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Elevated liver enzymes,

impaired fasting glucose and undiagnosed diabetes

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Resumen

Introducción: evidencia reciente sugiere que la elevación de las enzimas hepáticas está asociada con diabetes. En el presente estudio se examinó la prevalencia de enzimas hepáticas elevadas y su relación con glucosa anormal de ayuno (GAA) y diabetes no diagnosticada en medicina familiar.

Métodos: estudio transversal analítico y prospectivo en 100 pacientes de 25 a 60 años sometidos a detección de diabetes. Se evaluó índice de masa corporal, circunferencia de cintura, presión arterial, glucosa en ayunas, perfil lipídico, alanino aminotrasferasa (ALT), aspartato aminotrasferasa (AST), gammaglutamiltransferasa (GGT) y proteína *C* reactiva. La relación entre las enzimas hepáticas con la diabetes no diagnosticada y la GAA se calculó mediante χ^2. La *t* de Student fue utilizada para analizar las diferencias estadísticas en las variables continuas.

Resultados: en los pacientes con diabetes sin diagnosticar se identificaron niveles elevados de ALT, AST y GGT, en 16.9, 15.8 y 20.6 %; ante GAA se identificó 76.3, 68.4 y 77.8 %, respectivamente. Las relaciones entre la ALT elevada (0.001) y la GGT (0.000) con la diabetes no diagnosticada y la GAA fueron significativas.

Conclusiones: la elevación de ALT o GGT implica posibilidad de diabetes mellitus tipo 2 no diagnosticada en el primer nivel de atención.

Palabras clave

diabetes mellitus
trastornos del metabolismo de la glucosa
gamma-glutamiltransferasa
alanina transaminasa
aspartato aminotransferasas

Summary

Background: emerging evidence suggests that elevated liver enzymatic activity is associated with diabetes. The purpose was to investigate the prevalence of elevated liver enzymes and its relationship between impaired fasting glucose (IFG) and undiagnosed diabetes in family medicine practice.

Methods: a cross-sectional prospective analytic study was conducted in a representative sample of 100 patients aged 25 to 60 years who underwent to a screening for diabetes. Risk factors, BMI, waist circumference, blood pressure, fasting glucose, lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and C-reactive protein were evaluated. The relationships between liver enzymes, undiagnosed diabetes and IFG were analyzed through χ^2 and Student's *t* test to identify differences in continuous variables.

Results: the prevalence found in undiagnosed diabetes were ALT 16.9 %, AST 15.8 % and GGT 20.6 % and in IFG were 76.3 %, 68.4 % and 77.8 % respectively. The relationships between elevated ALT (0.001) and GGT (0.000) with undiagnosed diabetes and IFG were statistically significant.

Conclusion: elevated ALT or GGT raise the possibility of undiagnosed type 2 diabetes mellitus in family practice.

Key words

diabetes mellitus
glucose metabolism disorders
gamma-glutamyltransferase
alanine transaminase
aspartate aminotransferases

Introduction

The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide.[1] Because of its asymptomatic nature, between one third and a half of individuals with diabetes are undiagnosed.[2] In Mexico, the prevalence of T2DM previous medical diagnosis in adults over 20 years old according to the National Health and Nutrition Survey 2006 (ENSANUT 2006) has increased from 4.6 % in 1993 to 5.8 % in 2000 and 7 % in 2006. In Tamaulipas was 9.8 % being higher in women (10.6 %) than in men

(8.9 %).[3,4] Compared with those reported in the ENSANUT 2000, Tamaulipas presented an increase prevalence of T2DM of 28.9 % (from 7.6 % to 9.8 %). Consequently, different risk factors for undiagnosed diabetes have been identified as a guide for the screening strategy.[5,6]

The liver plays an important role in maintaining normal glucose concentrations during both, fast and postprandial phase. It is also a major site for insulin clearance. The loss of a direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes an increase in hepatic glucose production.[7] Hepatic dysfunction resulting from the insulin resistance syndrome may contribute to the development of T2DM. Few studies in Mexico have examined the relationship between liver enzymes and diabetes and have suggested that elevated liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) are associated with the development of diabetes and cardiovascular disease.[8-10]

There is no evidence in Tamaulipas as to whether the presence of elevated liver enzymes is associated with either current impaired fasting glucose (IFG) or undiagnosed diabetes. Thus, the purpose of the present study was to examine the prevalence of elevated liver enzymes and investigate its relationship between IFG and undiagnosed diabetes. We hypothesized that elevated liver enzymes will be associated with the presence of IFG and undiagnosed diabetes.

Methods

The study sample included patients aged 25-60 years who attended a family practice setting at Tamaulipas, Mexico, and underwent screening for diabetes. The sample size was calculated considering the prevalence of T2DM in Mexico on adults over 20 years that is approximately 7 %; the confidence level was established at 95 % and 5 %. The established number of subjects was 100. The protocol was approved by the ethics and research committee 2801 at the General Regional Hospital No. 6, Mexican Institute of Social Security and all subjects admitted into the study provided written informed consent. During screening for diabetes a questionnaire was applied. Alcohol drinking was assessed on the basis at the self-reported number of drinks consumed during the previous month. The questionnaires were also used to ask about smoking habits (no or yes), physical activity was measured by asking whether the participant practiced leisure time physical activity at least 20 to 30 minutes two times or more per week. Exclusion criteria were diabetes diagnosed previously by a physician, pregnant women and subjects who have a history for liver disease (hepatitis infection or liver cirrhosis), use of antihypertensive medication and non related clinical problems in alcohol drinkers. A drinking problem was defined as intake over 14 drinks per week for men or over 7 drinks per week for women.[11]

Anthropometric measurements

All measurements were conducted by trained examiner. Participants removed their shoes and wearing light clothing, weight was measured in the upright position to the nearest 0.1 kg using a calibrated beam scale with stadiometer, waist perimeter (WP) was measured at the level of the umbilical scar in upright position with subjects with legs separated 25 to 30 cm from each other, using a calibrated non flexible tape measure to the nearest 0.1 cm (SECA, Hamburg, Germany). The tape was placed over the skin without any compression and on the horizontal plane to the floor. The measurement was done after exhaling. Height was measured to the nearest 0.1 cm using a stadiometer graduated by cm. BMI was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured using a standard mercury sphygmomanometer in right arm in a sitting position following a 10 minutes rest period. Systolic blood pressure (SBP) was determined by the first Korotkoff sound and diastolic blood pressured (DBP) by the last heard Korotkoff sound. Three measurements were taken at 5 minutes intervals; the average of the last two was considered as the definitive value. We evaluated the presence or absence of acanthosis nigricans in neck and axilla.

Blood samples from all individuals were obtained after 12 hours fasting period. Fasting plasma glucose concentrations were measured using the glucose oxidase method, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) by enzymatic reaction oxidase/peroxidase, triglycerides by a colorimetric method, C-reactive protein (CRP) by turbidimetric method, hepatic enzyme ALT and AST by Henry technique and GGT by Szasz technique (Syncron CX 4; Beckman Instruments, Fullerton, CA).

Definitions of variables

Undiagnosed diabetes was defined as patients reporting that they had not been diagnosed by a doctor with diabetes but who had fasting plasma glucose over 126 mg/dL. Impaired fasting glucose was defined as patients not diagnosed with diabetes who had fasting plasma glucose between 100 and 125 mg/dL. Those no diagnosed with diabetes who had fasting plasma glucose less of 100 mg/dL and who were classified as normal.[12] Family history of diabetes and obesity were defined as a mother, father, sister or brother with diagnosed diabetes or obesity (no or yes). Overweight was defined as a BMI > 25 < 29.9 and obesity if BMI > 30.[13] Blood pressure was considered high if it was present the systolic > 130 mm Hg or diastolic > 85 mm Hg according our guides of clinical practice institutional.[14] Total cholesterol was classified as high with > 200 mg/dL, LDL anormal > 100 mg/dL, HDL anormal < 40 mg/dL, triglycerides high > 150 mg/dL,[15] PCR elevated > 0.3 mg/dL.[16] After previous research relating liver enzymes to the development of diabetes, liver enzymes were classified elevated with ALT > 27 U/L, AST > 25 U/L, GGT > 29 U/L.[8,17,18]

Table I Diagnosis, clinical and biochemical characteristic of the study participants*

	Impaired fastig glucose	Undiagnosed diabetes	Normal	p**
Age (years)	49.27 ± 9.52	47.57 ± 9.72	50.74 ± 5.49	0.54
Gender (*n*, %)				
Female	45 (68.2)	8 (12.1)	13 (19.7)	0.001
Male	22 (64.8)	6 (17.6)	6 (17.6)	
Family history diabetes (*n*, %)				
Yes	58 (69.9)	14 (16.8)	11 (13.3)	0.003
No	9 (52.9)	0	8 (47.1)	
Family history obesity (*n*, %)				
Yes	57 (67)	14 (16.5)	14 (16.5)	0.000
No	10 (66.7)	0	5 (33.3)	
Physical activity (*n*, %)				
Yes	0	0	4 (100)	0.000
No	67 (69.9)	14 (14.6)	15 (15.5)	
Alcohol consumption (*n*, %)				
Yes	16 (66.7)	6 (25)	2 (8.3)	0.09
No	51 (67.1)	8 (10.5)	17 (22.4)	
Smoking habit (*n*, %)				
Yes	10 (66.7)	4 (26.7)	1 (6.6)	0.17
No	57 (67)	10 (11.8)	18 (21.2)	
Acanthosis nigricans (*n*, %)				
Yes	62 (76.6)	12 (14.8)	7 (8.6)	0.000
No	5 (26.3)	2 (10.5)	12 (63.2)	
BMI	33.27 ± 3.74	38.12 ± 7.63	30.46 ± 2.96	
Overweight	9 (47.4)	1 (5.3)	9 (47.4)	0.002
Obesity	58 (71.6)	13 (16)	10 (12.3)	
Waist circumference (cm)	102.75 ± 10.05	104.64 ± 11.05	91.08 ± 10.69	0.53
SBP (mm Hg)	122.69 ± 13.24	127.86 ± 15.16	112.21 ± 11.52	0.19
DBP (mm Hg)	79.45 ± 6.67	80.29 ± 6.83	70.74 ± 9.38	0.67
FPG (mg/dL)	109.71 ± 7.23	222.71 ± 72.51	89.57 ± 8.09	0.000
Total cholesterol (mg/dL)	201.08 ± 46.69	243.57 ± 54.96	194.47 ± 47.64	
High	23 (57.5)	10 (25)	7 (17.5)	0.034
Low	44 (73.3)	4 (6.7)	12 (20)	
HDL cholesterol (mg/dL)	37.29 ± 6.36	33.35 ± 2.79	40.10 ± 10.10	
High	17 (70.8)	0	7 (29.2)	0.045
Low	50 (65.8)	14 (18.4)	12 (15.8)	
LDL cholesterol (mg/dL)	116.05 ± 27.62	132 ± 19.39	107.93 ± 18.91	
High	51 (67.1)	12 (15.8)	13 (17.1)	0.000
Low	16 (66.7)	2 (8.3)	6 (25)	
Triglycerides (mg/dL)	251.62 ± 90.23	297.85 ± 175.79	144.68 ± 47.21	
High	60 (75)	12 (15)	8 (10)	0.000
Low	7 (35)	2 (10)	11 (55)	
ALT (U/L)	38.36 ± 26.93	46 ± 26.50	27.26 ± 24.36	
High	45 (76.3)	10 (16.9)	4 (6.8)	0.001
Low	22 (53.7)	4 (9.8)	15 (36.6)	
AST (U/L)	31.32 ± 18.43	34.64 ± 13.54	26.68 ± 14.38	
High	39 (68.4)	9 (15.8)	9 (15.8)	0.588
Low	28 (65.1)	5 (11.6)	10 (23.3)	
GGT (U/L)	40.05 ± 21.40	77.92 ± 51.95	17.15 ± 7.33	
High	49 (77.8)	13 (20.6)	1 (1.6)	0.000
Low	18 (48.6)	1 (2.7)	18 (48.6)	
CPR (mg/dL)	6.83 ± 6.58	11.57 ± 8.05	2.04 ± 1.8	
High	66 (68.8)	14 (14.6)	16 (16.7)	0.014
Low	1 (25)	0	3 (75)	

* *Continuous variables values are mean ± SD and categorical*

** *Statically significant $p < 0.05$ (χ^2 test for categorical variables and Student t test for continuous variables)*

Analysis

Data are presented as means ± SD for continuous variables and number of subjects (percentage) for categorical variables. We evaluate relationships between liver enzymes with undiagnosed diabetes and IFG using χ^2 analysis and Student's *t* test was used to analyze statistical differences in continuous variables. All reported *p* values < 0.05 were considered statistically significant.

Results

The sample study included 100 subjects (*n* = 66 females, 34 males), the clinical characteristic of the study participants, according with undiagnosed diabetes and IFG are present in table I. A substantial proportion of the sample had elevated liver enzymes, the prevalence found in undiagnosed diabetes were ALT 16.9 %, AST 15.8 % and GGT 20.6 % and in IFG were 76.3 %, 68.4 % and 77.8 % respectively. Test for differences in undiagnosed diabetes and IFG patients were significant except for age, alcohol consumption smoking habits, waist circumference, systolic and diastolic blood pressure. Age was not significantly different between groups, although undiagnosed diabetics tended to be younger than IFG patients (47.57 ± 9.72 years). Elevated blood pressure was found in 30 subjects, four with undiagnosed diabetes 28.6 % and ten with IFG 71.4 %. The undiagnosed diabetes had higher fasting serum glucose, fasting serum total cholesterol, fasting serum LDL cholesterol, fasting serum triglycerides and low fasting serum HDL cholesterol concentrations that the IFG patients. The relationships between elevated ALT and GGT but not AST with undiagnosed diabetes and IFG were significant. There was a significance CRP levels with undiagnosed diabetes patients (mean 11.57 ± 8.05 mg/dL, $p < 0.014$).

Discussion

The type 2 diabetes mellitus is a chronic disease associated with premature mortality and various debilitating complications.[19] Early identification of risk factors is important so that appropriate interventions can be established. In our results we are concerned the high numbers of patients with prediabetes, acanthosis nigricans and physical inactivity. Insulin resistance is recognized to be a major factor in the pathophysiology of T2DM. Acanthosis nigricans is a skin disorder characterized by hyperpigmentation, hyperkeratosis, and papillomatosis, it is a clinical marker that has been linked to surrogate markers of insulin resistance.[20] It is known that increased physical activity such as walking (that is easily adoptable) can prevent or delay the development of T2DM. The mechanism of this beneficial effect of physical activity on glucose metabolism is that exercise enhances insulin signaling and, consequently, increases the rate of insulin-stimulated glucose uptake by GLUT 4 glucose transporter proteins. Independent of insulin signaling, muscle contraction also results in increased abundance and redistribution of GLUT 4, the promotion of muscle mass, capillary recruitment, and capillary proliferation in muscles and a higher proportion of insulin-sensitive muscle fiber types, thereby increasing overall insulin sensitivity. Current research suggests that exercise promotes partitioning of excessive fatty acid uptake within the muscle to triglycerides as opposed to fatty acid intermediates known to ultimately induce insulin resistance.[21] Therefore, in primary health care we need stimulate the motivation for adopting healthier lifestyle such as healthy diet and practice physical activity.

The results of this study showed significant associations between liver enzymes, especially GGT and ALT with undiagnosed diabetes and IFG. Currently, the mechanisms underlying these associations have not been elucidated, but there are at least two potential mechanisms: first, GGT and ALT may reflect the accumulation of hepatic fat[22] and, thus, may represent an indirect marker of hepatic insulin resistance.[23] The deposition of fat in the liver leads to an increase in gluconeogenesis and a decrease in the storage of glucose as hepatic glycogen.[24] Second, oxidative stress may play a role in the pathogenesis of diabetes,[25] and GGT may represent a nonspecific marker of oxidative stress.[26] Under conditions of oxidative stress, GGT is induced to help regulate the redox status by breaking down extracellular glutathione to provide cysteine for new intracellular synthesis of glutathione. In previous studies, elevated GGT or ALT and incident diabetes reported a positive association.[27-29] The findings from our study are consistent with those studies. The lack of positive association with AST could be explained because, although ALT is found primarily in the liver, AST is found not only in the liver but also in cardiac and skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. Thus, it may not be an specific marker of the liver injury that is associated with diabetes and impaired fasting glucose.

An explanation of the elevated CRP levels in undiagnosed diabetes patients (such as occur in our results) is that the levels of CRP are elevated in metabolic disorders such as obesity, hyperglycemia, and hypertriglyceridemia. There is no consensus regarding the mechanism for the association between metabolic disorders and chronic subclinical inflammation, and several possible explanations have been suggested; these include release of proinflammatory cytokines from adipose tissue. Although the liver is recognized as a major source of inflammatory mediators, it is generally assumed that hepatic production of CRP in subjects exhibiting metabolic abnormalities that characterize insulin resistance occurs under the influence of cytokines produced in other tissues. However, inflammatory processes occur in the liver in response to fatty infiltration independent of extra hepatic

stimulation. The liver has one of the largest resident population of macrophages (Kupffer cells), which are key components of the innate immune systems. Hepatic macrophages generate various inflammatory mediators and cytokines that modulate the phenotype of neighboring hepatocytes and other immune cells that travel through the liver. Similar to infiltration of lipoprotein particles into the arterial wall, fat accumulation in the liver stimulates hepatic cytokine production, which could further contribute to the increased CRP levels.[30]

Our study presents some limitations that is pertinent to comment; a measure of fasting plasma insulin was not available to estimate insulin resistance. However, other studies[31] that was able to adjust for true or surrogate measures of insulin resistance still reported significant associations between raised concentrations of liver enzymes and incident diabetes. Secondly, only a single measurement of concentration of liver enzymes was made. If regression dilution bias played a role, it is possible that our results underestimated the strength of the associations. Third information to eliminate participant with various sources of liver pathology based on self-report by the patients such a viral hepatitis or liver cirrhosis was not available. It is unclear how this may have affected our results.

A finding of elevated liver enzymes for family physicians implies to consider the investigation a possibility of undiagnosed diabetes or impaired fasting glucose, even in the absence of other common risk factors. Concentrations of liver enzymes (GGT/ALT) are simple measurements available in routine clinical practice and can be routinely measured as part of clinical chemistry panels and, thus, are readily available for many people, so it may be a need to discover how values of these enzymes can be incorporated into clinical practice to help identify people who are at potentially increased risk for developing diabetes and who may benefit from more intensive monitoring and perhaps treatment with behavioral interventions such as health promotion and education that can be play a critical role in decrease the emerging epidemic of diabetes.

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