www.endocrinologia.org.mx PERMANYER Rev Mex Endocrinol Metab Nutr. 2023;10:23-30

REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN ORIGINAL ARTICLE

A low percentage of patients with Type 2 diabetes and decreased adiponectin reach glycemic control

Un bajo porcentaje de pacientes con diabetes tipo 2 y adiponectina disminuida alcanza el control glucémico

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ABSTRACT

Background: Few studies classify individuals with type 2 diabetes (T2D) according to their body weight and compare their serum adipokines after a period of treatment. **Objective:** To know what percentage of T2D patients achieved glycemic control. **Material and method:** This cross-sectional and analytical study included 84 individuals, distributed into four groups: control (CNN, n = 13), control with obesity (CON, n = 38), patients with T2D, overweight or obesity but normal glucose (DON, n = 12), and patients with T2D, overweight or obesity and high glucose (DOH, n = 21). The selection criteria for T2D patients were daily treatment with metformin and a diagnosis of T2D within five years. **Results:** The 34% of patients in the DON group exhibited adequate glycemic control; however, their serum adiponectin levels were low (p = 0.001) compared to the CON group. **Conclusions:** Although patients in the DON group achieved normal glucose, adiponectin levels were decreased in these T2D patients compared with controls.

Keywords: Adipokines. Type 2 diabetes. Obesity. Overweight. Metformin. Adiponectine.

RESUMEN

Antecedentes: Pocos estudios clasifican a los individuos con diabetes tipo 2 (DM2) según su peso corporal y comparan sus adipocinas séricas después de un periodo de tratamiento. **Objetivo:** Determinar qué porcentaje de pacientes con DM2 logran un control glucémico. **Material y método:** Este estudio transversal y analítico incluyó a 84 individuos distribuidos en cuatro grupos: controles (CNN, n = 13), controles con obesidad (CON, n = 38), pacientes DM2 con sobrepeso u obesidad/glucosa normal (DON, n = 12) y pacientes con DM2 con sobrepeso u obesidad/glucosa alta (DOH, n = 21). Los pacientes tuvieron tratamiento diario con metformina y un diagnóstico de DM2 menor a cinco años. **Resultados:** El 34% de los pacientes del grupo DON alcanzaron un control glucémico; sin embargo, sus niveles séricos de adiponectina fueron bajos (p = 0.001) comparados con el grupo CON. **Conclusiones:** Aunque los pacientes del grupo DON alcanzaron un control glicémico, sus niveles de adiponectina fueron bajos comparados con los controles.

Palabras clave: Adipocinas. Diabetes tipo 2. Obesidad. Sobrepeso. Metformina. Adiponectina.

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Date of reception: 20-09-2021
Date of acceptance: 16-12-2022
DOI: 10.24875/RME.21000066
Available online: 23-02-2023
Rev Mex Endocrinol Metab Nutr. 2023;10:23-30

INTRODUCTION

Despite the wide variety of antidiabetic medications, most patients with Type 2 diabetes mellitus (T2D) develop vascular complications related to overweight and obesity[1]. Metformin is the principal first-line oral hypoglycemic agent for glycemic control in T2D patients according to international guidelines, and is safe, well tolerated, and used worldwide[2]. Obesity is associated with an increased risk of developing T2D[3]. In particular, adipokines are soluble factors derived mainly from adipocytes that interact with adipose tissue and play an essential role in inflammation and immunity associated with obesity[4]. The primary sources of adiponectin are adipocytes, in addition, a reduction in adiponectin levels plays a central role in obesity-related diseases, including T2D[5]. Furthermore, adiponectin has anti-inflammatory properties and downregulates the expression of many pro-inflammatory immune mediators. A high concentration of adiponectin in serum can improve insulin sensitivity in T2D patients[6]. Leptin is another adipokine that exerts metabolic effects on various tissues and the primary sources of leptin are adipocytes. However, in patients with obesity, leptin resistance could be the result of impairments in the leptin signaling pathway[7]. Thus, serum leptin levels increase throughout the course of T2D. Another important adipokine is retinol-binding protein 4 (RBP4), which is involved in systemic insulin resistance. RBP4 is physiologically essential for the transport of retinol (Vitamin A) from the liver to peripheral tissues[8] and plays a role in glucose homeostasis, and its level is inversely related to renal function and age[9]. On the other hand, for more than 20 years, the low percentage of T2D patients who achieve glycemic control has attracted attention; Harris et al. (1999) reported lower glycemic control in Mexican-American men (45%)[10]. In a recent study in a Kuwaiti population, only 37.8% of patients with diabetes receiving glucose-lowering treatment achieved adequate glycemic control[11]. In the present study, the goal was to assess what percentage of patients with T2D achieved glycemic control and if they regulated their adipokine levels compared to control subjects with overweight or with obesity and normal glucose.

MATERIALS AND METHODS

Participants

Residents from Armería, Colima, Mexico, were invited to participate in a cross-sectional and analytical study that included evaluation of body mass index (BMI). Out of the residents who voluntarily attended the health center, 84 participants were selected to participate in the present study. A total of 51 non-diabetic control subjects and 33 diabetic patients were distributed into four groups based on weight and fasting glucose level (FGL). Control normal weight and normal glucose (CNN, n = 13), control with overweight or obesity and normal glucose (CON, n = 38), patients with T2D, overweight or obesity but normal glucose (DON, n = 12), and patients with T2D, overweight or obesity and high glucose (DOH, n = 21). The diagnosis of T2D was made according to the criteria of the American Diabetes Association, which considers a FGL ≥ 126 mg/dL as an indicator of T2D[12]. Only patients with TD2 who only received metformin monotherapy treatment (850 mg twice daily) were selected and with glycemic control for < 5 years and presented no cardiovascular disease; because metformin is a first-line therapy for T2D, given its relative safety and has beneficial effects on hemoglobin A1c, weight, and cardiovascular mortality (compared with sulfonylureas) [13]. The control subjects included in the study had FGL ≤ 125 mg/dL. Patients with the following conditions were excluded from the study: malignant tumors, liver disorders, renal insufficiency, neurological disorders, and ongoing infections or autoimmunity.

Serum isolation

Peripheral blood samples were collected by venipuncture and serum was then stored in 1 mL aliquots at −80°C until needed[14].

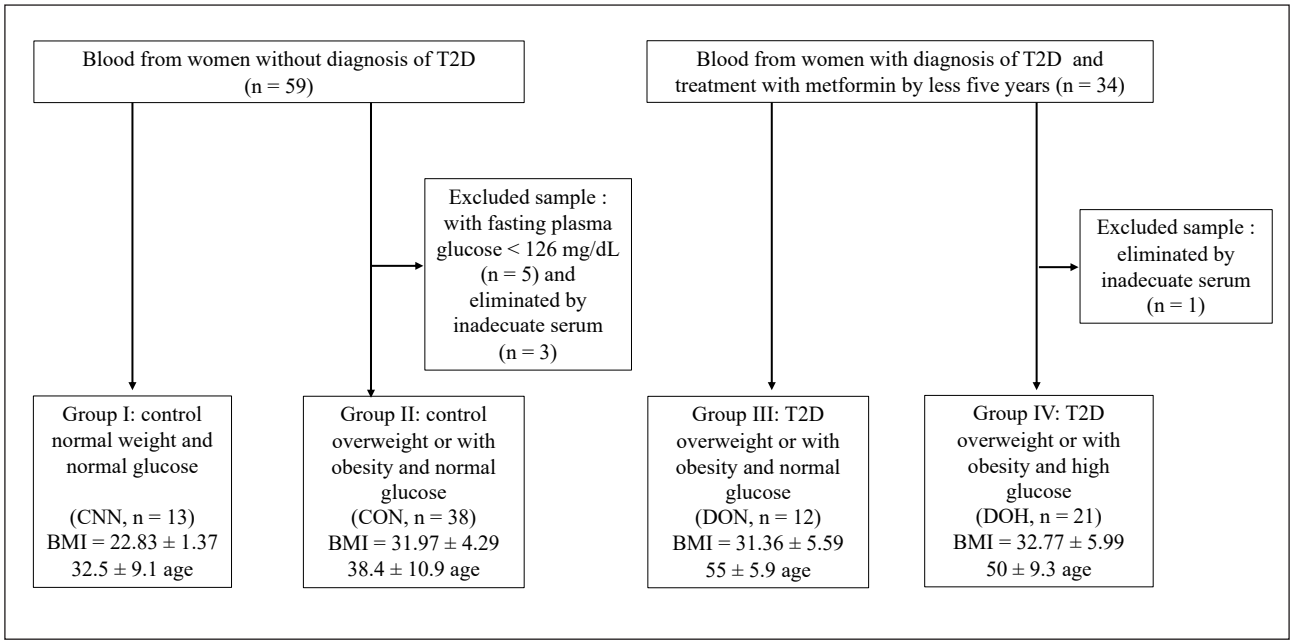

Figure 1. Selection of the study cohort. The control normal weight and normal glucose (CNN, n = 13), control overweight or obese and normal glucose (CON, n = 38), T2D overweight or obese and normal glucose (DON, n = 12), and T2D overweight or obese and high glucose (DOH, n = 21) groups.

Glucose and triglycerides level measurement and flow cytometry

Blood glucose and triglycerides were measured using an enzymatic method with a Gluc-Pap kit (RANDOX Laboratories). A BioLegend LEGENDplex™ bead-based immunoassay was used for simultaneous quantification of serum adiponectin, leptin, and RBP4 levels using a FACSAria I cell separator (BD Biosciences, San Jose, CA, USA) flow cytometer[15].

Data analysis

To determine the type of data distribution, we used the Shapiro–Wilk test for a small sample size. The ANOVA was used to evaluate differences in normally distributed continuous variable data of glucose and age, between the four study groups. The data of triglycerides, adiponectine, leptine, and RBP4 showed an abnormal distribution in some groups and the non-parametric tests of comparison of medians for independent samples H of Kruskal–Wallis and U de Mann–Whitney were used to compare the median between study groups. Pearson and Spearman's correlation coefficients were calculated to study the relationships between variables in all participants. $p < 0.05$ was considered statistically significant; all calculations were performed using SPSS version 24.0 for Windows (SPSS, Chicago, IL).

Ethics statements

This study was carried out with the approval of both the Institutional Committee of Bioethics under number 0252019 and was performed in accordance with the Declaration of Helsinki[16].

RESULTS

Characteristics of the individuals included in the study

Twelve of T2D patients (36.36 %) had achieved glycemic control and presented normal glucose (DON group). The rest of these patients (63.64 %, n = 21, DOH group) had not achieved glycemic control (Fig. 1).

Comparison of age, glucose, and triglycerides between study groups

The age averages of the subjects who were overweight or presented obesity (CON, DON, and DOH groups) were similar. However, age differed significantly between the DON ($p < 0.001$) and DOH ($p < 0.001$) groups compared to the CNN group (Fig. 2A). As expected, glucose levels average was significantly higher ($p < 0.001$) in the group of T2D patients who had not achieved glycemic control (DOH group) than in the other groups (Fig. 2B). Thus, the median of triglyceride level was 80 mg/dL in the CNN, 119 mg/dL for the CON, 120 mg/dL for the DON and 150 mg/dL for DOH. These median was different between the groups ($p = 0.015$) (Fig. 2C).

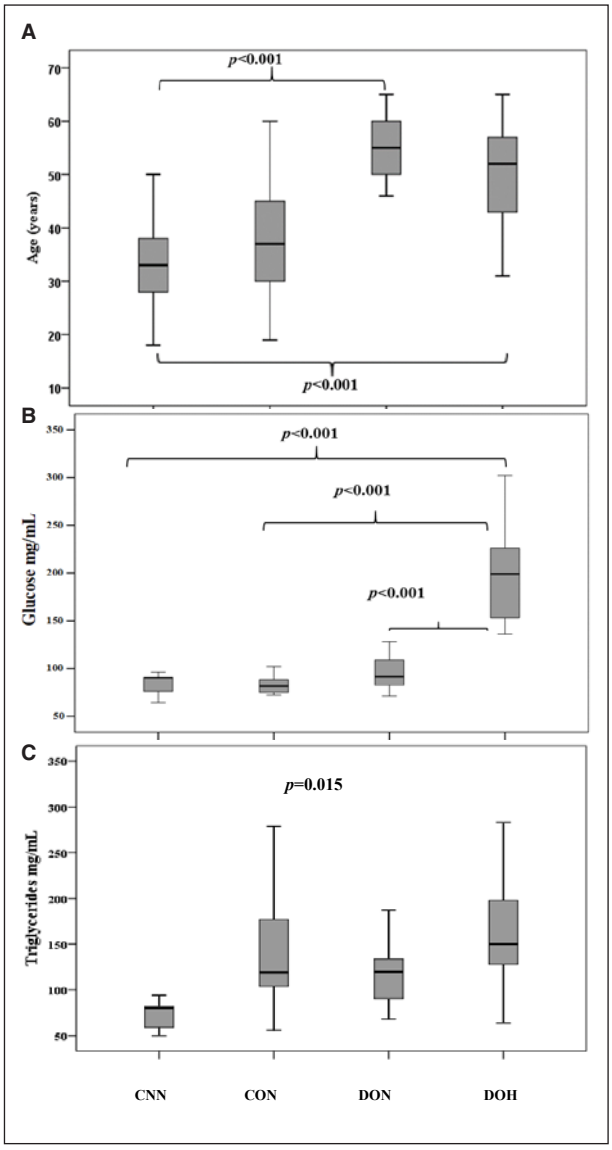

Figure 2. Comparison of age, fasting glucose and triglycerides levels between the four study groups. (1) CNN: control normal weight and normal glucose. (2) CON: control overweight or obese and normal glucose. (3) DON: T2D overweight or obese and normal glucose. (4) DOH: T2D overweight or obese and high glucose. A value of $p < 0.05$ was considered statistically significant.

Comparison of adiponectin, leptin, and RBP4 levels between study groups

When the medians of the quantitative variable adiponectin were compare, the null hypothesis was reject, because were statistically significant differences intergroup in the medians of these data with $p < 0.001$. The median of adiponectin level was 8.16 ng/mL for the CNN, 10.80 ng/mL for the CON, 6.12 ng/mL for the DON, and 6.51 ng/mL for DOH (Fig. 3A). Regarding leptin, in median, no significant difference ($p = 0.023$) were observed between the groups (Fig. 3B). Furthermore, the level of RBP4 in serum was similar between the study groups ($p = 0.508$) (Fig. 3C).

Correlation between age, BMI, fasting glucose, triglycerides, and adipokine levels

The correlations between age, BMI, glucose, triglycerides, adiponectin, leptin, and RBP4 across individuals in the four groups were evaluated, using Pearson and Spearman's correlation analyses. We observed that six correlations were significantly correlated as a result of both Pearson (P) and Sperman (S)´s analyses, respectively: age versus glucose (P: $r = 0.323$, $p = 0.003$, and S: $r = 0.275$, $p = 0.011$); age versus adiponectin (P: $r = -0.400$, $p \leq 0.001$ and S: $r = -0.478$, $p < 0.001$); BMI versus triglycerides (P: $r = 0.237$, $p = 0.030$ and S: $r = 0.358$, $p = 0.011$); BMI versus leptin (P: $r = 0.463$, $p < 0.001$ and S: $r = 0.456$, $p < 0.001$); glucose versus adiponectin (P: $r = -0.206$, $p = 0.006$ and S: $r = -0.292$, $p = 0.007$), and adiponectin versus RBP4 (P: $r = 0.298$, $p = 0.006$ and S: $r = 0.250$ $p = 0.022$) (Table 1).

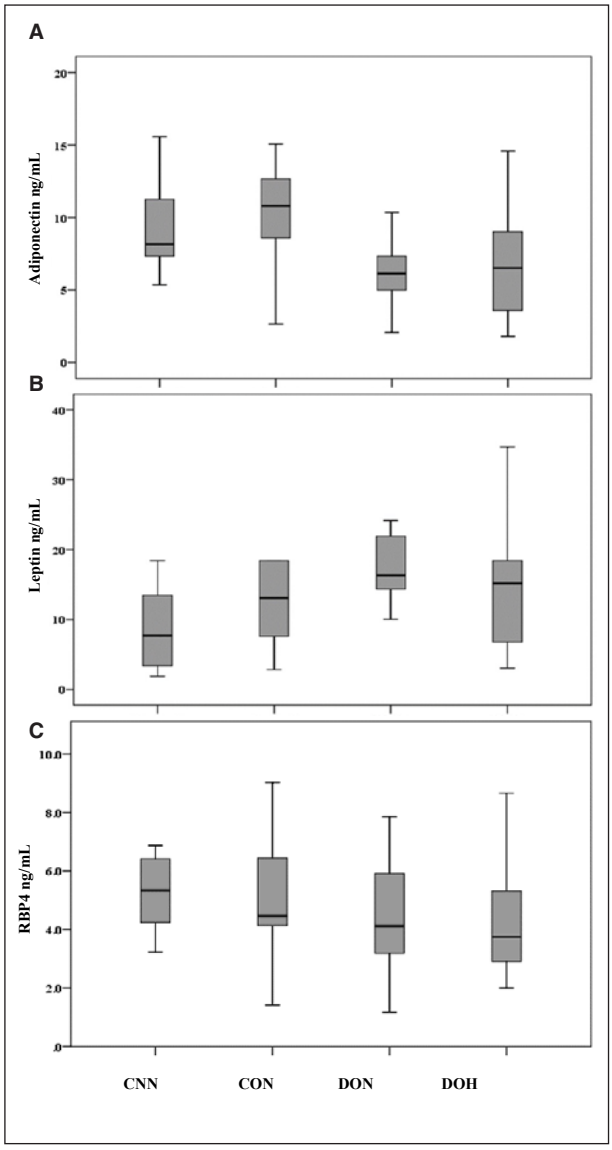

Figure 3. Comparison of adiponectin, leptin, and RBP4 levels between the four study groups, i.e., the CNN, CON, DON and DOH. A value of $p < 0.05$ was considered statistically significant.

DISCUSSION

T2Ds mellitus is a chronic illness with the highest burden worldwide, and the prevalence of diabetes in Mexico is even higher (9.4%) than the world average (8.5%)[17]. Thus, urgent prophylactic and control measures must be undertaken as primary treatment strategies[18]; moreover, patients must be urged to comply with strict periodic medical checkups, in particular in Mexico where 30.5% of adults with T2D do not report any control strategy[19].

The results of the present study are relevant and alarming because they indicate that despite accessibility to diabetes diagnostic services and public health efforts to administer hypoglycemic agents and recommend healthy lifestyle changes, most of the T2D subjects had not achieved glycemic control at the time of the questionnaire. In the present work, the percentage of metformin-treated overweight or obese T2D patients in a controlled glycemic state was low. This observation is consistent with the study carried out by Abdulla et al. (2020) in 278 drug-treated diabetic patients where only 37.8% had achieved glycemic control[11]. The results may reflect a decrease in metformin treatment adherence over the years in the DOH group, as well as a lack of both medical and psychological monitoring. Thus, it is essential to provide interventions at the local level that encourage reduced energy intake and regular physical activity and to monitor adherence to hypoglycemic agents.

We found that the average age of the DON and DOH groups was similar to the CON group, which also presents overweight or obesity. It was observed that the glucose and triglycerides data exhibited a similar increasing trend across the four study groups. In addition, we found that the healthy group with normal weight (CNN) had a lower level of triglycerides in serum compared with individual with overweight or obesity. This is interesting, because the triglycerides and glucose index may be useful for the identification of subjects with decreased insulin sensitivity[20].

Moreover, we found significantly lower levels of adiponectin in T2D patients than CON and CNN groups, even in glucose-controlled patients (DON group). This could be explained by the fact that adiponectin production in adipocytes is inhibited by oxidative stress and hypoxia[6]. The clinical implication of these results is that hypoadiponectinemia is associated with increased levels of inflammatory markers such as C-reactive protein, IL-6, and TNF[21]. In particular, adiponectin decreased in the DON and DOH groups contributed to insulin resistance, while leptin increased in the DON group compared to the healthy group, which indicates an alteration in energy homeostasis[22].

Table 1. Pearson's and Spearman's correlation of variables analyzed in this study

Variable 1*	Variable 2*	Pearson r value (p-value)	Spearman r value (p-value)
Age	BMI	0.184 (0.093)	0.166 (0.130)
	Glucose	0.323* (0.003)	0.275* (0.011)
	Triglycerides	0.135 (0.220)	0.176 (0.109)
	Adiponectin	−0.400* (< 0.001)	−0.478** (< 0.001)
	Leptin	0.234** (0.032)	0.182 (0.097)
	RBP4	−0.117 (0.288)	−0.178 (0.105)
BMI	Glucose	0.211 (0.054)	0.159 (0.148)
	Triglycerides	0.237** (0.030)	0.358** (0.001)
	Adiponectin	−0.204 (0.062)	−0.133 (0.228)
	Leptin	0.463* (< 0.001)	0.456** (< 0.001)
	RBP4	−0.031 (0.781)	−0.022 (0.845)
Glucose	Triglycerides	0.339* (0.002)	0.139 (0.209)
	Adiponectin	−0.206* (0.006)	−0.292** (0.007)
	Leptin	0.061 (0.584)	0.013 (0.904)
	RBP4	−0.154 (0.162)	−0.147 (0.183)
Triglycerides	Adiponectin	0.215** (0.049)	0.138 (0.211)
	Leptin	0.058 (0.602)	0.226* (0.039)
	RBP4	−0.210 (0.055)	−0.190 (0.083)
Adiponectin	Leptin	−0.218** (0.046)	−0.147 (0.181)
	RBP4	0.298* (0.006)	0.250* (0.022)
Leptin	RBP4	0.056 (0.616)	0.079 (0.476)

*Age (years), BMI (calculated as weight in kilograms divided by the square of height in meters), glucose (mg/dL), triglycerides (mg/mL), adiponectin (ng/mL), leptin (ng/mL) and RBP4 (ng/mL) in subjects with and without T2D (n = 84). T2D patients had been receiving metformin treatment for < 5 years and reported treatment adherence to the hypoglycemic drug.
*The correlation is significant at the 0.01 level (two-sided p-value).
**The correlation is significant at the 0.05 level (two-sided p-value).

In addition, the hypothesis of this cross-sectional study was that women with T2D have low levels of adiponectin, so we also measured the odds ratio (OR = 7.15, CI 95%: 2.63-19.46). Thus, this OR of 7.15 is read as 7.15:1, which means that there is a 7.5 times greater probability that a low concentration of adiponectin will be found in total women with DM2 in this sample compared whit total controls. Whit this information and the results of this study, the alternative hypothesis was accepted: the medians of adiponectin between the different study group are different. The above reinforces the idea that adiponectin is anti-inflammatory and is found in lower concentrations in people with T2D, who have a chronic inflammatory process.

For other hand, adiponectin and leptin were heterogeneous in the DOH group, which could be related to the fact that these patients had not achieved glycemic control, and a possible relationship with hypothalamic insulin and leptin signaling, which play a crucial role in the development of insulin resistance[23]. In addition, adiponectin has anti-inflammatory properties, this may suggest that the CNN and CON groups have a lower degree of inflammation compared to the DON group, which although it reached glycemic control, had significantly less adiponectin in serum. T2D is a metabolic disease that triggers an inflammatory response of the immune system to hyperglycemia as well as the presence of inflammatory mediators

produced by adipocytes and macrophages in fat tissue[24]. From the pathophysiological aspect, it implies that the metabolic burden caused by hyperglycemia also implies oxidative stress and tissue inflammation, in the kidney, known as diabetic nephropathy[25]. Thus, a low concentration of adiponectin can already be observed in the groups with T2D even though they still do not present complications.

In addition, correlation analyses confirmed a negative correlation between age and adiponectin levels and a positive correlation between age and leptin levels in all participants. This last finding may be because aging is also associated with resistance to leptin and/or to a decrease in receptors for this hormone[26]. Furthermore, although there were no differences in RBP4 between the study groups (Fig. 3C), a positive correlation between RBP4 and adiponectin in all studied individuals was observed, which could be related with a previous study showing a positive correlation between RBP4 and the levels of high-density lipoprotein cholesterol and other lipids in T2D patients[9].

In addition, RBP4 levels did not correlate with glucose or leptin in any of the studied groups. This is similar to a report by Kwanbunjan et al. (2018), who did not find a relationship between these molecules in individuals with a high risk of T2D[27]. In a Chinese population, the association between RBP4 and the risk of T2D was assessed and it was reported that increased plasma RBP4 levels were associated with a higher risk of T2D in women but not in men[28]. In another study, RBP4 levels were inversely correlated with age[9]; even if a correlation was found in our study, it did not reach significance.

Notably, the Spearman's analysis showed a no significant correlation between adiponectin and leptin across the four study groups with normal weight, overweight, or obesity. Although Forny-Germano et al. (2019), reported that obese patients, increased leptin and decreased adiponectin[29]. Furthermore, in a non-diabetic Japanese-American population, a higher concentration of leptin was associated with more intra-abdominal fat (IAF), and a lower concentration of adiponectin was associated with less IAF[30]. One of the strengths of the present study is that our results are consistent with other studies that include a greater number of samples, according to serum levels of adipokines reported in T2D patients of different ethnic origin. An inconvenient during data analysis was the biological variability, in part associated with the relatively low number of patients per sub-study group, as four of the six variables evaluated here presented a non-normal distribution in more than one group.

CONCLUSIONS

Patients who did not achieve metabolic control (DOH group) had a high variability in the concentration of glucose, adiponectine, and leptin compared with DON group, a recommendation is to implement a lifestyle therapy in these patients. In relation to the low levels of adiponectin in T2D patients without metabolic control, more studies are needed about the metabolism of this molecule and its potential therapeutic use, since it increases insulin sensitivity and decreases cardiovascular risk.

AUTHORS' CONTRIBUTIONS

MLPL wrote the manuscript and researched data. EJHO researched data and invited the patients and control subjects to participate in the study. PCOL contributed to the discussion and reviewed/edited the manuscript/researched data. EPMO contributed to the discussion and reviewed/edited the manuscript. A.S. reviewed/edited the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We thank CUSUR, Universidad de Guadalajara and Kresge Library (Scripps Research, La Jolla Campus) for information resources.

FUNDING

Research Coordination, Southern University Center, Universidad de Guadalajara.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient's data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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