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PHARMACOLOGICAL TREATMENT AND OTHER FACTORS ASSOCIATED WITH FATTY LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

TRATAMIENTO FARMACOLÓGICO Y OTROS FACTORES ASOCIADOS A ENFERMEDAD DE HÍGADO GRASO EN PACIENTES CON DIABETES MELLITUS TIPO 2

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity in individuals with type 2 diabetes mellitus (T2DM). **Objective:** To identify pharmacological treatments and other factors associated with NAFLD in patients with T2DM. **Methods:** An analytical cross-sectional study was conducted in Morelos, Mexico, among T2DM patients treated at the DiabetIMSS Module of the Instituto Mexicano del Seguro Social (IMSS). A total of 109 patients over 18 years of age receiving pharmacological treatment were included, selected through simple random sampling. Sociodemographic, clinical, and biochemical variables were collected. NAFLD was diagnosed by hepatic ultrasound. Statistical analyses included ANOVA, chi-square tests, and multilevel logistic regression, with a p-value <0.05 considered statistically significant. **Results:** In the adjusted logistic regression model, cholesterol levels were significantly associated with NAFLD (OR = 1.05; 95% CI: 1.00–1.10; p = 0.038), while statin use showed an inverse association (OR = 0.01; 95% CI: 0.00–0.18; p = 0.003). In the adjusted multilevel model, the associations with cholesterol (OR = 1.05; 95% CI: 1.00–1.10; p = 0.040) and statin use (OR = 0.01; 95% CI: 0.00–0.25; p = 0.005) remained significant for grade I NAFLD. For grade II, significant associations were identified with female sex (OR = 91.20; 95% CI: 2.54–328.00; p = 0.014), mean arterial pressure (OR = 1.19; 95% CI: 1.01–1.40; p = 0.032), and statin use (OR = 0.01; 95% CI: 0.00–0.02; p < 0.001). **Conclusion:** In patients with T2DM, elevated cholesterol and high mean arterial pressure were associated with an increased risk of NAFLD. Statin use demonstrated a strong potential protective effect. Further research is needed to confirm these findings and evaluate new therapeutic alternatives.

Keywords: Type 2 Diabetes Mellitus; Non-Alcoholic Fatty Liver Disease; Pharmacotherapy; Risk Factors. (Source: MESH-NLM)

RESUMEN

Introducción: La enfermedad de hígado graso no alcohólico (EHGNA) es una comorbilidad frecuente en personas con diabetes mellitus tipo 2 (DMT2). **Objetivos:** Determinar el tratamiento farmacológico y otros factores asociados a EHGNA en pacientes con DMT2. **Métodos:** Se realizó un estudio transversal analítico en Morelos, México, en pacientes con DMT2 atendidos en el Módulo DiabetIMSS del Instituto Mexicano del Seguro Social (IMSS). Se incluyeron 109 pacientes mayores de 18 años bajo tratamiento farmacológico, seleccionados por muestreo aleatorio simple. Se recolectaron variables sociodemográficas, clínicas y bioquímicas. La EHGNA se diagnosticó mediante ultrasonido hepático. Se aplicaron pruebas estadísticas como ANOVA, chi cuadrada y regresión logística multinivel ajustada, considerando un valor de p<0,05 como significativo. **Resultados:** En el modelo ajustado de regresión logística, se observó asociación significativa entre niveles de colesterol y EHGNA (OR=1,05; IC95%: 1,00–1,10; p=0,038). El uso de estatinas se asoció de manera inversa (OR=0,01; IC95%: 0,00–0,18; p=0,003). En el modelo ajustado multinivel, se mantuvo la asociación con colesterol (OR=1,05; IC95%: 1,00–1,10; p=0,040) y estatinas (OR=0,01; IC95%: 0,00–0,25; p=0,005) en grado I. Para grado II, se identificaron asociaciones con sexo femenino (OR=91,20; IC95%: 2,54–328,00; p=0,014), presión arterial media (OR=1,19; IC95%: 1,01–1,40; p=0,032) y estatinas (OR=0,01; IC95%: 0,00–0,02; p<0,001). **Conclusión:** En pacientes con DMT2, el colesterol elevado y la presión arterial media alta se asocian con mayor riesgo de EHGNA. El uso de estatinas mostró un potencial efecto protector robusto. Se requiere mayor investigación para confirmar estos hallazgos y evaluar nuevas alternativas terapéuticas.

Palabras clave: Diabetes Mellitus Tipo 2; Enfermedad del Hígado Graso no Alcohólico; Farmacoterapia; Factor de Riesgo. (Fuente: DeCS- BIREME)

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INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is the most prevalent liver disease worldwide and includes both non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Both conditions result from a chronic accumulation of fat in the liver, which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma[1,2]. In Europe and the United States, NAFLD represents one of the leading causes of chronic liver disease, with its prevalence increasing from 47% to 75% between 1988 and 2008, in association with metabolic risk factors such as obesity, type 2 diabetes mellitus (T2DM), and hypertension[3].

In 2016, the global prevalence of NAFLD was 25.2%, with the highest rates in the Middle East (31.8%) and South America (30.5%), and the lowest in Africa (13.5%)[4]. In Mexico, prevalences between 10.3% and 30.9% have been reported, although in populations with obesity or T2DM, these rates reach between 70% and 86%[5-8]. This is related to the global rise in obesity and diabetes. According to the World Health Organization (WHO), in 2022, 43% of adults over 18 years old (2.5 billion) were overweight, and 16% (890 million) were obese[9]. The World Obesity Atlas 2022, published by the World Obesity Federation, projects that by 2030, one billion people will live with obesity, which equates to one in five women and one in seven men[10]. Meanwhile, the 2021 Diabetes Atlas of the International Diabetes Federation (IDF) estimates that 537 million adults have diabetes (10.5%), a number that will rise to 643 million in 2030 and 783 million in 2045, representing a 46% increase[11]. These figures reflect the close association between NAFLD, obesity, and diabetes, as well as the need for preventive strategies and early diagnosis in vulnerable populations.

In Mexico, deaths from cirrhosis secondary to NAFLD increased by 128% between 1991 and 2021, reaching 6.9 deaths per 100,000 inhabitants, with similar patterns in Morelos[12], highlighting the need for more accurate and accessible diagnostic methods. The treatment of NAFLD combines non-pharmacological interventions, such as diet and exercise, with pharmacological options. Exercise improves clinical and biochemical parameters depending on its type, intensity, and frequency[13-15]. Low-carbohydrate diets[15] and the Mediterranean diet offer biochemical benefits, though without consistent clinical improvements[16]. While adherence is crucial[17], pharmacological treatment is also essential.

Major international guidelines — including the European Association for the Study of the Liver, the European Association for the Study of Diabetes, the European Association for the Study of Obesity, the American Association for the Study of Liver Diseases, and the National Institute for Health and Care Excellence — recommend a range of drugs targeting pathophysiological mechanisms such as oxidative stress, insulin resistance, and inflammation. These include vitamin E, polyphenols, glutathione, bile acids (ursodeoxycholic, obeticholic), oral antidiabetics (pioglitazone, metformin,

DPP-4 inhibitors, GLP-1 agonists), omega-3 fatty acids, berberine, statins, fibrates, pentoxifylline, microbiome modulators, and antifibrotics such as pirfenidone[18-22]. Pharmacotherapy should be individualized according to the patient, the stage of the disease, and comorbidities. Some medications, originally indicated for other diseases, have shown benefits in managing NAFLD, emphasizing the need for a comprehensive approach. However, combining these treatments with sustained lifestyle changes remains essential for effective management. Therefore, the aim of this study was to determine the pharmacological treatment and other factors associated with fatty liver disease in patients with T2DM.

METHODS

Study design and area

A cross-sectional analytical study was conducted in the state of Morelos, Mexico. The research was carried out at the Family Medicine Unit No. 3 of the Instituto Mexicano del Seguro Social (IMSS), specifically at the DiabetIMSS Module, where comprehensive services are provided to patients with T2DM. The study was designed to assess

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the association between pharmacological treatment and the presence of NAFLD in this population.

Population and sample

The study population consisted of patients with a confirmed diagnosis of T2DM enrolled at the DiabetIMSS Module of Family Medicine Unit No. 3 of IMSS. Participants were 18 years or older, receiving pharmacological treatment for T2DM, and willing to participate by signing an informed consent form. Exclusion criteria included a history of hepatitis C, HIV infection, or chronic alcoholism documented in the electronic medical record. The sample consisted of 109 patients selected through simple random sampling; the sample size was calculated based on an expected odds ratio (OR) of 3.72 according to a previous study[23] with hypertriglyceridemia as the independent variable. The sample size was determined based on epidemiological criteria and operational feasibility within the medical unit.

Variables and instruments

Sociodemographic variables (age, sex, marital status, education level, occupation) were collected using a structured questionnaire. Clinical history was accessed through the Family Medicine Information System to obtain relevant clinical background. Somatometric measurements such as weight, height, body mass index (BMI), and blood pressure were taken by a trained and standardized field worker, under direct supervision of the principal investigator.

Additionally, blood samples were taken at the institutional clinical laboratory to analyze the following biochemical parameters: glucose, total cholesterol, triglycerides, urea, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Values were recorded according to the International System (SI) units. NAFLD was evaluated using liver ultrasound performed by a trained radiologist, initially interpreted by the same radiologist and later by two additional radiologists independently, to determine inter-observer agreement.

Procedures

After signing the informed consent form, participants were given clear instructions to attend the clinical laboratory in a fasted state for blood sample collection. Participants were then referred to the imaging department, where liver ultrasound was performed. The ultrasound findings were classified into three grades based on the visualized characteristics: Grade I (mild), with a normal-sized liver, well-defined borders, and clear visualization of the portal vein vessels; Grade II (moderate), with mild enlargement of the liver, difficulty identifying the diaphragm and portal vessels, and increased echogenicity of the hepatic parenchyma; and Grade III (severe), with marked liver enlargement, limited visualization of the diaphragm, vascular pattern, and deep areas of the organ. All collected information was coded alphanumerically to ensure participant confidentiality.

Statistical analysis

A descriptive statistical analysis was performed. For qualitative variables, absolute frequencies and percentages were calculated, while for quantitative variables, central tendency measures (mean and median) and dispersion measures (standard deviation and interquartile range) were determined, depending on the data distribution, assessed using the Kolmogorov-Smirnov test. Comparisons between groups were made using ANOVA or Kruskal-Wallis for quantitative variables, and the chi-square test or Fisher's exact test for qualitative variables.

Logistic regression and multilevel logistic regression analyses were conducted, both in crude and adjusted models, to identify factors associated with the presence and severity of NAFLD. Finally, a multiple model was constructed to adjust for potential confounding factors. A p-value <0.05 was considered statistically significant.

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Ethical aspects

This study was approved by the Local Research Committee 1701 of IMSS Morelos, under registration number R-2019-1701-015. The ethical principles established in the Declaration of Helsinki and the national regulations regarding human research were respected.

RESULTS

The data from 109 patients with T2DM were analyzed. The average age was 56.6 ± 10.6 years. Female patients predominated, comprising 67.9%. Regarding marital status, 66.1% of the participants were married.

The majority had secondary education level (34.9%), and 47.7% were dedicated to household tasks. Regarding habits, 65.1% did not consume alcohol, and 87.2% were non-smokers. The median duration of T2DM was six years, with a significant difference between the groups with and without hepatic steatosis (p-value = 0.003). The median energy consumption was 1,866 kcal (Table 1).

Table 1. Sociodemographic characteristics of patients with Type 2 Diabetes Mellitus from the DiabetIMSS Module at the No. 3 Family Medicine Unit, Jiutepec, Morelos.

Table 1. Continuation

Variable	Total (n=109)	No Steatosis (n=16)	Steatosis GI (n=58)	Steatosis GII (n=35)	p-value
Occupation					
• Homemaker	**52 (47.7%)**	6 (37.5%)	**29 (50.0%)**	**17 (48.6%)**	0.893£
• Laborer	4 (3.7%)	--	3 (5.2%)	1 (2.9%)	
• Employee	41 (37.6%)	**8 (50.0%)**	19 (32.8%)	14 (40.0%)	
• Self-employed	12 (11.0%)	2 (125%)	7 (12.1%)	3 (8.6%)	
Alcohol consumption					
• No	**71 (65.1%)**	**11 (68.8%)**	**38 (65.5%)**	**22 (62.9%)**	0.916†
• Yes	38 (347%)	5 (31.3%)	20 (345%)	13 (37.1%)	
Smoking					
• No	**95 (87.2%)**	**15 (93.8%)**	**51 (87.9%)**	**29 (82.9%)**	0.578£
• Yes	14 (128%)	1 (6.3%)	7 (12.1%)	6 (17.1%)	
T2DM Duration (years)	6 (2-15)	**15.5 (5-21)**	7 (2-16)	3 (1-9)	**0.003¥**
Energy Consumption	1866 (1427–2539)	1798 (1164–2233)	**1957 (1522 – 2573)**	1856 (1380–2594)	0.452¥

*ANOVA, † Chi square, £Fisher's exact, ¥ Kruskal-Wallis,

Grade I, GII: Grade II, T2DM: Type 2 Diabetes Mellitus.

Regarding clinical characteristics, 51.4% of the patients were obese. The median BMI was 30.2 kg/m^2, with significant differences between the groups (p-value <0.001).

Regarding dyslipidemia, 55.1% of participants had it, more frequently in those with Grade II hepatic steatosis (74.3%), followed by Grade I (53.5%), and absent in those with no steatosis (18.8%) (p-value <0.001). The median waist circumference was 98 cm. The median diastolic blood pressure was 70 mmHg, while the mean mean arterial pressure was 86.6 ± 8.4 mmHg, with significant differences between groups (p-value = 0.038) (Table 2).

With respect to the biochemical characteristics, The median triglycerides level was 145.2 mg/dL, with statistically significant differences (p-value <0.001). The total cholesterol median was 172.2 mg/dL (p-value = 0.047).

Likewise, the very low-density lipoprotein (VLDL) cholesterol median was 31.5 mg/dL (p-value = 0.010). Regarding the hepatic profile, no significant differences were observed between groups in the concentrations of AST, ALT, bilirubin, urea, or creatinine (p-value >0.05). However, the glomerular filtration rate had a median of 102 mL/min/1.73 m^2, with significant differences between groups (p-value <0.001) (Table 2).

Table 2. Clinical and biochemical characteristics of patients with Type 2 Diabetes Mellitus from the DiabetIMSS Module at the No. 3 Family Medicine Unit, Jiutepec, Morelos.

Variable	Total (n=109)	Sin esteatosis (n=16)	Esteatosis GI (n=58)	Esteatosis GII (n=35)	Valor de p
Body Mass Index					
•Normal	9 (8.2%)	4 (25.0%)	3 (5.2%)	2 (5.7%)	
•Overweight	44 (40.4%)	11 (68.75%)	25 (43.1%)	8 (22.8%)	<0.001*
•Obesity	56 (51.4%)	1 (6.25%)	30 (51.7%)	25 (71.5%)	
Systemic hypertension					
•No	62 (56.9%)	9 (56.2%)	34 (58.6%)	19 (54.3%)	0.918†
•Yes	47 (43.1%)	7 (43.8%)	24 (41.4%)	16 (45.7%)	
Dislipidemia					
•No	49 (45.0%)	13 (81.3%)	27 (46.6%)	9 (25.7%)	<0.001£
•Yes	60 (55.0%)	3 (18.7%)	31 (53.4%)	26 (74.3%)	
Body Mass Index (kg/m^2)	30.18 (27.31-34.86)	26.04 (25.09-27.87)	30.34 (27.83-33.71)	33.17 (29.53-36.85)	<0.001‡
Waist Circumference (cm)	98 (94-106)	95 (87-98)	98 (93-105)	106 (95-113)	<0.001‡
Systolic Blood Pressure (mmHg)	118.22 ±11.8	115.06± 13.39	117.5 ± 11.14	120.85 ± 11.97	0.213§
Diastolic Blood Pressure (mmHg)	70 (60-80)	69.5 (60-70)	70 (60-80)	75 (60-80)	0.043∞
Mean Arterial Pressure (mmHg)	86.62 ± 8.41	83.14± 8.17	86.01 ±7.52	89.23 ± 9.32	0.038*
Glucose (mg/dL)	141 (112.6-182.8)	175.4 (116.7-223.6)	139.25 (109.1-169.16)	137.7 (118-182.5)	0.285∞
HbA1c (%)	7.8 (6.3-9.7)	7.9 (7.1-10.5)	7.4 (6.15-9.7)	8.2 (7.1-9.3)	0.390∞
Triglycerides (mg/dL)	145.2 (104.3-219.9)	104.4 (77.6-127.8)	137.5 (109.4-198.9)	210.8 (117.4-262.2)	<0.001∞
Total Cholesterol (mg/dL)	172.2 (143.5-201.3)	146 (124.3-182.2)	171.1 (148.2-197.5)	185.7 (141.6-215.6)	0.047∞
HDL-C (mg/dL)	41.6 (35-48.5)	43.8 (38.1-51.8)	41.8 (36.6-49.8)	38.1 (32-46.1)	0.155∞
LDL-C (mg/dL)	93.8 (72.5-118.6)	76.2 (71.6-105.5)	92.8 (73.6-118)	105.3 (75-122)	0.317∞
VLDL-C (mg/dL)	31.5 (21.2-43.9)	21.9 (16.4-29.9)	30.9 (22.4-44.2)	39.6 (22.6-47)	0.010∞
AST (U/L)	23.1 (18.7-32.2)	19.7 (18.4-24)	23.3 (17.7-32)	25 (19.9-33.6)	0.107∞
ALT (U/L)	27.2 (20-42.2)	21.9 (19.4-27.4)	28.25(19.9-43.5)	29.8 (21.2-51.5)	0.215∞
Total Bilirubin (mg/dL)	0.4 (0.3-0.5)	0.4 (0.4-0.5)	0.4 (0.3-0.5)	0.4 (0.3-0.6)	0.187∞
Direct Bilirubin (mg/dL)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.313∞
Indirect Bilirubin (mg/dL)	0.3 (0.2-0.3)	0.3 (0.3-0.3)	0.3 (0.2-0.3)	0.3 (0.2-0.4)	0.313∞
Creatinine (mg/dL)	0.7 (0.6-0.8)	0.8 (0.65-0.85)	0.7 (0.6-0.8)	0.7 (0.6-0.81)	0.482∞
Urea (mg/dL)	28 (24.3-34)	29.7 (24.8-39.4)	27.7 (24.7-33.1)	28.5 (18.5-36.6)	0.724∞
Glomerular Filtration Rate	102(80-135)	86 (80-99)	104 (80-130)	125 (79-159)	<0.001∞

*Fisher's Exact, † Chi square, ‡Kruskalwallis, §ANOVA
GI: Grade I, GII: Grade II, HbA1c: Glycated Hemoglobin,
HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, VLDL: Very Low-Density Lipoprotein,
AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase.

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Pharmacological treatment data showed that the most prescribed oral antidiabetic drugs were: metformin (86.2%), sitagliptin (37.6%), glibenclamide (36.7%), acarbose (21.1%), and pioglitazone (3.7%). Among insulins, the most frequently used were NPH (22.0%), glargine insulin (6.4%), rapid insulin (5.5%), and insulin mixtures (3.7%).

For dyslipidemia management, the most common drugs were bezafibrate (33.9%), pravastatin (24.8%), and atorvastatin (16.5%), with the overall use of statins at 37.6%. Statistically significant differences were found in the use of pioglitazone (p-value=0.004) and statins (p-value=0.042) between groups with and without hepatic steatosis (Table 3).

Table 3. Pharmacotherapy of patients with Type 2 Diabetes Mellitus at the DiabetIMSS Module of the Family Medicine Unit No. 3, Jiutepec, Morelos.

Variable	Total (n=109)	No steatosis (n=16)	Steatosis GI (n=58)	Steatosis GII (n=35)	p-value
Metformin					
No	15 (13.76%)	2 (12.50%)	7 (12.07%)	6 (17.14%)	
Yes	94 (86.24%)	14 (87.50%)	51 (87.93%)	29 (82.86%)	0.861*
Glibenclamide					
No	69 (63.30%)	7 (43.75%)	39 (67.24%)	23 (65.71%)	0.211†
Yes	40 (36.70%)	9 (56.25%)	19 (32.76%)	12 (34.29%)	
Acarbose					0.516†
No	86 (78.90%)	11 (68.75%)	46 (79.31%)	29 (82.86%)	
Yes	23 (21.10%)	5 (31.25%)	12 (20.69%)	6 (17.14%)	
Pioglitazone					
No	105 (96.33%)	13 (81.25%)	58 (100%)	34 (97.14%)	0.004*
Yes	4 (3.67%)	3 (18.75%)	--	1 (2.86%)	
Sitagliptin					
No	68 (62.39%)	6 (37.50%)	40 (68.97%)	22 (62.86%)	0.085†
Yes	41 (37.61%)	10 (62.50%)	18 (31.03%)	13 (37.14%)	
Rapid insulin					
No	103 (94.50%)	14 (87.50%)	56 (96.55%)	33 (94.29%)	0.285*
Yes	6 (5.50%)	2 (12.50%)	2 (3.45%)	2 (5.71%)	
NPH insulin					
No	85 (77.98%)	10 (62.50%)	48 (82.76%)	27 (77.14%)	0.221†
Yes	24 (22.02%)	6 (37.50%)	10 (17.24%)	8 (22.86%)	
Glargine insulin					
No	102 (93.58%)	14 (87.50%)	55 (94.83%)	33 (94.29%)	0.559*
Yes	7 (6.42%)	2 (12.50%)	3 (5.17%)	2 (5.71%)	
Insulin lispro protamine Mix					
No	105	15 (93.75%)	56 (96.55%)	34 (97.14%)	

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Table 3. Continuation

Variable	Total (n=109)	No steatosis (n=16)	Steatosis GI (n=58)	Steatosis GII (n=35)	p-value
Yes	105 (96,33%)	15 (93,75%)	56 (96,55%)	34 (97,14%)	0,629*
	4 (3,67%)	1 (6,25%)	2 (3,45%)	1 (2,86%)	
Bezafibrate					
No	72 (66,06%)	12 (75,00%)	41 (70,69%)	19 (54,29%)	0,204*
Yes	37 (33,94%)	4 (25,00%)	17 (29,31%)	16 (45,71%)	
Atorvastatin					
No	91 (83,49%)	12 (75,00%)	48 (82,76%)	31 (88,57%)	0,429*
Yes	18 (16,51%)	4 (25,00%)	10 (17,24%)	4 (11,43%)	
Pravastatin					
No	82 (75,23%)	10 (62,50%)	44 (75,86%)	28 (80,00%)	0,400*
Yes	27 (24,77%)	6 (37,50%)	14 (24,14%)	7 (20,00%)	
Statins					
No	68 (62,39%)	6 (37,50%)	36 (62,07%)	26 (74,29%)	0,042*
Yes	41 (37,61%)	10 (62,50%)	22 (37,93%)	9 (25,71%)	

*Fisher's Exact Test, † Chi-squared

GI: Grade I, GII: Grade II.

Logistic regression analysis identified, in the multivariate analysis, three variables significantly associated with the presence of hepatic steatosis. An increase of 1 mg/dL in cholesterol levels was associated with a 5% increase in the probability of presenting steatosis (OR=1.05; 95% CI: 1.00–1.10; p-value=0.038). The use of statins was associated with a 99% reduction in this probability (OR=0.01; 95% CI: 0.00–0.18; p-value=0.003). Additionally, although borderline, BMI showed a positive association with the presence of steatosis, with a 1.65-fold increase in probability for each additional kg/m^2 (OR=1.65; 95% CI: 0.99–2.72; p-value=0.051), but did not reach statistical significance (Table 4).

Table 4. Crude and adjusted model of factors associated with hepatic steatosis in patients with Type 2 Diabetes Mellitus at the DiabetIMSS Module of the Family Medicine Unit No. 3, Jiutepec, Morelos.

	Crude model			Adjusted model*		
	OR	p-value	95% CI	OR	p-value	95% CI
Age (years)	0.97	0.310	0.92-1.02	0.99	0.973	0.88-1.13
Female sex	1.80	0.285	0.61-5.33	23.1	0.059	0.88-604
Alcoholism	1.21	0.743	0.38-3.78	0.50	0.584	0.04-5.92
Smoking	2.43	0.407	0.29-20	52.9	0.180	0.15-1757
Time with T2DM	0.92	0.012	0.87-0.98	0.97	0.687	0.85-1.10
Systemic hypertension	0.97	0.956	0.33-2.82	0.88	0.920	0.089.27
Body mass index (kg/m^2)	1.47	0.001	1.18-1.84	1.65	0.051	0.99-2.72
Waist circumference (cm)	1.06	0.006	1.01-1.12	0.96	0.520	0.85-1.08

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Table 4. Continuation

	Crude model			Adjusted model*		
	OR	p-value	95% CI	OR	p-value	95% CI
Mean arterial pressure (mmHg)	1.06	0.077	0.99-1.13	1.14	0.079	0.98-1.32
Glucose (mg/dL)	0.99	0.177	0.98-1.00	0.98	0.113	0.96-1.00
Triglycerides (mg/dL)	1.01	0.024	1.00-1.02	1.00	0.322	0.99-1.02
Cholesterol (mg/dL)	1.02	0.028	1.00-1.03	1.05	0.038	1.00-1.10
Metformin	0.87	0.874	0.17-4.32	7.13	0.316	0.15-332
Bezafibrate	1.65	0.417	0.49-5.52	0.26	0.471	0.00-9.57
Statins	0.3	0.032	0.09-0.90	0.01	0.003	0.00-0.18
Energy consumption (Kcal)	1.00	0.196	0.99-1.00	1.00	0.112	0.99-1.00

*Adjusted multiple model for age, sex, alcohol consumption, cigarette consumption, time with T2DM, systemic hypertension, body mass index, waist circumference, mean arterial pressure, glucose levels, triglycerides, cholesterol, use of metformin, bezafibrate and statins, and energy consumption. OR: Odds Ratio. 95% CI: 95% Confidence Interval. T2DM: Type 2 Diabetes Mellitus.

In the multinomial adjusted model for Grade I steatosis, an increase of 1 mg/dL in cholesterol levels was associated with a 5% increase in the probability of presenting this grade of steatosis (OR=1.05; 95% CI: 1.00–1.10; p-value=0.040). Additionally, the use of statins was associated with a 99% reduction in this probability (OR=0.01; 95% CI: 0.00–0.25; p-value=0.005). For Grade II hepatic steatosis, female sex was associated with a 91-fold increase in the probability of developing this grade of steatosis (OR=91.2; 95% CI: 2.54–328; p-value=0.014). Furthermore, for each additional mmHg in mean arterial pressure, the probability increased by 19% (OR=1.19; 95% CI: 1.01–1.40; p-value=0.032), while the use of statins reduced the probability of presenting Grade II steatosis by 99% (OR=0.01; 95% CI: 0.00–0.02; p-value<0.001) (Table 5).

Table 5. Multilevel analysis of the crude and adjusted models of factors associated with the degree of hepatic steatosis in patients with Type 2 Diabetes Mellitus at the DiabetIMSS Module of the Family Medicine Unit No. 3, Jiutepec, Morelos.

	Crude model			Adjusted model**		
	OR	*P*	95% CI	OR	*P*	95% CI
Without hepatic steatosis	(Reference)					
Grade I Steatosis						
Age (years)	0.98	0.607	0.93-1.04	0.99	0.984	0.88-1.13
Female sex	1.72	0.344	0.55-5.36	22.0	0.065	0.82-591
Alcoholism	1.15	0.809	0.35-3.79	0.52	0.604	0.04-6.07
Smoking	2.05	0.515	0.23-18	48.7	0.183	0.16-149

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Table 5. Continuation

Without hepatic steatosis Grade I Steatosis	Crude model OR (Reference)	*P*	95% CI	Adjusted model** OR	*P*	95% CI
Time with T2DM	0.94	0.072	0.88-1.00	0.98	0.788	0.86-1.11
Systemic hypertension	0.90	0.865	0.29-2.77	0.91	0.936	0.08-9.50
Body mass index (kg/m^2)	1.43	**0.002**	1.14-1.79	1.64	**0.055**	0.99-2.71
Waist circumference (cm)	1.05	**0.040**	1.00-1.10	0.96	0.499	0.84-1.08
Mean arterial pressure (mmHg)	1.04	0.218	0.97-1.12	1.13	0.091	0.98-1.32
Glucose (mg/dL)	0.99	0.241	0.98-1.00	0.98	0.122	0.96-1.00
Triglycerides (mg/dL)	1.01	0.090	0.99-1.02	1.00	0.411	0.99-1.02
Cholesterol (mg/dL)	1.02	**0.050**	0.99-1.03	1.05	**0.040**	1.00-1.10
Metformin	1.04	0.963	0.19-5.57	7.90	0.296	0.16-381
Bezafibrate	1.24	0.735	0.35-4.40	0.25	0.454	0.00-9.03
Statins	0.36	0.085	0.11-1.14	0.01	**0.005**	0.00-0.25
Energy consumption (Kcal)	1.00	0.197	0.99-	1.00	0.107	0.99-1.00
Grade II Steatosis						
Age (years)	0.95	0.105	0.89-1.01	1.01	0.883	0.88-1.16
Female sex	1.94	0.289	0.56-6.65	91.2	**0.014**	2.54-328
Alcoholism	1.3	0.683	0.36-4.58	0.64	0.753	0.04-10.3
Smoking	3.10	0.315	0.34-28.2	122	0.116	0.30-4941
Time with T2DM	0.87	**0.001**	0.80-0.94	0.86	0.084	0.74-1.02

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Table 5. Continuation

Without hepatic steatosis Grade I Steatosis	Crude model OR (Reference)	*P*	95% CI	Adjusted model* OR	*P*	95% CI
Systemic hypertension	1.08	0.896	0.32-3.56	0.97	0.986	0.07-13.1
Body mass index (kg/m^2)	1.60	**<0.001**	1.26-2.02	1.55	0.110	0.90-2.67
Waist circumference (cm)	1.12	**<0.001**	1.05-1.19	1.05	0.542	0.89-1.23
Mean arterial pressure (mmHg)	1.09	**0.019**	1.01-1.18	1.19	**0.032**	1.01-1.40
Glucose (mg/dL)	0.99	0.185	0.98-1.00	0.97	0.075	0.95-1.00
Triglycerides (mg/dL)	1.01	**0.003**	1.00-1.02	1.01	0.077	0.99-1.03
Cholesterol (mg/dL)	1.02	**0.016**	1.00-1.04	1.05	**0.029**	1.00-1.10
Metformin	0.69	0.673	0.12-3.86	3.70	0.531	0.06-221
Bezafibrate	2.52	0.166	0.67-9.38	0.62	0.807	0.01-27.3
Statins	0.20	**0.015**	0.06-0.73	0.01	**<0.001**	0.00-0.02
Energy consumption (Kcal)	1.00	0.262	0.99-1.00	1.00	0.317	0.99-1.00

*Multiple model adjusted for age, sex, alcohol consumption, smoking, duration of T2DM, systemic arterial hypertension, body mass index, waist circumference, mean arterial pressure, glucose levels, triglycerides, cholesterol, use of metformin, bezafibrate, and statins, and energy consumption.
OR: Odds ratio. 95% CI: 95% confidence interval. T2DM: Type 2 Diabetes Mellitus.

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DISCUSSION

The results identified a high body mass index (BMI), high triglyceride and cholesterol levels as significant risk factors for non-alcoholic fatty liver disease (NAFLD), consistent with previous findings, such as those reported by Van Den Berg EH et al., who pointed to a direct relationship between these metabolic parameters and the associated cardiovascular risk [24]. Our study highlighted that statins appear to play a protective role by reducing the frequency of NAFLD, a result consistent with research by Sfikas G et al., where statins such as atorvastatin and rosuvastatin could limit the development of NAFLD and liver fibrosis markers [25]. This emphasizes the role of statins not only in lipid control but also as a potential tool for the comprehensive management of NAFLD in patients with type 2 diabetes mellitus (T2DM). This approach is complemented by the care provided at the Diabetes Care Centers of the IMSS (CADIMSS), formerly known as DiabetIMSS modules, whose goal is to provide

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comprehensive care to patients diagnosed with diabetes, improving their metabolic control and delaying the onset of chronic complications. However, further studies are needed to validate the role of statins in addressing the population with T2DM and a potential NAFLD profile.

Statins confer cardiovascular protection primarily through the inhibition of the HMG-CoA reductase enzyme, which reduces hepatic cholesterol synthesis and enhances the uptake of low-density lipoproteins (LDL) by the liver, thus lowering their plasma concentrations. In addition, statins have beneficial pleiotropic effects, including improving endothelial function, reducing systemic inflammation—evidenced by decreased C-reactive protein levels—stabilizing atherosclerotic plaques, and providing antioxidant and antithrombotic properties. Together, these effects contribute to a significant reduction in the risk of cardiovascular events, even in individuals with normal cholesterol levels, as demonstrated in the JUPITER study[26].

A noteworthy finding was the inverse relationship between the duration of diabetes and the risk of NAFLD. This result suggests that patients with a longer duration of T2DM may have developed better self-care practices and metabolic control or may be receiving statins as a protective therapy due to the increased cardiovascular risk associated with diabetes, which could explain the lower incidence of NAFLD. This aspect, although rarely explored in the literature, highlights the importance of long-term educational and preventive strategies such as CADIMSS in managing patients with T2DM, promoting the control of metabolic comorbidities.

Regarding pharmacological treatment, although the use of statins seemed to show a clear benefit in the population studied, the evaluation of the impact of other medications such as metformin, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), and pioglitazone revealed areas of controversy in the literature. In our study, no clear benefits were observed with metformin use regarding the presence of NAFLD. However, research by Huang Y et al. and Zachou M et al. has reported improvements in hepatic steatosis and transaminase levels but with inconsistent results, such as a possible worsening of liver fibrosis [27-29]. These discrepancies have led to international guidelines not recommending metformin as a specific treatment for NAFLD, highlighting the need for studies with greater scientific rigor and methodological quality.

On the other hand, pioglitazone, although used by a small number of participants in our study, has shown significant improvements in hepatic inflammation, transaminase levels, and steatosis in studies such as those by Yaghoubi M et al. and Zachou M et al.[29.30]. However, with the adverse effect of weight gain, this finding suggests that its use should be carefully considered, prioritizing patients with specific characteristics such as significant fibrosis or active inflammation, as well as monitoring for the development of primarily metabolic adverse reactions.

SGLT2 inhibitors and GLP-1RA have emerged as promising options for treating NAFLD. Although not evaluated in this study, as they were not yet part of the essential diabetes medication regimen, they have recently been included in IMSS, opening the possibility for future studies with these drugs. According to Jang H et al., SGLT2 inhibitors not only improve hepatic steatosis and metabolic parameters but also reduce long-term hepatic complications. GLP-1RAs, on the other hand, have demonstrated benefits in weight reduction, transaminase levels, and hepatic steatosis, although their effects on fibrosis remain inconsistent. Both agents represent innovative therapeutic alternatives for complementing the management of NAFLD in patients with T2DM[31]. Regarding the impact of fenofibrate, reviews such as those by Mahmoudi A et al. highlight its antioxidant, anti-inflammatory, and antifibrotic potential in NAFLD. Although its use in our population was limited, previous studies suggest it may be useful for patients with altered lipid profiles and early hepatic damage[32].

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Finally, our study contributes to the literature by emphasizing the importance of comprehensive control of metabolic factors and the protective role of statins in patients with T2DM and NAFLD. However, the reviewed evidence suggests that the management of NAFLD should be personalized, integrating pharmacological options based on metabolic characteristics, the degree of liver damage, and the individual needs of patients. While statins, SGLT2 inhibitors, GLP-1RAs, and pioglitazone offer specific benefits, further large-scale and long-term studies are required to directly compare their efficacy and safety, especially in specific subgroups such as those with advanced fibrosis or insulin resistance.

The study has several important limitations that must be considered when interpreting its results. The sample was relatively small and limited to a single medical unit, which reduces the representativeness of the findings and their applicability to other populations. Additionally, the cross-sectional design prevents establishing cause-and-effect relationships between the studied factors and NAFLD. The diagnosis based on ultrasound, while practical, has limitations in detecting mild grades of steatosis and does not adequately assess liver fibrosis. On the other hand, the study presents relevant biases that could affect its conclusions. There is a selection bias, as the participants come from a single location, excluding patients from other regions with different characteristics. Pharmacotherapy data were obtained from clinical records, which may lead to incomplete or inaccurate information. Finally, the lack of geographic and cultural diversity limits the applicability of the findings to populations other than the Mexican one studied. These aspects underline the need for broader, longitudinal, and multicenter future studies.

CONCLUSION

The findings of this study show that in patients with T2DM, elevated cholesterol and high mean arterial pressure are significantly associated with the presence and severity of NAFLD. Additionally, the use of statins robustly decreased the frequency of development and progression of NAFLD, both in the overall and stratified analyses by degree of steatosis. Female sex and an increase in mean arterial pressure were associated with a higher frequency of developing grade II hepatic steatosis. These results highlight the importance of a comprehensive clinical approach in the T2DM population, considering strict control of metabolic factors and the rational use of statins as a potential strategy for the prevention or management of NAFLD. Longitudinal and multicenter studies are required to confirm these associations and explore the efficacy of other emerging therapeutic options, such as SGLT2 inhibitors and GLP-1RA agonists, in diverse clinical contexts.

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REFERENCES

1.Instituto Nacional de la Diabetes y las Enfermedades Digestivas y Renales Enfermedad del hígado graso no alcohólica (EHGNA) y esteatohepatitis no alcohólica (EHNA) [Internet]. Estados Unidos de America: Institutos Nacionales de Salud 2021. Available from: https://www.niddk.nih.gov/health-information/informacion-de-la-salud/enfermedades-higado/esteatohepatitis-no-alcoholica/definicion-informacion#graso.

2.Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocr Disord. 2022;22(1):63. doi: 10.1186/s12902-022-00980-1.

3.Weiß J, Rau M, Geier A. Non-alcoholic fatty liver disease: epidemiology, clinical course, investigation, and treatment. Dtsch Arztebl Int. 2014;111(26):447-52. doi: 10.3238/arztebl.2014.0447.

4.Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. doi: 10.1002/hep.28431.

5.Ortega Chavarría MJ, Corneelio Rodríguez G, Rodríguez Weber F, Díaz Greene E. Prevalencia del hígado graso no alcohólico y su asociación con alteraciones bioquímicas en una población mexicana asintomática. Acta Med Grupo Angeles. 2020;18(2):127-32. doi: 10.35366/93885.

6.Bernal-Reyes R, Icaza-Chávez ME, Chi-Cervera LA, Remes-Troche JM, Amieva-Balmori M, Priego-Parra BA, et al. Prevalencia y características clínico-epidemiológicas de una población mexicana con enfermedad del hígado graso asociada a disfunción metabólica: un estudio en población abierta. Revista de Gastroenterología de México. 2023;88(3):199-207. doi: 10.1016/j.rgmx.2021.09.002.

7.Castro-Martinez MG, Banderas-Lares DZ, Ramirez-Martinez JC, Escobedo-de la Pena J. Prevalence of nonalcoholic fatty liver disease in subjects with metabolic syndrome. Cir Cir. 2012;80(2):128-33. Available from: https://pubmed.ncbi.nlm.nih.gov/22644007/.

8.Mendez-Sanchez N, Chavez-Tapia NC, Uribe M. Actualización en enfermedad del hígado graso no alcohólico. Rev Invest Clin. Available from: https://pubmed.ncbi.nlm.nih.gov/15144045/.

9.World Health Organization. Obesidad y sobrepeso [Internet]. Geneva: World Health Organization; 2024 [cited 2025 Jan 12]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight.

10.World Obesity Federation. World Obesity Atlas [Internet]. London: World Obesity Federation; 2024 [cited 2025 Jan 12]. Available from: https://data.worldobesity.org/publications/?cat=22.

11.International Diabetes Federation. IDF Diabetes Atlas. Brussels, Belgium 2021. [cited 2025 Jan 12]. Available from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf.

12.Institute for Health Metrics and Evaluation. GBD Compare [Internet]. Seattle, WA: University of Washington; 2021 [cited 2025 Jan 12]. Available from: https://vizhub.healthdata.org/gbd-compare/.

13.Zeng Y, Zhang X, Luo W, Sheng Y. Effect of exercise intervention on clinical parameters in patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Eur J Gastroenterol Hepatol. 2024;36(1):1-12. doi: 10.1097/MEG.0000000000002662.

14.Qi F, Li T, Deng Q, Fan A. The impact of aerobic and anaerobic exercise interventions on the management and outcomes of non-alcoholic fatty liver disease. Physiol Res. 2024;73(5):671-86. doi: 10.33549/physiolres.935244.

15.Chai XN, Zhou BQ, Ning N, Pan T, Xu F, He SH, et al. Effects of lifestyle intervention on adults with metabolic associated fatty liver disease: A systematic review and meta-analysis. Front Endocrinol (Lausanne). 2023;14:1081096. doi: 10.3389/fendo.2023.1081096.

16.Sualeheen A, Tan SY, Georgousopoulou E, Daly RM, Tierney AC, Roberts SK, et al. Mediterranean diet for the management of metabolic dysfunction-associated steatotic liver disease in non-Mediterranean, Western countries: What's known and what's needed? Nutr Bull. 2024;49(4):444-62. doi: 10.1111/nbu.12707-

17.Zhu W. Effective roles of exercise and diet adherence in non-alcoholic fatty liver disease. World J Gastroenterol. 2024;30(29):3456-60. doi: 10.3748/wjg.v30.i29.3456.

18.Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53(3):362-76. doi: 10.1007/s00535-017-1415-1.

19.Wang H, Ma Q, Chen Y, Luo L, Ye J, Zhong B. Optimized strategy among diet, exercise, and pharmacological interventions for nonalcoholic fatty liver disease: A network meta-analysis of randomized controlled trials. Obes Rev. 2024;25(6):e13727. doi: 10.1111/obr.13727.

20.Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018;24(30):3361-73. doi: 10.3748/wjg.v24.i30.3361.

21.Moctezuma-Velazquez C. Current treatment for non-alcoholic fatty liver disease. Rev Gastroenterol Mex (Engl Ed). 2018;83(2):125-33. doi: 10.1016/j.rgmx.2017.10.003.

22.Mantovani A, Dalbeni A. Treatments for NAFLD: State of Art. Int J Mol Sci. 2021;22(5). doi: 10.3390/ijms22052350.

23.Leite NC, Salles GF, Araujo ALE, Villela-Nogueira CA, Cardoso CRL. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver International. 2009;29(1):113–9. doi: 10.1111/j.1478-3231.2008.01718.x.

24.Van den Berg EH, Wolters AAB, Dullaart RPF, Moshage H, Zurakowski D, de Meijer VE, et al. Prescription of statins in suspected non-alcoholic fatty liver disease and high cardiovascular risk, a population-based study. Liver Int. 2019;39(7):1343-54. doi: 10.1111/liv.14116.

25.Sfikas G, Psallas M, Koumaras C, Imprialos K, Perdikakis E, Doumas M, et al. Prevalence, Diagnosis, and Treatment with 3 Different Statins of Non-alcoholic Fatty Liver Disease/Non-alcoholic Steatohepatitis in Military Personnel. Do Genetics Play a Role? Curr Vasc Pharmacol. 2021;19(5):572-81. doi: 10.2174/1570161118666201015152921.

26. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM Jr, Kastelein JJP, Koenig W, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195–2207. doi: 10.1056/NEJMoa0807646

27.Huang KH, Lee CH, Cheng YD, Gau SY, Tsai TH, Chung NJ, et al. Correlation between long-term use of metformin and incidence of NAFLD among patients with type 2 diabetes mellitus: A real-world cohort study. Front Endocrinol (Lausanne). 2022;13:1027484.

28.Huang Y, Wang X, Yan C, Li C, Zhang L, Zhang L, et al. Effect of metformin on nonalcoholic fatty liver based on meta-analysis and network pharmacology. Medicine (Baltimore). 2022;101(43):e31437. doi: 10.1097/MD.0000000000031437.

29.Zachou M, Flevari P, Nasiri-Ansari N, Varytimiadis C, Kalaitzakis E, Kassi E, et al. The role of anti-diabetic drugs in NAFLD. Have we found the Holy Grail? A narrative review. Eur J Clin Pharmacol. 2024;80(1):127-50. doi: 10.1007/s00228-023-03586-1.

30.Yaghoubi M, Jafari S, Sajedi B, Gohari S, Akbarieh S, Heydari AH, et al. Comparison of fenofibrate and pioglitazone effects on patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol. 2017;29(12):1385-8. doi: 10.1097/MEG.0000000000000981.

31.Jang H, Kim Y, Lee DH, Joo SK, Koo BK, Lim S, et al. Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease. JAMA Intern Med. 2024;184(4):375-83. doi: 10.1001/jamainternmed.2023.8029.

32.Mahmoudi A, Jamialahmadi T, Johnston TP, Sahebkar A. Impact of fenofibrate on NAFLD/NASH: A genetic perspective. Drug Discov Today. 2022;27(8):2363-72. doi: 10.1016/j.drudis.2022.05.007.