods

**Study population.** T2DM patients from the rural community of Cuncunul, Yucatan, and attending the local health center for their follow-up appointments, were invited to participate in this study. Data were collected between March 2, 2018 and June 19, 2018. Only subjects  $\geq 18$  years-old and taking oral glucose-lowering drugs (metformin and/or glibenclamide) were included. Subjects on insulin regimen were excluded since in this type of diabetic patients the association between depressive symptoms and poor glycemic control has already been established<sup>16</sup>. Likewise, patients taking antidepressant medication or presenting T2DM complications (diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, retinopathy, nephropathy, or coronary artery disease), were also excluded.

**Ethical considerations.** This study was approved by the ethics board of the CIR-UADY, being classified as 'risk-free' research (article 17- I: application of surveys, physical exams, or routine tests) according to the guidelines of the Regulation of the General Health Law on Health Research Topics in Mexico (last amendment in March 28, 2014). Subjects received information regarding the aim, procedures, likely benefits of the study, and the guarantee of data confidentiality, and those willing to participate signed a letter of informed consent (articles 20-22).

**General procedures.** The questionnaire used to assess the presence or absence of depressive symptoms was applied first, and then the one concerning QoL. All interviews ( $\leq 40$  min) were performed by the same person (LASD), who was performing his social service in medicine in the community of Cuncunul at the time of the study. Since most patients were not proficient in reading because of their low education level, the interviewer read aloud all the questions from both questionnaires, explaining their meaning in words that the subjects could better understand. Afterwards, the interviewer asked them to indicate the answer that best approximated how they had felt and recorded it. Body weight and height were measured at this time. Diagnosis of arterial hypertension was obtained from the clinical record (blood pressure cut-off points: systolic  $\geq 140$  mmHg and/or diastolic  $\geq 90$  mmHg)<sup>21</sup>. Having at least one Mayan surname was the criterion for Mayan ethnicity. In Mexico, two last names are used (from the father's side and from the mother's side).

**CES-D questionnaire.** The Center for Epidemiological Studies - Depression (CES-D) questionnaire (20 questions) was developed as a screening test to identify people at risk of clinical depression by assessing the subjective perception of mood and the level of daily functioning<sup>22,23</sup>. Each response is scored from zero to three on a scale of frequency of occurrence of the symptom during the previous week. Four

of the items are worded considering positive affect conditions and are scored inversely, so that their interpretation is the same as for the other questions. The resulting 20 values are added to obtain the total score (max. 60). Values  $\geq 16$  indicate clinically relevant depressive symptoms<sup>22</sup>. A meta-analysis reported that with the above criterion CES-D has a sensitivity of 0.87, a specificity of 0.70, and a diagnostic odds ratio of 16.2<sup>23</sup>.

**Diabetes-39 questionnaire.** The Diabetes-39 (D-39) questionnaire was used since it was specifically designed to evaluate QoL in patients with type 1 and type 2 diabetes<sup>24</sup>. A Spanish version has been validated in Mexican subjects with T2DM, searching for associations between QoL and glycemic indicators, such as HbA1c and fasting plasma glucose, resulting in high internal consistency and construct validity<sup>24</sup>. The 39 queries are grouped into five dimensions: energy-mobility (EM), diabetes control (DC), anxiety-worry (AW), social burden (SB), and sexual functioning (SF). Patients indicate how much their QoL was affected during the previous month by the action described in each question. Results for each section are converted into a 0 to 100 scale using a linear transformation formula. The total score is obtained from the five sections and reflects the impact of diabetes on QoL as a whole (better QoL for lower scores). It also contains two final questions that rate the patient's perception of his or her overall QoL and diabetes severity (DS)<sup>24</sup>.

**Body mass index.** Body weight (kg) and height (m) were measured with a mechanical weighing scale with stadiometer. Body mass index (BMI) was calculated with the formula: body weight / (height squared) and expressed in kg/m<sup>2</sup>; then subjects were classified as normal (20–24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>) or obese ( $\geq 30$  kg/m<sup>2</sup>)<sup>13,16</sup>.

**Glycosylated hemoglobin.** The levels of HbA1c determined during the previous three months were obtained from the medical records (n=9). In the absence of such measurement, the lab test was ordered during the visit (n=12). If the patient could not go to the lab, the measurement was made with a portable glucometer (ACINow<sup>®</sup>, PTS Diagnostics) at the end of the visit (n=12). No significant differences were found between HbA1c values (mean  $\pm$  SD) from clinical records (9.9 $\pm$ 2.5%), those requested to the lab (8.9 $\pm$ 2.7%), and those measured with glucometer (9.4 $\pm$ 2.3%) (One-way ANOVA,  $F_{2,30}=0.44$ ,  $p=0.65$ ). HbA1c  $< 8\%$  was chosen as the criterion for good glycemic control, according to the guidelines of the American College of Physicians<sup>25</sup>.

**Statistical analysis.** Reported values are means  $\pm$  SD, unless otherwise noted. HbA1c and BMI data sets (n=33) had a Normal distribution (D'Agostino-Pearson omnibus test), and unpaired comparisons were made with Student's

*t*-test (two-tailed). For questionnaire scores, some were normally distributed (CES-D, and the EM, DC, AW and QoL dimensions of D-39), while others were not (SB, SF, and DS dimensions, and total D-39 score). Hence, the Mann-Whitney *U*-test (two-tailed) was deemed appropriate to compare CES-D and D-39 scores from patients having good (HbA1c <8%, n=11) or poor (HbA1c ≥8%, n=22) glycemic control, or for having depression (CES-D ≥16, n=12) or not (CES-D <16, n=21). For some questionnaire scores that had significant differences, box plots were made to illustrate the dispersion of values in quartiles. Fisher's exact test was applied to ascertain associations between some variables, such as depression, D-39 dimensions, glycemic control, BMI or hypertension. Pearson determination coefficient (two-tailed) was obtained to establish the possible covariation between normally distributed variables. A *p* value < 0.05 was considered significant. Graphs and statistical analyses were made using Prism Ver. 8.0.2 (GraphPad Software Inc., San Diego, CA, USA).

## Results

A total of 33 patients with T2DM were studied, with a mean age of 58.5 ± 11.5 years (range: 38-80 years), and most were of Mayan descent (≈83%). Only a third of the patients had good glycemic control (HbA1c <8%), slightly more than one third had depression (CES-D ≥16), the majority (≈88%) was overweight or obese, and about half (54.5%) had hypertension (Table 1). No significant differences were found in the proportion of women and men within the categories of these variables (Fisher's exact test).

In this sample, 69.7% were women and 30.3% men. No significant differences were found between women and men with respect to age, HbA1c levels or BMI (Student's *t*-test), nor in the CES-D or D-39 total scores (Mann-Whitney *U*-test) (Table 2). Thus, the data from both genders were pooled for subsequent analyses.

### Relationship between HbA1c levels and CES-D questionnaire scores

Fifty percent (11/22) of T2DM patients with poor glycemic control (HbA1c ≥8%) had CES-D scores ≥16, while only 9.1% (1/11) of those with good glycemic control (HbA1c <8%) surpassed this cutoff value (*p*=0.027, Fisher's exact test). In diabetics with poor glycemic control (n=22) CES-D scores were significantly higher than in those with good control (n=11) (Figure 1a). Similarly, HbA1c levels in patients with depression (10.7±2.5%, n=12) were higher than in those without depression (8.6±2.2%, n=21; *p*=0.015, Student's *t*-test). When CES-D scores were plotted against HbA1c levels, a significant positive correlation was found between the two variables (Figure 1b).

**Table 1.** General characteristics of the group of T2DM patients studied.

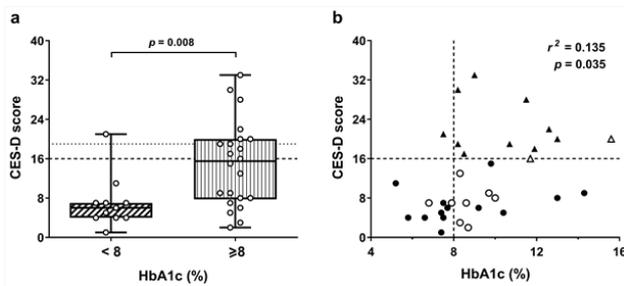
Variable	Female		Male		Total	
	n	%	n	%	n	%
<b>Age (y)</b>						
<50	3	13.0	3	30.0	6	18.2
≥50	20	87.0	7	70.0	27	81.8
<b>Mayan surnames</b>						
0	3	13.0	2	20.0	5	15.2
1	9	39.1	2	20.0	11	33.3
2	11	47.8	6	60.0	17	51.5
<b>Glycemic control</b>						
Yes (HbA1c <8%)	9	39.1	2	20.0	11	33.3
No (HbA1c ≥8%)	14	60.9	8	80.0	22	66.7
<b>Depression</b>						
No (CES-D <16)	13	56.5	8	80.0	21	63.6
Yes (CES-D ≥16)	10	43.5	2	20.0	12	36.4
<b>BMI</b>						
Normal	3	13.0	1	10.0	4	12.1
Overweight	6	26.1	4	40.0	10	30.3
Obese	14	60.9	5	50.0	19	57.6
<b>Blood pressure</b>						
Normal	10	43.5	5	50.0	15	45.5
Hypertension	13	56.5	5	50.0	18	54.5

Source: compiled and designed by the authors from demographic and clinical data (age, Mayan surnames, blood pressure, and BMI), laboratory tests (glycemic control), and CES-D scores (depression).

**Table 2.** Age, HbA1c levels, BMI, CES-D scores and D-39 scores in women and men.

	Women (n = 23)	Men (n = 10)	Total (n = 33)
Age (years)	58.8 ± 12.0	57.9 ± 10.8	58.5 ± 11.5
HbA1c (%)	9.3 ± 2.5	9.6 ± 2.5	9.3 ± 2.5
BMI	31.9 ± 6.2	30.8 ± 4.2	31.6 ± 5.6
CES-D (score) *	11 (1, 33)	7.5 (2, 20)	9 (1, 33)
D-39 (total score) *	17 (2, 51)	14.5 (2, 43)	17 (2, 51)

For Age, HbA1c, and BMI mean ± SD values are shown. \*Median (min, max). Source: compiled and designed by the authors from demographic and clinical data (age and BMI), laboratory tests (HbA1c), and scores of CES-D and D-39.

**Figure 1.** CES-D scores as a function of glycemic control.

a) Box-plots showing CES-D score distributions in T2DM patients grouped according to their glycemic control (good or poor). Open symbols represent individual CES-D scores. Values on or above the cut-off value of 16 (horizontal dashed line) indicate depression. The dotted line marks a more stringent cut-off value (19) for depression. The p value is from the Mann-Whitney U-test ( $U=52.5$ ). b) Scatterplot of CES-D scores and HbA1c % values measured in each diabetic patient. Points to the right of the cut-off value of 8 (vertical dashed line) indicate poor glycemic control. Triangles represent patients with depression; circles, patients without depression. Solid symbols are women; open symbols, men.  $r^2$  is the Pearson coefficient of determination.

Source: design and elaboration by the authors with Prism software, using CES-D scores, and HbA1c values from laboratory tests.

#### Relationship between glycemic control and D-39 questionnaire scores

No significant differences were found in the total score of D-39, or any of its dimensions, between subjects with poor (HbA1c  $\geq 8\%$ ,  $n=22$ ) and good (HbA1c  $< 8\%$ ,  $n=11$ ) glycemic control (Table 3). In addition, D-39 scores showed no correlation with HbA1c levels.

#### Relationship between D-39 questionnaire dimensions and CES-D scores

Although the D-39 questionnaire does not specify cut-off points for good or poor QoL, some authors have used the median of the values to sort them into these two categories<sup>24</sup>. In our sample, only the anxiety-worry (AW) dimension scores (median =20), had significant associations with other variables. Nineteen (57.6%) of the 33 diabetic patients scored  $\geq 20$  on the AW dimension. Among those classified as depressed (CES-D  $\geq 16$ ,  $n=12$ ), a significant proportion (83.3%) had AW scores  $\geq 20$  ( $p=0.033$ , Fisher's exact test). Indeed, after grouping T2DM subjects according to the absence or presence of depression, the AW dimension scores were significantly higher in those with CES-D scores  $\geq 16$

than in those with lower values (Figure 2a). Noticeably, among the ten patients with AW scores  $\geq 20$  and CES-D scores  $\geq 16$ , nine were women. When AW scores were plotted against CES-D scores, a significant positive correlation was found (Figure 2b). None of the other D-39 dimensions correlated with CES-D scores.

## Discussion

Here we describe the characteristics of a sample of patients with T2DM, analyzing the relationship between their glycemic control (assessed through HbA1c levels), depressive symptoms (CES-D scores) and quality of life (D-39 scores). A notorious finding was the significant difference in CES-D scores between patients with HbA1c blood levels  $< 8\%$  and those having higher values, which defines good or poor glycemic control, respectively, according to the Clinical Guidelines of the American College of Physicians<sup>25</sup>. In addition, in T2DM patients, a significant positive correlation was found between the magnitudes of the intensity of depressive symptoms and HbA1c levels, suggesting that they are directly related. Regarding QoL, assessed with the D-39 questionnaire, a significant difference was found only in the scores of the anxiety-worry dimension between patients with and without depression<sup>22</sup>. In this case, a significant positive correlation was also found, which suggests that the two variables influence each other.

#### Relationship between CES-D scores and glycemic control

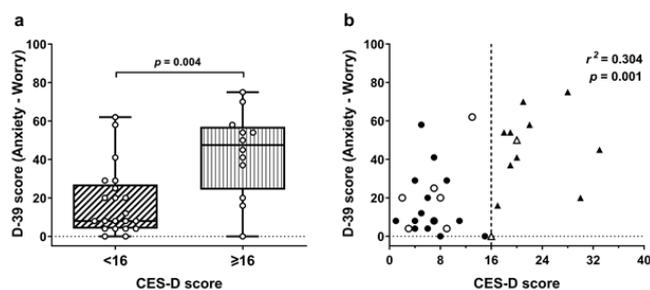
In our sample of 33 T2DM patients living in a rural community the prevalence of depression was 36.4%, which lies within the range (28 to 73%) reported in other studies performed in Mexican diabetic subjects<sup>7,11,12,13,14,17,18,19</sup>. The variability of depression prevalence is common and has been found in populations from other low- and middle-income countries<sup>26</sup>. This could arise from differences in the type of diagnostic instrument used, or from the wide range of answers obtained for some items, and which may be attributed to distinct cultural idiosyncrasies.

In the present study depression was detected in only 9.1% of T2DM subjects with good glycemic control, and this figure significantly rose to 50% in patients with HbA1c levels  $\geq 8$ . This finding resembles the results of a study conducted in 220 T2DM subjects in whom the Patient Health Questionnaire-9 was used to assess depression, finding that depression was a comorbidity in  $\approx 41\%$  of diabetics with HbA1c  $> 8.0\%$ <sup>16</sup>. In another study, the MINI International Neuropsychiatric Interview was used to survey 186 T2DM outpatients attending an urban hospital in the state of Yucatán, México, resulting in the diagnosis of depression in 32.3% of the subjects with uncontrolled blood glucose ( $n=133$ ), but only in 15.1% of those with good glycemic control ( $n=53$ )<sup>12</sup>.

**Table 3.** Quality of life dimensions (D-39) in T2DM patients according to good or poor glycemic control, and to absence or presence of depression.

Dimension	HbA1c <8% (n=11)	HbA1c ≥8% (n=22)	M-W* p	CES-D <16 (n=21)	CES-D ≥16 (n=12)	M-W* p
Energy & mobility	13 (0-45)	13 (1-43)	U=106.5 p=0.591	14 (0-45)	11.5 (5-37)	U=113.0 p=0.638
Diabetes control	11 (1-52)	21 (0-59)	U=74.5 p=0.077	13 (1-54)	22.5 (0-59)	U=106.5 p=0.477
Anxiety-worry	8 (4-70)	22.5 (0-75)	U=111.5 p=0.727	<b>8 (0-62)</b>	<b>47.5 (0-75)</b>	<b>U=51.5</b> <b>p=0.004</b>
Social burden†	6 (0-70)	8 (0-63)	U=95.5 p=0.334	6 (0-70)	6 (0-50)	U=120.5 p=0.845
Sexual functioning†	0 (0-77)	0 (0-94)	U=93.5 p=0.221	0 (0-77)	0 (0-94)	U=114.0 p=0.622
Total score†	14 (2-49)	18 (2-51)	U=85.5 p=0.180	14 (2-49)	20 (2-51)	U=84.0 p=0.119
Quality of life	66 (33-100)	66 (33-100)	U=111.0 p=0.712	66 (50-100)	66 (33-100)	U=112.5 p=0.595
Diabetes severity†	50 (0-66)	33 (0-83)	U=119.0 p=0.959	33 (0-83)	41.5 (0-83)	U=112.0 p=0.623

Values are Medians (Interquartile range). †Non-Normal distribution. \*Mann-Whitney U-test. Source: compiled and designed by the authors from D-39 scores, and statistical analyses performed with Prism software.

**Figure 2.** D-39 anxiety-worry scores as a function of CES-D scores.

a) Box-plots showing the distribution of D-39 AW dimension scores in T2DM patients grouped according to the absence (<16) or presence (≥16) of depression. Open symbols represent individual AW scores. The p value was obtained with the Mann-Whitney U-test (U=51.5). b) Scatterplot of D-39 AW scores and CES-D scores measured in each diabetic patient. The vertical dashed line indicates the cut-off value (16) of CES-D. Triangles represent patients with depression; circles, patients without depression. Solid symbols are women; open symbols, men.  $r^2$  is the Pearson coefficient of determination. Source: design and elaboration by the authors with Prism software, using D-39 and CES-D scores.

A relevant finding of the present study was that the CES-D scores were significantly correlated with the blood levels of HbA1c in a group of diabetic patients living in a rural community, and whose ethnicity is predominantly Mayan, a characteristic that was identified through their surnames. This agrees with the results of a study performed in 112 T2DM individuals, also of predominant Mayan descent and residing in Baca, a rural community in the same state (Yucatán). In this group of diabetics, the fasting glucose capillary levels were directly proportional to the severity of depression measured with the BDI and the Clinical Scale for Depression Diagnosis<sup>14</sup>. Likewise, in a study in patients with T2DM who attended the outpatient service of a hospital in Mexico City, the average of the last five blood glucose values was positively correlated with BDI depression scores<sup>11</sup>.

#### Relationship between D-39 scores and glycemic control

In the present study, no differences were found in the total score of D-39, or in any of its dimensions, between subjects with good (HbA1c <8%) or poor (HbA1c ≥8%) glycemic control, likely because of the small sample size. In contrast, in a study carried out in 249 Mexican subjects with T2DM, significant associations were found between HbA1c levels >8% and D-39 scores (odds ratio, 95% CI): diabetes control

(2.36, 1.42-3.94), social burden (1.78, 1.07-2.95), and total score (1.81, 1.09-2.99)<sup>24</sup>. Similarly, in a sample of 200 African T2DM patients, significant associations emerged between HbA1c levels and the diabetes control and social burden dimensions, as well as in the total D-39 score<sup>27</sup>.

#### Relationship between D-39 and CES-D scores

An interesting finding was that the group of T2DM subjects categorized as depressed (CES-D  $\geq 16$ ) had higher scores in the D-39 anxiety-worry dimension compared with those without depression (CES-D  $< 16$ ), and the scores of both parameters had a significant correlation. This is in line with the results of a cross-sectional study performed in 300 T2DM patients in whom stepwise multiple logistic regression analysis disclosed that comorbid anxiety increased the odds of suffering depression by a factor of 9.9<sup>28</sup>. Another interesting result of the present study was that among the ten patients in whom anxiety (AW scores  $\geq 20$ ) and depression (CES-D  $\geq 16$ ) coexisted, nine (90%) were female. This agrees with the results of a study conducted in 179 Mexican outpatients with T2DM attending an urban hospital, in whom 84.5% of the 81 individuals diagnosed with anxious depression (Goldberg Anxiety and Depression Scale) were women<sup>29</sup>. Logistic regression analysis also showed that anxious depression had a significant negative impact on medication adherence<sup>29</sup>. In two other multinational studies in larger groups of patients with T2DM, in which the 9-item Patient Health Questionnaire for depression and the 7-item Generalized Anxiety Disorder Questionnaire were used, the percentages of patients with comorbid depression and anxiety were correspondingly lower: 6.7% (133/1990)<sup>30</sup>, and 9.3% (354/3808)<sup>31</sup>. The co-occurrence of anxiety and depression in diabetics was associated with an increased likelihood of having reduced physical activity and poor eating habits<sup>30</sup>, as well as suboptimal diabetes self-care behaviors<sup>31</sup>.

#### Importance of diagnosing depression and anxiety in patients with T2DM

In patients with T2DM, comorbid depression and/or anxiety is associated with higher HbA1c levels<sup>15,16,29</sup>, supporting the idea of a bidirectional relationship between these mood disorders and poor glycemic control, which worsens functional disabilities and increases complications and premature mortality<sup>6,8,9</sup>. Therefore, the timely diagnosis of depression and anxiety in diabetic patients is essential for the implementation of interventions aimed at the elimination or reduction of the severity of symptoms, in order to increase treatment adherence, and, ultimately, to achieve better glycemic control. This notion is supported by the results from a longitudinal study carried out in 36 Mexican patients with T2DM, who were subjected to a problem-

solving therapy program at weekly intervals for 6-8 weeks<sup>32</sup>. Upon completion, they experienced significant reductions in HbA1c levels, and in depression and anxiety scores assessed with the BDI and the Beck Anxiety Inventory, respectively, and which remained low for an additional four months<sup>32</sup>.

#### Limitations

The present study had several limitations. First, the sample size was small, and could not be increased because the physician in charge of collecting the data was performing his social service, and was required to stay permanently in the health center. Thus, he could only interview the patients that went to the health center for medical consultation during the study period and met the inclusion criteria. Another limitation was the lack of a control group, in which HbA1c measurement would have been required to rule out subclinical diabetes. This was not feasible because of the limited availability of glucometer kits, and the alternative of requesting a laboratory test was discarded because this would have implied traveling to the city where the clinical laboratory is located, imposing an economic burden on these low-income patients. For the same reason, the assessment by a psychiatrist to confirm or rule out the diagnosis of depression was not possible because these specialists are not among the staff at the Cuncunul health center. The above limitations were partly due to the lack of external funding to conduct the study. Despite the restrictions, it is important to highlight that the study allowed achieving two of the goals promoted by the Health Ministry of Mexico: to provide research training to undergraduate MD students in the last stage of their career, and to gain insight on the knowledge about the main comorbidities suffered by low-income patients residing in rural communities.

#### Conclusions

From the results of this study, it is concluded that T2DM subjects classified as depressed according to the CES-D criteria have higher levels of HbA1c than those without depression. The finding that HbA1c levels were positively correlated with CES-D scores suggests that, as the glycemic control in T2DM patients worsens, their risk of suffering from depression increases. This is supported by the observation that depression occurred in 33.3% of the diabetics with poor glycemic control (HbA1c  $\geq 8\%$ ), but only in 3.0% of those with good control (HbA1c  $< 8\%$ ). The fact that D-39 "Anxiety-Worry" (AW) dimension scores were higher in diabetics with depression than in those without depression, and that both variables were correlated, suggests that T2DM subjects with depression have a higher risk of suffering anxiety disorders.

Considering that depression and anxiety have been associated with poor self-care to achieve good glycemic control, we propose the concomitant use of CES-D and D-39, which are validated and easy-to-apply instruments, as screening tests to detect depression and anxiety in DM2 patients residing in rural communities. Therefore, if patients test positive on one or both instruments, they can be referred to a psychiatrist to confirm the diagnosis and provide appropriate therapy. This would help promote adherence to diabetes control measures and to improve their quality of life.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## Contribuciones de los autores

Conceptualization and design, L.A.S.D., J.L.G.A.; Methodology, L.A.S.D., J.L.G.A.; Data acquisition (interviews, questionnaires, BMI, HbA1c), L.A.S.D.; Statistical analysis and data interpretation, L.A.S.D., F.J.A.C., J.L.G.A.; Principal investigator, J.L.G.A.; Bibliographic search, L.A.S.D., J.L.G.A.; Writing of manuscript — Preparation of the original draft, J.L.G.A.; Writing, revising and editing the manuscript, L.A.S.D., F.J.A.C., J.L.G.A.; Preparation of graphs and figures, J.L.G.A.; Supervision, F.J.A.C., J.L.G.A.; Acquisition of funds, does not apply.

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