Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Metabolic Comorbidities Among Relatives of Type 2 Diabetes Patients Stratified by Weight: Implications for Prevention and Care

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Introduction: Diabetes, affecting 18.3% of young adults in Mexico (6), is influenced by both genetic factors and shared unhealthy habits within families.

Objective: To determine the metabolic abnormalities in relatives of people with T2D, stratified by body mass index.

Materials and Methods: This observational, descriptive study was conducted at the Center for Comprehensive Care for Patients with Diabetes (CAIPaDi). The study involved relatives of participants with type 2 diabetes mellitus (T2DM), recruited between June 2017 and December 2020. The relatives were people without diabetes, including spouses, siblings, offspring, or close family members aged 18 to 65 who spent over four days a week with the patient. Exclusion criteria included relatives diagnosed with diabetes, smokers, or any individual from a patient-relative pair that was excluded. All participants underwent laboratory tests and body measurements. Relatives were classified into three groups based on body weight: normal weight, overweight, and obesity. The relatives attended four monthly visits and then annual evaluations. Ethical approval was obtained.

Results: The study enrolled 220 relatives of people with T2DM, 69% women, median age 49±12 years; 19.5% with normal weight, 40.4% overweight, and 40% with obesity. Prediabetes (39.4%), dyslipidemia (67.2%), and abnormal liver function tests (32.2%) were prevalent. Higher levels of triglycerides and LDL cholesterol were associated with increased risk for comorbid conditions. Anxiety and depression showed no significant differences across weight categories.

Conclusion: These results highlight the importance of overweight and obesity as factors associated with the presence of comorbidities and the metabolic syndrome. It is essential to implement strategies to promote healthy habits among family members of people with diabetes, especially in those who are overweight or obese to reduce the risk of developing future metabolic and cardiovascular diseases.

Keywords: obesity, metabolic diseases, relatives, body mass index, diabetes prevention

Introduction

Diabetes is a public health problem affecting young adults, with an estimated national prevalence in Mexico of 18.3%.[1] Obesity, is not only a risk factor for T2DM but is also associated with arrange of other diseases, including hypertension, cardiovascular disease, dyslipidemia, hepatic steatosis, stroke, gallbladder disease, osteoarthritis, sleep apnea, certain types of cancer (endometrial, breast, ovary, prostate, liver, gallbladder, kidney, and colon), Alzheimer's disease, and depression.[2–16] Four obesity phenotypes have been described: normal weight obese (NWO); metabolically unhealthy normal weight obese; metabolically healthy obese; metabolically unhealthy obese.[7,8,17,18] In Mexico, the National Health and Nutrition Survey (ENSANUT) 2022 revealed that 38.3% of adults are overweight, while an additional 36.9% are

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obese.[1] This dual burden of diabetes and obesity presents significant challenges for public health and healthcare systems in Mexico.

Diabetes and obesity are associated with both genetic and environmental factors; for this reason they tend to occur within families.[19] First degree relatives of patients with diabetes, have an increased risk of developing obesity and diabetes.[19–21] Several studies have reported the presence of metabolically unhealthy non-obese and metabolically unhealthy obese phenotypes in subjects with a family history of diabetes.[19] Subcutaneous adipose tissue of non-obese individuals with a family history of diabetes exhibits markers of an "obese" cell phenotype.[21] Even young adults with a family history of diabetes and normal glucose tolerance a may have a deteriorated metabolic profile, including energy imbalance, increased adipose tissue and endothelial dysfunction, manifested as increased BMI (body mass index) and dyslipidemia, both associated with the metabolic syndrome.[19,20]

Khan et al reported that the spouses of people with type 2 diabetes had a significantly higher prevalence of impaired glucose tolerance and type 2 diabetes (19.1% versus 9.4%) compared to the control group. This elevated risk remained significant even after adjusting for body mass index (BMI) and age. The study also noted that spouses of patients with diabetes had higher levels of fasting glucose and triglycerides, in addition to a trend towards higher blood pressure. Furthermore, their BMI was higher, which partly contributed to their increased likelihood of developing diabetes. The multivariate analysis indicated that the odds of developing diabetes in the spouses of diabetic individuals were 2.11 (95% CI 1.74–5.1), suggesting that shared environmental factors, such as dietary and lifestyle habits, may contribute to this risk.[22] Weijnen et al estimated the sibling recurrence-risk ratio for type 2 diabetes in families with diabetes occurring in middle age. The research explored both genetic and environmental factors that contribute to the transmission of type 2 diabetes within families. By surveying 563 patients diagnosed with type 2 diabetes between the ages of 35 and 59, the researchers gathered data on the occurrence of diabetes in their 1,675 siblings, comparing these rates to those of the general population. The study found that the overall sibling recurrence-risk ratio for type 2 diabetes was relatively low, around 1.8. The risk increased significantly in families where one or both parents had diabetes. Notably, the sibling recurrence-risk ratio was higher in families where diabetes was present in both a parent and a grandparent. Interestingly, siblings of non-obese index cases had an even higher risk of developing diabetes, highlighting the complex interaction of genetic and environmental factors.[23]

Other studies have found an association between first-degree family history of diabetes and components of metabolic syndrome, independently of lifestyle habits indicating a pivotal role of genetic predisposition.[24,25] Moon et al showed that among participants with metabolic syndrome, 21.3% had a family history of diabetes. Furthermore, a family history of obesity and hypertension was associated with being obese in subjects with metabolic syndrome.[19] There was a strong correlation with BMI, waist circumference, fasting glucose and triglycerides levels and insulin resistance between parents and their offspring, identifying probable inherited metabolic parameters.[19] This evidence supports the association between familial risk and co-occurrence of metabolic disorders such as diabetes and obesity.

There is limited research exploring the metabolic health of non-diabetic relatives, especially when categorized by weight phenotypes.

This gap is critical, as early identification and intervention in high-risk groups may delay or prevent the onset of T2DM and other obesity-related conditions. Additionally, understanding how metabolic comorbidities vary with weight in these relatives could inform personalized approaches in prevention and care.[25,26] The aim of this study was to identify the metabolic conditions and profiles of the non-diabetic relatives of persons with diabetes attending a multidisciplinary diabetes care program in Mexico City.

Materials and Methods

Study Design

This was an observational, descriptive study that included relatives of people with T2DM who attended the Center of Comprehensive Care for Patients with Diabetes (CAIPaDi) at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ).

Participants

Participants were family members who accompanied their relative with diabetes to the first CAIPaDi session between June 2017 and December 2020. These make up the patient-relative par referred to in the study, being a total of 220 index cases.

CAIPaDi Model

CAIPaDi is a multidisciplinary program hosted at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) in Mexico City. The model comprises four monthly visits and then annual evaluation. In every visit, sessions were conducted by a physician, dietitian, psychologist, psychiatrist, physical activity expert, diabetes educator, dentist, foot care specialist, and ophthalmologist/optometrist. Also, in each visit, participants had laboratory tests, anthropometric measurements, and in the first and annual evaluations an ECG, liver ultrasound scan and sudomotor evaluations were performed. Each intervention has established parameters attached to quality indicators in clinical care. Results were recorded ion a platform that serves as a database to analyze patient follow-up.

The International Physical Activity Questionnaire assessed physical activity (IPAQ)[27] Performance of aerobic, resistance, or both types of exercise was also registered. We requested a three-day meal recall of two week days and one week end day to quantify energy intake (calories/day)[28]. We utilized the Hospital Anxiety and Depression Scale (HAD) to assess anxiety and depression, with a score of 0–7 indicating normal, 8–10 borderline, and 11–21 abnormal.[29]

Selection Criteria

We invited relatives aged 18 or older (spouses, siblings, offspring, or second-degree relatives) who lived with the person with diabetes for at least four days/week to participate in the study. Relatives were excluded if they had diabetes, tobacco use, BMI >45 kg/m², or any health condition affecting life expectancy. Participants were excluded if they or one member of the patient-relative pair was excluded.

Ethics and Registration

The CAIPaDi program was endorsed by the INCMNSZ Research and Ethics Board (Ref. 1198) and is registered in ClinicalTrials.gov (NCT02836808). This project also received approval from the National Institute of Public Health and the local Research and Ethics Board (Ref. 2145) and is likewise registered in ClinicalTrials.gov (NCT03234946). The study complies with the Declaration of Helsinki, and all participants signed an informed consent form.

Procedures

Relatives were invited to accompany their family member with diabetes to undergo every intervention, following all the indications received from the specialists, or they could undergo their interventions separately from the patient with diabetes. All relatives had laboratory tests and anthropometric measurements. Relatives arrived at the Center at 07:00 am for the collection of blood samples and body measurements. Laboratory tests were conducted at every visit, which included fasting glucose (FG), creatinine, lipid profile, urinary albumin/creatinine ratio (ACR, using the SYNCHRON-CX system with the colorimetric method), and glycated hemoglobin (HbA1c) (measured using the Bio-Rad Variant II Turbo HbA1c Kit 2, with the HPLC method). Additionally, a 12-lead ECG, as well as weight and height measurements, were taken upon arrival.

Body composition was assessed via bioimpedance, using the JAWON Medical ioi-353 body composition analyzer. Following the initial assessment, annual evaluations were carried out, for each relative.

Groups

Relatives were classified in three groups: those with normal weight (BMI 18.5–24.9 kg/m2), concurrent overweight (BMI 25–29.9 kg/m2), and concurrent obesity (BMI >30 kg/m2).

We identified abnormalities in parameters by measuring various health indicators including the presence of pre-diabetes, hypertension, altered electrocardiogram, dyslipidemia, albumin-to-creatinine ratio in urine sample, uric acid

levels, and abnormalities in liver enzymes (ALT, AST, and GGT). Based on these parameters, we quantified the number of comorbidities/ abnormalities for each individual. Additionally, we assessed overweight/obesity status and the presence of retinopathy. We also evaluated the presence or absence of metabolic syndrome (≥3 parameters: high triglycerides, low HDL, hypertension, altered fasting glucose, BMI ≥25 kg/m2) in each BMI category.

Objectives

Our primary objective is to describe the clinical characteristics and prevalence of comorbidities, as well as dietary and exercise habits, among participants (relatives) with normal weight, overweight, and obesity. In addition we aim to identify the characteristics associated with having one or more metabolic comorbidities and those associated with the presence of the metabolic syndrome.

Statistical Analysis

Descriptive statistics were calculated for both quantitative and qualitative variables. Specifically, we evaluated frequencies and means, as well as interquartile ranges and standard deviations for all variables in the study. For the quantitative variables, a one-way ANOVA was conducted for the three groups (normal weight, overweight, and obesity). These were categorized within subgroups, which are detailed later in the analysis. All results were considered with a significance level of alpha = 0.05% and a p-value of 0.05 was deemed significant.

Utilizing the presence of any comorbidity as the dependent variable and the remaining variables as predictors, we conducted multiple logistic regression analyses. All statistical analyses were executed using STATA software (v14.2, College Station, TX).

Results

We enrolled 220 relatives of people with T2D. Among these participants, 152 individuals (69%) were women, the mean age was 49±12 years. The relatives included were 13.4% siblings, 6.7% parents, 25.2% offspring, and 49.9% spouses. Besides familial history of T2D 65.5% had a family history of dyslipidemia, 64.2% hypertension, and 35.9% myocardial infarction. No significant differences were found between sexes.

Table 1 shows the comparison of metabolic, lifestyle and mental health parameters among relatives with normal weight, overweight or obesity. The distribution of body weight within groups revealed that 43 individuals (19.5%) had normal weight, 89 individuals (40.4%) were overweight, and 88 individuals (40%) exhibited obesity. Up to 42.7% of the

Table 1 Comparison of Metabolic, Lifestyle and Mental Health Parameters Among Relatives with Normal Weight, Overweight or Obesity

	Total Population n=220 (100%)	**Normal Weight n=43 (19.55%)**	**Overweight n=89 (40.45%)**	**Obesity n=88 (40.0%)**	**p value**
Women, n (%)	152 (30.9)	33 (76.7)	64 (71.9)	55 (62.5)	0.19
Men, n (%)	68 (69.0)	10 (23.2)	25 (28.0)	33 (37.5)	
Age, years, (RIQ)	50 (39–59)	47 (36–57)	50 (41–59)	50 (39–58)	0.49
Metabolic syndrome (≥3 factors)	94 (42.7)	1 (2.3)	43 (48.3)	50 (56.8)	<0.001
Hypertriglyceridemia (≥150mg/dL)	106 (48.1)	10 (23.2)	45 (50.5)	51 (57.9)	0.001
Low HDL (<40mg/dl in men, <50mg/dL in women)	127 (57.7)	18 (41.8)	53 (59.5)	56 (63.6)	0.055
Arterial hypertension (>130/80 mmHg)	44 (20.0)	5 (11.6)	15 (16.8)	24 (27.2)	0.07
Altered fasting glucose (≥100mg/dL)	40 (18.1)	5 (11.6)	18 (20.2)	17 (19.3)	0.48
BMI ≥25 kg/m2	177 (80.4)	—-	89 (100)	88 (100)	

(*Continued*)

Table 1 (Continued).

	Total Population n=220 (100%)	Normal Weight n=43 (19.55%)	Overweight n=89 (40.45%)	Obesity n=88 (40.0%)	p value
BMI, kg/m2, (RIQ)	28.9 (25.6–32.6)	23.3 (21.5–24.2)	27.4 (26.2–28.9)	33.3 (31.9–36.4)	<0.001
Systolic blood pressure, mmHg (RIQ)	119 (110–126)	112 (101–120)	119 (110–127)	120 (113–128)	<0.001
Diastolic blood pressure, mmHg (RIQ)	74 (69–88)	69 (64–76)	73 (69–79)	77 (73–80)	<0.001
Triglycerides, mg/dl, (RIQ)	146 (110–205)	119 (88–146)	154 (111–220)	162 (124–205)	<0.001
Total cholesterol, mg/dl (RIQ)	185 (163–209)	188 (173–209)	185 (159–207)	185 (168–210)	0.82
Non-HDL-cholesterol, mg/dl (RIQ)	141 (123–162)	140 (115–162)	142 (119–159)	141 (126–166)	0.52
HDL-cholesterol, mg/dL (RIQ)	44 (36–51)	50 (39–58)	44 (38–51)	42 (36–49)	0.01
Cholesterol-LDL cholesterol, mg/dl, (RIQ)	120 (100–138)	114 (95–140)	118 (94–137)	126 (105–139)	0.35
TG/HDL <3.5	3.4 (2.2–4.9)	2.3 (1.6–3.5)	3.5 (1.3–5.6)	3.8 (2.5–5.9)	0.001
TG/HDL >3.5	109 (49.5)	12 (27.9)	45 (50.5)	52 (59.0)	0.004
Glucose, mg/dl (RIQ)	89 (81–95)	86 (80–92)	89 (83–97)	90 (82–97)	0.03
HbA1c, %, (RIQ)	5.6 (5.3–5.9)	5.5 (5.3–5.8)	5.5 (5.3–5.9)	5.7 (5.4–6.0)	0.04
Prediabetes, n (%)	86 (39.4)	16 (37.2)	31 (34.8)	39 (45.3)	0.34
Creatinine, mg/dl, (RIQ)	0.73 (0.64–0.83)	0.72 (0.64–0.83)	0.74 (0.65–0.81)	0.71 (0.63–0.87)	0.84
ALT, U/L, (RIQ)	21 (15–31)	16 (13–23)	20 (16–28)	26 (18–39)	<0.001
AST, U/L, (RIQ)	20 (16–25)	18 (16–22)	20 (16–24)	21 (16–26)	0.13
GGT, U/L, (RIQ)	26 (16–43)	17 (15–35)	25 (15–38)	33 (23–49)	<0.001
Uric acid, mg/dl (RIQ)	5.2 (4.5–6.1)	5.0 (4.3–5.4)	5.1 (4.4–5.9)	5.7 (4.8–6.4)	0.001
Albumin/creatinine index, mg/dl (RIQ)	6.0 (4.3–9.4)	6.0 (4.6–8.3)	5.8 (3.7–7.9)	6.2 (4.6–12.9)	0.06
Altered Electrocardiography, n (%)	36 (18.0)	9 (21.4)	12 (14.8)	15 (19.7)	0.60
Presence of retinal microaneurysms, n (%)	6 (3.7)	1 (2.9)	2 (3.2)	3 (4.7)	0.86
Fat mass, % (RIQ)	36.1 (31.6–40.1)	30.1 (27.8–33.5)	35.9 (31.2–37.6)	41.1 (36.7–43.1)	<0.001
Lean mass, kg (RIQ)	42.1 (37.6–49.6)	36 (34–41)	40 (37–45)	46 (41–55)	<0.001
Daily calories consumed, median (RIQ)	1607 (1321–1909)	1529 (1261–1859)	1571 (1260–1896)	1737 (1416–1972)	0.24
Abnormal waist circumference, n (%)	193 (87.7)	25 (58.1)	80 (89.89)	88 (100)	<0.001
Daily carbohydrates consumed, % (RIQ)	46 (40–52)	47 (42–51)	47 (40–52)	45 (40–52)	<0.001
Daily protein intake, % (RIQ)	19 (17–20)	19 (17–20)	18 (16–20)	19 (17–20)	0.85
Daily fat intake, % (RIQ)	36 (31–40)	36 (30–40)	35 (31–41)	35 (31–40)	0.96
Abnormal score for HADS, anxiety, n (%)	82 (37.2)	13 (30.2)	34 (38.2)	35 (39.7)	0.55
Abnormal score for HADS, depression, n (%)	77 (35.0)	18 (41.8)	27 (30.3)	32 (36.3)	0.4
Emotional eating, n (%)	29 (13.1)	4 (9.30)	9 (10.11)	16 (18.18)	0.2
Moderate exercise per week, min, (RIQ)	90 (0–110)	60 (0–200)	120 (0–240)	90 (0–195)	0.73

(*Continued*)

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Table 1 (Continued).

	Total Population n=220 (100%)	Normal Weight n=43 (19.55%)	Overweight n=89 (40.45%)	Obesity n=88 (40.0%)	p value
Number of comorbidities, n (%)					
0	29 (13.3)	7 (16.2)	14 (15.7)	8 (9.3)	0.18
1	77 (35.3)	16 (37.2)	37 (41.5)	24 (27.9)	
2	62 (28.4)	13 (30.2)	21 (23.6)	28 (32.5)	
3 or more	50 (22.9)	7 (16.2)	17 (19.1)	26 (30.2)	

Notes: This table presents the metabolic, lifestyle, and mental health parameters compared across three distinct groups: normal weight, overweight, and obesity. The number of participants (n) and their respective percentages (%) within each weight category are shown. Systolic and diastolic blood pressure (BP), measured in millimeters of mercury (mmHg), triglyceride levels, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hemoglobin A1c (HbA1c) percentages are reported as means with their interquartile ranges (IQR) in parentheses. Alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) levels are presented in units per liter (UI/L). Body mass index (BMI) is shown in kilograms per square meter (kg/m²). Caloric intake is reported in kilocalories (KCal). The percentage of participants engaging in emotional eating, and the median time spent on moderate exercise per week (min/wk), are also included. The 'p' values indicate the statistical significance of the differences observed between the groups, with a value of less than 0.05 generally considered significant.

Abbreviations: BMI, body mass index; HDL, high-density Lipoprotein; LDL, low-density lipoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HADS, Hospital anxiety and depression scale.

patients had three or more parameters for the metabolic syndrome, of these 2.3% were normal weight, 48.3% were overweight, and 56.8% had obesity.

Regarding comorbidities, 86 relatives (39.4%) had prediabetes, 148 (67.2%) dyslipidemia, 19 (8.64%) hypertension, 44 (20.0%) hyperuricemia and 71 individuals (32.2%) had abnormal levels of ALT, AST, or GGT. Only 29 (13.3%) had no comorbid conditions or abnormalities.

Only 20 relatives showed abnormal ACR levels, with a median of 102.7 mg/dL, whereas those with normal ACR levels had a median level of 7.57 mg/dL. Out of 36 relatives with electrocardiographic alterations the highest percentage was noted in the normal weight group (21.4%) followed by the obesity group (19.7%), and the overweight group (14.8%).

The number of comorbidities among groups displayed marginal differences. Three or more comorbidities were present in 16.2% of the normal weight group, 19.1% in the overweight group and 30.2% in the obesity group; this did not reach statistical significance (p=0.18).

Clinical Characteristics

Our investigation revealed noteworthy metabolic distinctions among the normal weight, overweight, and obese groups of relatives. Disparities emerged in triglyceride and HDL cholesterol levels. Triglyceride levels were significantly higher in relatives with overweight and obesity (154 and 162 mg/dL) compared to their normal weight counterparts (119 mg/dL), with a p-value <0.001. Conversely, HDL cholesterol levels were lower in individuals with overweight and obesity (44 and 42 mg/dL vs 50 mg/dL, p=0.01) compared to those with normal weight.

With respect to glucose and glycated hemoglobin values, differences were identified between normal weight relatives and those with obesity (86 vs 90 mg/dL) and between normal weight and overweight groups compared to the group with obesity (HbA1c 5.5% for normal weight and overweight relatives vs HbA1c 5.7% in relatives with obesity).

Liver function tests revealed that alanine transaminase (ALT) and gamma-glutamyl transpeptidase (GGT) values were significantly lower in the normal weight group (ALT 16 and 26 IU/L, p<0.001) compared to the group with obesity (GGT 17 and 33 IU/L, p<0.001). Uric acid levels, while within the normal range for all participants, were significantly lower in normal weight and overweight individuals compared to the group with obesity (5.0 and 5.1 vs 5.7 mg/dL, p<0.001).

Systolic (SBP) and diastolic (DBP) blood pressure was significantly higher in the overweight and obese groups compared to those with normal weight (SBP 119 and 120 vs 112 mmHg, p<0.001 and DBP 73 and 77 vs 69 mmHg, p<0.001, respectively). The mean creatinine level was 0.72 mg/dL for normal weight (0.64–0.83 mg/dL), 0.74 mg/dL (0.65–0.81 mg/dL) for those with overweight, and 0.71 mg/dL for those with obesity (0.63–0.87 mg/dL, p =0.84). The

Table 2 Logistic Regression Model for Risk Factors Associated to the Presence of Any Comorbidity

	Odds Ratio	P value	95% CI
Age, years	1.03	0.13	0.98–1.08
Sex, female	0.48	0.39	0.09–2.56
Diastolic blood pressure, mmHg	0.97	0.56	0.90–1.05
Triglycerides, mg/dL	1.02	<0.001	1.01–1.03
LDL-cholesterol, mg/dL	1.04	0.001	1.01–1.06
AST, IU/L	1.07	0.10	0.98–1.16
Uric acid, mg/dl	1.89	0.11	0.98–3.64

Abbreviations: LDL, low-density lipoprotein; AST, aspartate aminotransferase.

mean ACR level was 6 mg/dL for normal weight (4.6–8.3 mg/dL), 5.8 mg/dL (3.7–7.9 mg/dL) for those with overweight, and 6.2 mg/dL for those with obesity (4.6–12.9 mg/dL, p =0.06).

Body composition analyses demonstrated predictable differences among the groups. Normal-weight individuals had a lower median fat mass (30.1%) compared to their overweight (35.9%) and obesity (41.1%) counterparts (p<0.001). The prevalence of abnormal waist circumference was significantly lower in the normal weight group (25%) compared to the overweight (80%) and obese (88%) groups (p<0.001).

Carbohydrate consumption percentages exhibited a significant difference, with the obesity group reporting a lower percentage (47%) compared to the normal weight and overweight groups (45%, p<0.001).

Moderate exercise measured by minutes of activity per week ranged from 60 min/week in those of normal weight (0–200 min/week), 120 min/week for those of overweight (0–240 min/week) and 90 min/week for those of obesity (0–195 min/week, p=0.73).

The outcomes from the multiple logistic regression, with the presence of any comorbidity as the dependent variable, reveal that an elevation in triglycerides (OR: 1.02 per unit, 95% CI: 1.01–1.03, p<0.001) and LDL-Cholesterol (OR: 1.04 per unit, 95% CI: 1.01–1.06, p=0.001) is associated with an increased likelihood of having any comorbidity. While an increase per unit in AST and uric acid increased the odds of comorbidity, this was a marginal association and did not reach statistical significance. The model was statistically significant (p<0.001), with an R2=0.41, AUC 0.89, and Hosmer Lemeshow = 0.60 (Table 2).

We also compared the relatives who were genetically related vs relatives not genetically related to the patient with diabetes. We did not find any statistical difference between the two groups.

Mental Health Parameters

Relatives completed the HAD questionnaire and an interview/ questionnaire for the identification of eating disorders. Results for the HAD score were positive for anxiety in 13 participants with normal weight (30.2%), 34 participants with overweight (38.2%) and 35 participants with obesity (39.7%) [p=0.55]. The HAD score was positive in 18 participants with normal weight (41.8%), 27 participants with overweight (30.3%) and 32 participants with obesity (36.3%) [p=0.4]. Emotional eating was present in 29 participants with normal weight (67.4%), 67 participants with overweight (75.2%) and 58 participants with obesity (65.9%) [p=0.36].

Discussion

This study aimed to identify metabolic comorbidities among non-diabetic relatives of people with T2DM stratified by BMI. This study holds considerable significance due to its potential impact on diabetes prevention and the broader understanding of metabolic health in high-risk populations. By focusing on the non-diabetic relatives of T2DM patients, it targets a group that is often overlooked but is at heightened risk due to genetic predisposition and shared environmental

factors. This focus on family members provides an opportunity to intervene early before diabetes and other metabolic diseases manifest, which is crucial for reducing the disease burden in the population.

One of the main findings of this work is the high prevalence of overweight (40.4%) and obese (40%) individuals, consistent with other studies where a positive family history was associated with being overweight or obese.[19–21,30] However we found a higher percentage of obesity compared with 18% reported by Cederberg et al.[20]

Although the prevalence of metabolic syndrome nor a stratified analysis of metabolically healthy status according to BMI status were assessed in our study, Table 1 shows that triglyceride levels were significantly higher and HDL cholesterol levels lower in relatives with overweight and obesity, being both essential components of metabolic syndrome. This correlates with Moon's findings of a higher prevalence of metabolic syndrome according to BMI and persistent hypertriglyceridemia after adjustment for BMI in persons with a positive family history of diabetes.[19] Other studies in the Asian population have described susceptibility to dyslipidemia with hypertriglyceridemia in first degree relatives.[20] Significant differences were also found among the BMI groups with regards to fasting plasma glucose and glycated hemoglobin. Multiple studies have described higher fasting glucose levels in relatives of subjects with diabetes independent of BMI.[19–21,30]

The logistic regression model revealed that each unit increase in triglycerides and LDL cholesterol enhanced the likelihood of having a comorbidity by 0.02 and 0.04, respectively. Our descriptive results showed significant differences in lipid profiles across weight categories. Given the observed differences, it is crucial to describe the biological plausibility of weight impact on lipids, insulin resistance, blood pressure, and fatal outcomes.

Relatives with obesity reported significantly lower carbohydrate intake. However, this disparity likely stems from underreporting rather than actual consumption. Studies indicate that people with obesity often underreport food intake, suggesting that using portable electronic devices, direct observation, or photographic records might be more accurate than self-reporting.[31,32] Additionally, an inverse association might exist, where individuals with obesity consumed less food at the time of reporting due to weight loss efforts.

Several studies have explored the risk of developing prediabetes or diabetes in individuals with a family history of diabetes. For example, Awa Feizi found that 29% of first-degree relatives developed impaired fasting glucose, 11% had impaired glucose tolerance, and 3% developed diabetes over seven years.[33] While our results do not specify the risk of developing prediabetes or diabetes, they highlight the relevance of abnormal metabolic profiles in increasing the likelihood of comorbid conditions in relatives of people with T2D.

Several studies have explored the risk of developing prediabetes or diabetes in individuals with a family history of diabetes. For example, Awa Feizi found that 29% of first-degree relatives developed impaired fasting glucose, 11% had impaired glucose tolerance, and 3% developed diabetes over seven years.[33] While our results do not specify the risk of developing prediabetes or diabetes, they highlight the importance of lipid profiles in increasing the likelihood of metabolic comorbidities in relatives of people with T2D.

Khan et al underscored the importance of considering shared environmental and lifestyle factors in the risk of developing type 2 diabetes. The increased prevalence of glucose intolerance and diabetes in spouses of individuals with type 2 diabetes suggests that common habits, such as diet and physical activity, may contribute significantly to disease development.[22] This supports the idea that prevention strategies should not only focus on individuals with diabetes but also on those in close contact with them, persons who may share similar environmental exposures. Screening and early intervention in these high-risk groups could be valuable in reducing the overall incidence of type 2 diabetes.

Weijnen et al showed that siblings of individuals with diabetes had a higher risk of developing the disease, particularly when one or both parents were affected.[23] This points to the importance of family history in understanding diabetes risk. However, what's interesting is that the risk was even higher for non-obese siblings, which shows that genetics may have a stronger influence than lifestyle factors such as weight.[34] These findings suggest that future studies should focus on families with clear genetic patterns, especially when it comes to understanding and mapping diabetes-related genes.[23]

In the analysis comparing relatives genetically related to those not genetically related, we did not find any difference in clinical, metabolic, or mental health parameters. These findings highlight the high prevalence of diabetes in our country, which likely means that the spouses have a family history of the condition, which can impact their metabolism.

This family history suggests that their metabolic responses may mirror those of their genetically related relatives who have diabetes.

Our study's strength lies in its extensive evaluation of health metrics, providing a thorough understanding of body weight's multifaceted impacts on health. Analyzing factors such as blood pressure, cholesterol levels, glucose metabolism, and organ function, the research offers a nuanced view of weight categories and health outcomes. This approach allows for informed discussions on the implications of weight categories, uncovering deeper, interconnected health dynamics.

A limitation of the study is the cross-sectional design. This limits our ability to establish causal relationships and track changes over time, crucial for understanding the progression and long-term implications of weight-related health issues. While valuable for identifying correlations, cross-sectional studies do not offer insights into obesity's dynamic and evolving nature.

Conclusion

Our findings align with the current literature concerning the health risks linked to weight categories. Moreover, relatives of persons with diabetes show an increased possibility of experiencing comorbidities related to an increase in LDL-cholesterol and triglycerides. Therefore, interventions targeted at lifestyle modification to alter these parameters are imperative for primary prevention. The study's findings could inform public health strategies highlighting the need for personalized prevention approaches. Tailoring interventions based on an individual's metabolic profile and weight phenotype can lead to more effective management for those at high risk of developing T2DM. This would be highly relevant in Mexico, where the combined prevalence of obesity and diabetes presents a growing public health challenge.

Future studies should focus on understanding the impact of elevated triglycerides and LDL-cholesterol on the development of comorbidities in relatives of individuals with T2D. Research regarding mental health outcomes of this population, particularly anxiety, depression, and emotional eating, could provide important insights into long-term psychological and metabolic health. Public health initiatives and policies need to raise awareness among relatives of T2D patients about their increased risk for metabolic conditions. This ensures access to preventive practices including family members and community-based support programs.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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