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Prevalence of type 2 diabetes mellitus and chronic liver disease: A retrospective study of the association of two increasingly common diseases in Mexico

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ABSTRACT

Background. Recent studies have demonstrated a relationship between insulin resistance (IR) and type 2 diabetes mellitus (T2DM). The aim of this study was to determine the prevalence of T2DM among patients with liver disease. **Methods.** A retrospective study was performed by examining the charts of patients who presented with a diagnosis of liver disease at a university hospital between January 2006 and April 2010. **Results.** Liver disease was found in 129 patients. The most prevalent liver disease was cirrhosis, with 61 patients (47.2%), 44 patients had hepatitis C virus (34.1%) and 28 patients had hepatocellular carcinoma (21.7%). T2DM was diagnosed in 30 patients, 18 of whom were male (18/60; 30%) and 12 of whom were female (12/69; 17.4%). Only liver cirrhosis was significantly related to T2DM (21 of 61 patients; 34.4%, $p < 0.004$). **Conclusions.** The prevalence of T2DM among patients with liver disease (23.2%) is well established and similar to that reported in Western and some Eastern countries.

Key words. Chronic liver disease. Insulin resistance. Nonalcoholic fatty liver disease. Cirrhosis. Hepatocellular carcinoma.

INTRODUCTION

In Mexico, liver disease has increased over the last few decades, with its incidence estimated to be 39.4 per 100,000 inhabitants. Mortality trends from liver disease have increased considerably. For example, in 2002 liver diseases represented the fifth leading cause of death in the general population, whereas in 2007 liver disease became the third leading cause of death, after cardiovascular diseases and T2DM.[1,2]

The most common liver diseases include fatty liver disease, such as alcoholic and NAFLD, infection with HAV, HBV and HCV, hemochromatosis and advanced disease states such as NASH, cirrhosis, liver failure and HCC.[3] Autoimmune hepatitis and drug-induced liver disease also have an important impact on the liver.

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In contrast, diabetes mellitus is a chronic disease that has increased in prevalence and incidence around the world over the last few decades. T2DM is responsible for about 90-95% of cases of diabetes and studies show that some populations are more prone to developing this disease, such as the Mexican population. In Mexico, an alarming increase in the prevalence of this disease has occurred. In 1995 4% of the population had T2DM,[4] by 2006 this had risen to 7%.[5] It is estimated that, in Latin America, the overall prevalence of T2DM in 2025 will be 8.7%, and is expected to be even higher in Mexico and Brazil.[6]

The physiological basis of the T2DM is IR, which is defined as an increased need for insulin in the peripheral tissues (muscle and adipose) to achieve normal blood-glucose levels and to reduce the glucose output in the liver[7]. IR is responsible for causing micro- and macrovascular complications throughout the body. Some studies relate IR with deleterious effects on the biliary tract and liver, such as the induction of gallstones and NAFLD. NAFLD is considered the most common chronic liver disease in Western countries and is involved in the manifestation of metabolic syndrome, a pathology already proven to be intrinsically related to IR.[8] Furthermore,

IR tends to favor the progression of NAFLD to NASH, cirrhosis and HCC.[9]

Recent studies have also confirmed a close relationship between IR and other liver diseases. Chronic hepatitis, like that caused by HBV, HCV, hemochromatosis, cirrhosis and HCC, has also been associated with IR. Some authors have reported "hepatogenous diabetes", which is recognized by the World Health Organization as an independent entity that refers to the development of the T2DM due to cirrhosis.[10]

Because of the large impact T2DM has on the epidemiology of liver disease, the aim of this study was to determine the prevalence of T2DM among patients with liver disease.

METHODS

Population

A retrospective study was performed examining medical data of patients' charts from a university hospital in Mexico City who presented with a discharged diagnosis of liver disease between January 2006 and April 2010. The liver diseases considered were NAFLD, NASH (both of them confirmed through a biopsy report in the file), HBV, HCV, hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, nonspecific hepatitis, cirrhosis, HCC and metastatic hepatic carcinoma.

Demographic, anthropometric, biochemical and metabolic variables including age, sex, type of liver disease, presence or absence of T2DM diagnosis, weight, size, BMI, SBP and DBP were registered. Laboratory results including serum glucose, platelets (PLTs) lipids profile (cholesterol, triglycerides (TG), high density lipoprotein cholesterol (c-HDL) and low density lipoprotein cholesterol (c-LDL)), liver function tests (alanino amitransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamil transpeptidase (GGT), lactic dehydrogenase (LDH)), bilirubins (total, direct and indirect), prothrombin time (PT) and activated partial thromboplastin time (aPTT) were also registered. Of these laboratory measurements, only the presence of serum glucose was essential to our analysis.

Some variables were separated according to the values established in the Adult Treatment Panel III to assess whether metabolic syndrome was present. This entity can be detected if there are three or more of the following criteria: serum glucose > 110 mg/dL; overweight (BMI ≥ 25) or obesity (BMI ≥ 30); hypertension (SBP ≥ 130 and/or DBP ≥ 85); HDL < 40 for men and < 50 mg/dL for women; LDL ≥ 150 mg/dL and waist circumference ≥ 88 cm for women and ≥ 102 cm for men; however, the final criterium of waist circumference was not considered for this study.

Statistical analysis

Data was organized using Microsoft Office Excel 2007 software (Microsoft Office Enterprise 2007). Statistical analysis was performed with SPSS Statistics v.17 software (LEAD Technologies, Chicago, IL). The mean ± SD and independent samples t tests were used to describe the distribution of continuous variables when comparing for the presence or absence of T2DM. Chi-square testing for linear trends was used to assess whether there was an association between the T2DM and each liver disease. For multivariate analyses, logistic regression was conducted to complement and corroborate results.

RESULTS

A total of 129 patients were detected with the diagnosis of chronic liver disease: 65 were male (46.5%), 74 were female (53.5%) and all were diagnosed with chronic liver disease. The mean age was 53 ± 16 years. Age, weight, BMI, SBP, DBP and serum glucose were significantly higher in the diabetic patients, whereas PLTs, AST and total proteins presented a trend to significance. The remaining parameters are shown in Table 1.

The most prevalent liver disease was cirrhosis with 61 patients (47.2%) having this condition, followed by 44 patients with HCV (34.1%), 28 patients with HCC (21.7%), 18 patients with NAFLD (13.9%) of which 8 cases presented NASH (9.3%), 12 patients with metastatic carcinoma (9.3%), 8 patients with autoimmune hepatitis and nonspecific hepatitis (6.2% each), six patients with HBV (4.6%), three patients with primary biliary cirrhosis (2.3%), and one patient with hemochromatosis (0.77%). There were also found some cases in which several pathologies coexisted: 31 cirrhotic patients and 15 with HCC presented HCV (50.8% and 53.6% respectively). 16 patients with HCC also presented cirrhosis (57.1%). Lesser cases of other relationships were presented, but due they are not relevant to the study, they are not mentioned.

T2DM was diagnosed in 30 patients, 18 male (60%) and 12 female (40%). The prevalence of T2DM in males was 30% and 17.4% in females ($p = 0.076$).

Table 1. Anthropometric, metabolic and biochemical characteristics registered according to the absence or presence of T2DM diagnosis.

Variable	Without T2DM	With T2DM	p Value
Age (yr)	50 ± 16	64 ± 11	0.000
Weight (kg)	66.4 ± 13	73.1 ± 14.1	0.022
BMI	24.3 ± 5.6	26.3 ± 4	0.036
SBP (mmHg)	110.4 ± 13	117.6 ± 11.9	0.008
DBP (mmHg)	69.9 ± 9	75 ± 10	0.010
Hemoglobin (g/dL)	12.6 ± 2.2	12 ± 2.6	0.3
Platelets (cells/mm3)	159.4 ± 112.9	132.1 ± 72	0.133
Serum glucose (mg/dL)	105 ± 24.3	183.8 ± 89.4	0.000
Triglycerids (mg/dL)	141.3 ± 128.7	176.1 ± 105	0.49
Cholesterol (mg/dL)	136.4 ± 62.6	163.7 ± 69.2	0.288
c-HDL (mg/dL)	27.7 ± 13.8	25.8 ± 10.8	0.737
c-LDL (mg/dL)	126.4 ± 153.9	110.6 ± 79.9	0.754
Direct Bilirubin (mg/dL)	3 ± 4.8	2.6 ± 5	0.762
ALT (IU/L)	466.9 ± 1137	238.5 ± 918.2	0.291
AST (IU/L)	453 ± 1188	186.4 ± 514.8	0.102
PA (IU/L)	179.8 ± 205.1	164.2 ± 149	0.666
GGT (IU/L)	175.2 ± 271	146.5 ± 172.3	0.515
LDH (IU/L)	394.9 ± 779.7	268.5 ± 203.4	0.176
PT (sec)	13.3 ± 3.8	13.8 ± 3.8	0.541
aPTT (sec)	30.4 ± 6.5	28.7 ± 4.1	0.307
Total Proteins (g/L)	6.6 ± 2.5	6 ± 1	0.071
Albumin (g/L)	2.9 ± 0.74	2.7 ± 0.74	0.355

BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. PLT: platelets. TG: triglycerides. TC: total cholesterol. c-HDL: high-density lipoproteins cholesterol. c-LDL: low-density lipoproteins cholesterol. DB: direct bilirubin. ALT: alanine aminotranferase. AST: aspartate-aminotransferase. AP: alkaline phosphatase. GGT: gamma-glutamyl transpeptidase. LDH: lactic dehydrogenase. PT: prothrombin time. aPTT: activated partial thromboplastin time.

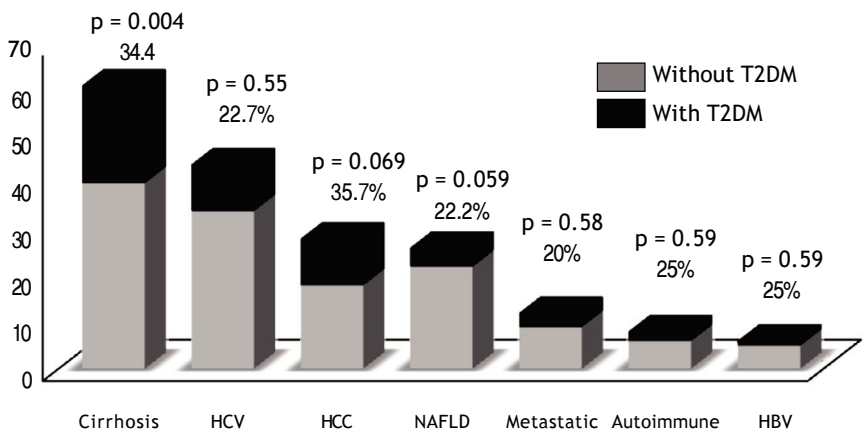

Figure 1. Prevalence of T2DM in patients with liver disease. The figure shows the prevalence of liver disease in patients with T2DM compared with patients without T2DM. Only cirrhosis was statistically significant whereas HCC showed a tendency towards significance. **T2DM:** type 2 diabetes mellitus. **HCV:** hepatitis C virus. **HCC:** hepatocellular carcinoma. **NAFLD:** nonalcoholic fatty liver disease. **NASH:** nonalcoholic steatohepatitis. **VHB:** hepatitis B virus.

Table 2. Prevalence of T2DM within age groups.

Age group (yrs)	Patients	Prevalence (%)	p Value
0-19	0/2	0	0.588
20-29	0/8	0	0.112
30-39	1/18	5.6	0.043
40-49	3/16	18.8	0.462
50-59	4/35	11.4	0.039
60 or older	22/50	44	0.000

Figure 1 shows the prevalence of T2DM in patients with each liver disease.

According to the ATPIII standardized variables used, there was a significant relationship between high BMI (overweight; 31.4%, p = 0.061), overweight/obesity (30.9%, p = 0.024), SBP ≥ 130 (41.2%, p = 0.063), DBP ≥ 85 (44.4%, p = 0.12) and T2DM in these patients. Obesity alone was not significant (29.4%, p = 0.29).

A greater prevalence of T2DM was observed in older patients. Table 2 shows the prevalence of T2DM according to group age.

Liver cirrhosis was related to T2DM (21/61patients with cirrhosis; 34.4%, p < 0.004) and when submitted to the multivariate study (including variables with p < 10) and adjusted for variables such as sex, age > 60 years, weight, BMI, SBP ≥ 130, DBP ≥ 85 and PLT, it remained significant.

DISCUSSION

The overall prevalence of T2DM in the population studied was 21.5%. Among patients with cirrhosis, the prevalence of T2DM we found was similar to that found in the United States (US) (25-34%);[7,11,12] however, it was lower than that found in Brazil and Japan (64.5%[13] and 30.8%,[14] respectively).

The prevalence of HCV in our study was similar to that reported in Europe (Italy 23%, Greece 13%, Spain 23%)[15-17] and Asia (Israel 39%, Saudi Arabia 22%, Japan 20.9%)[14,18,19] but lower than that in the US (33%). Interestingly, HCV genotypes 1 and 4 have been associated with the development of IR and T2DM compared with genotypes 2 and 3 (37% *vs.* 17%).[20]

The prevalence of HCC among diabetics in our study was lower than that found in some regions of Europe, such as Italy (31.2%)[21] but higher than that reported in Greece (18%)[22] or the US (9.7%).[23]

The prevalence of NAFLD is reported to be 20-25% in the general population and up to 75-92% in obese people in the US.[24,25] The Dionysos study, a cohort follow-up study carried out in Italy, reported a prevalence of T2DM of 30-50% in patients with NAFLD;[24,26] however, in other case-controlled studies, the prevalence has been reported to be up to 80%.[27] In the Philippines the prevalence of NAFLD in patients with T2DM is reportedly 60%[28] and in Mexico it is estimated to be around 15.9%, which is corroborated by USG, although a proton magnetic resonance spectroscopy-based study in the US with Hispanics showed a prevalence of NAFLD of 45% in patients with T2DM.[29,30] In the present study, we found a lower prevalence of NAFLD in patients with T2DM.

In our study, the prevalence of NASH in patients with T2DM was similar to that found in other studies conducted in Asia (India), which report prevalences of 25%[31] and 27%,[32] and other regions such as the US where the overall prevalence is reportedly 3-5.7% and as high as 25-45% in diabetic patients.[24,32,34]

Autoimmune hepatitis may not be as common as other liver diseases; however, in Western countries it is estimated to have a prevalence of 11-20%, which is somewhat lower than the prevalence we found. In Eastern countries, such as India, the prevalence is even lower, at 1.5%, although it can be as high as 39.5% in diabetics,[35] which is much higher than the prevalence we found. Additionally, in Brunei, Asia, a prevalence of T2DM of 21% in patients with autoimmune liver disease has been reported.[36] It is important to notice the "drug-induced diabetes" since most patients with autoimmune hepatitis undergo a corticosteroid treatment; nevertheless, in only one patient was referred the use of prednisone and he was not a case of T2DM.

Some studies have reported a prevalence of hemochromatosis in patients with T2DM of 0.4%[37] to 1.34%[38] within the US; however, it can reach up to 50-85% in patients with hereditary hemochromatosis.[39] We found only one patient with hemochromatosis in our study; however, he did not present T2DM. Some authors also suggest that hemochromatosis is poorly diagnosed in diabetic patients and among patients with liver disease.

Concerning chronic hepatitis of viral origin, in the US HBV has been reported to be associated with diabetes in up to 8%[16] or 12%[40] of patients. In Japan, the prevalence is about 11.9%[14] whereas we found it to be somewhat higher. Table 3 shows the relevant data.

We found a significant relationship between cirrhosis and T2DM confirming the presentation of the "hepatogenous diabetes" in our population. Garcia-Compean, et al. comment that in hepatogenous diabetes, IR, which is induced by cirrhosis, forms the pathophysiological basis of the development of T2DM. At the same time HCV, AFLD and NAFLD, NASH and hemochromatosis may lead to cirrhosis or even dysfunction of the pancreatic b-cells, which directly promotes T2DM.[40] Nevertheless, in our study there was no significant correlation between NAFLD, NASH and HCV with T2DM, as have been documented in several other reports.[16,36,41] This may be explained since the small population studied. We also found that HCC correlated with T2DM; however, when submitted to multivariate analysis this correlation lost its significance. This may be explained by more than half of the

Table 3. Prevalence of T2DM in association with liver disease worldwide.

Study	Country	Prevalence (%)
Hepatitis B Virus		
Arao M, *et al*. 2003	Japan	16.7
Knobler H, *et al*. 2000	US	12
This study	**Mexico**	**16.7**
Hepatitis C Virus		
Moucari R, *et al*. 2008	US	33
Mangia A, *et al*. 1998	Italy	23
Lecube A, *et al*. 2004	Spain	
Arao M, *et al*. 2003	Japan	20
Singal AK, *et al*. 2008	Saudi Arabia	22
Fraser GM, *et al*. 1996	Israel	39
This study	**Mexico**	**22.7**
Non-Alcoholic Fatty Liver Disease		
Dixon JB, *et al*. 2001	US	20-45
Gaiani S, *et al*. 2009	Italy	80
Bellentani S, *et al*. 2007		30-50
Targher G, *et al*. 2007		
Mendez N, *et al*. 2007	Mexico	15.9-45
DeLusong MAA, *et al*. 2008	Philippines	60
This study	**Mexico**	**17.6**
Non-Alcoholic Steato-Hepatitis		
Nugent C, *et al*. 2007	US	25-45
Harrison SA, *et al*. 2006		
Prashanth M, *et al*. 2009	India	25
Amarapurkar DN, *et al*. 2008		27
This study	**Mexico**	**25**
Cirrhosis		
Tolman KG, *et al*. 2007	US	25-30
Hickman IJ, *et al*. 2007		
Zeinn NN, *et al*. 2000		34
Arao M, *et al*. 2003	Japan	30.8
Costa-Braganca, *et al*. 2010	Brazil	64.5
This study	**Mexico**	**34.4**
Hepatocellular Carcinoma		
Davila JA, *et al*. 2010	US	9.7
Donadon V, *et al*. 2008	Italy	31.2
Lagiou P, *et al*. 2000	Greece	18
This study	**Mexico**	**35.7**
Hemochromatosis		
Sampson MJ, *et al*. 2000	US	0.4
Conte D, *et al*. 1998		1.34
Adams PC, *et al*. 1991		50-85 (hereditary)
This study	**Mexico**	**0.77 (general)**
Autoimmune hepatitis		
Jalihal A, *et al*. 2009	Brunei	21
Choudohuri G, *et al*. 2003	India	39.5
This study	**Mexico**	**25**

HCV: Hepatitis C virus. HCC: hepatocellular carcinoma. NAFLD: alcoholic fatty liver disease. NASH: nonalcoholic steatohepatitis. HBV: hepatitis B virus. US: United States.

patients with HCC also having cirrhosis (16 out of 28) rather than other liver disease.

Because this study was retrospective, there was no follow-up conducted.

The prevalence of T2DM among patients with liver disease is important and this prevalence is predicted to increase. It is estimated that chronic liver diseases will increase in incidence because of improvements in treatment, which will augment life expectancy, allowing for the development of diabetes in patients with these diseases. Additionally, diabetes mellitus is also predicted to increase in prevalence and incidence around the world, including in Mexico where it is already a significant public health issue as the ninth most frequent cause of morbidity and the first cause of mortality.[4,42]

As seen in our study population, who were prone to glucose intolerance, IR and related complications, hepatogenous diabetes should be thoroughly investigated with the diagnosis of T2DM or chronic liver disease. For this, we recommend screening of serum glucose in patients with liver diseases and screening of liver function in patients with T2DM (this last point is important to note because liver studies are rarely performed in diabetics as confirmed in our research). This recommendation is based on the knowledge that T2DM also complicates and exacerbates the severity of chronic liver diseases and mortality trends. Several studies have demonstrated that T2DM promotes more fibrosis and reduces response to pegylated interferon-based treatment in HCV-infected patients,[43] increases in the incidence and severity of liver failure in patients with cirrhosis[44,45] and induces a more extensive disease in HCC. In addition, comorbidity of this altered insulin state with HBV, HCV, NAFLD, NASH and cirrhosis tends to facilitate the development of HCC.[7,46]

In conclusion the prevalence of T2DM among patients with chronic liver disease in this study is similar to that reported for Western countries, although we expected it to be higher considering the Mexican population is more prone to developing these diseases, specifically T2DM. The impact of liver diseases and T2DM is important and more prospective studies involving larger populations that assess the presence of liver compromise in diabetic patients are needed to confirm and recognize the true impact of this comorbidity in the Mexican population.

ABBREVIATIONS

- **IR:** Insulin resistance.
- **T2DM:** Type 2 diabetes mellitus.
- **NAFLD:** Nonalcoholic fatty liver disease.
- **HBV:** Hepatitis B virus.
- **HCV:** Hepatitis C virus.
- **NASH:** Nonalcoholic steatohepatitis.
- **HCC:** Hepatocellular carcinoma.
- **BMI:** Body mass index.
- **SBP:** Systolic blood pressure.
- **DBP:** Diastolic blood pressure.

REFERENCES

1. Méndez-Sánchez N, Villa AR, Vázquez-Elizondo G, Ponciano-Rodriguez G, Uribe M. Mortal*ity trends for liver cancer in Mexico from 2000 to 2050. Ann Hepatol* 2005; 7(3): 226-9.
2. Data from the Dirección General de Epidemiología, available at http://sinais.salud.gob.mx/mortalidad.
3. Lizardi-Cervera J, Aguilar-Zapata D. Nonalcoholic fatty liver disease and its association with cardiovascular disease. *Ann Hepatol* 2009; 8(1): S40-S43.
4. Aguilar-Salinas CA, Velásquez-Monroy O, Gómez-Pérez FJ, et al. Characteristics of the patients with type 2 diabetes in Mexico: results from a large population-based nationwide survey. *Diab Care* 2003; 26: 2021-6.
5. Encuesta Nacional de Salud y Nutrición 2006. Instituto Nacional de Salud Pública; 2006.
6. Andrade F. Estimating diabetes and diabetes-free life expectancy in Mexico and seven major cities in Latin America and the Caribbean. *Pan Am J Public Health* 2009; 26(1): 9-16.
7. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. *Am J Med* 2007; 120: 829-34.
8. Ryan MC, Wilson AM, Slavin J, et al. Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. *Diabetología* 2004; 28(5): 1222-4.
9. Méndez-Sánchez N, Chávez-Tapia NC, Zamora-Valdés D, Medina-Santillán R, Uribe M. Hepatobilliary diseases and insulin resistance. *Curr Med Chem* 2007; 14(18): 1988-99.
10. Holstein A, Hize S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol* 2002; 17: 677-81.
11. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care* 2007; 30: 734-43.
12. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol or cholestatic disease. *J Hepatol* 2000; 32: 209-17.
13. Costa-Braganca AC, Álvarez da Silva MR. Prevalence of diabetes mellitus and impaired glucose tolerance in patients with decompensated cirrhosis being evaluated for liver transplantation: the utility of oral glucose tolerance test. *Arq Gastroenterol* 2010; 47(1): 22-7.
14. Arao M, Murase K, Kusakabe A, et al. Prevalence of diabetes mellitus in Japanese patients infected chronically with hepatitis C virus. *J Gastroenterol* 2003; 38: 355-60.
15. Mangia A, Schiavone G, Lezzi G, et al. HCV and diabetes mellitus: evidence for a negative association. *Am J Gastroenterol* 1998; 93: 2363-7.
16. Mehta SH, Strathdee SA, Thomas DL. Association between hepatitis C virus infection and diabetes mellitus. *Epidemiol Rev* 2001; 23(2): 302-12.

17. Lecube A, Hernández C, Genesca J, et al. High prevalence of glucose abnormalities in patients with hepatitis C virus infection. *Diabetes Care* 2004; 27: 1171-5.
18. Fraser GM, Harman I, Meller N, Niv Y, Porath A. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci* 1996; 32(7): 568-70.
19. Singal AK, Ayoola AE. Prevalence and factors affecting occurrence of type 2 diabetes mellitus in Saudi patients with chronic liver disease. *Saudi J Gastroenterol* 2008; 14(3): 118-21.
20. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008; 134: 416-23.
21. Donadon V, Balbi M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: Potential role of insulin. *World J Gastroenterol* 2008; 14(37): 5695-700.
22. Lagiou P, Kuper H, Stuver SO, et al. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. *J Natl Cancer Inst* 2000; 92(13): 1096-9.
23. Davila JA. Editorial: Diabetes and hepatocellular carcinoma: What role does diabetes have in the presence of other known risk factors? *Am J Gastroenterol* 2010; 105: 632-4.
24. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis* 2010; 28(1): 155-60.
25. Erikson SK. Nonalcoholic liver disease. *J Lipid Res* 2009; 50: S412-16.
26. Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007; 30: 1212-18.
27. Gaiani S, Avogaro A, Bombonato GC, et al. Nonalcoholic fatty liver disease (NAFLD) in nonobese patients with diabetes: Prevalence and relationships with hemodynamic alterations detected with Doppler sonography. *J Ultrasound* 2009; 12(1): 1-5.
28. De Lusong MAA, Labio E, Daez L, Gloria V. Non-alcoholic fatty liver disease in the Philippines: comparable with other nations? World J Gastroenterol 2008; 14(6): 913-17.
29. Méndez-Sánchez N, Zamora-Valdés D, Vázquez-Fernández F, Uribe M. Hepatocellular carcinoma in Hispanics. *Ann Hepatol* 2007; 6(4): 279-80.
30. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severe obese. *Gastroenterology* 2001; 121: 91-100.
31. Prashanth M, Ganesh HK, Vimal MV, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. *JAPI* 2009; 57: 205-10.
32. Amarapurkar DN, Patel ND, Kamani PM. Evaluating risk factors for development of non-alcoholic steatohepatitis in type-II diabetes mellitus. *Hepatitis Monthly* 2008; 8(3): 197-200.
33. Nugent C, Younossi ZM. Evaluation and management of obesity-related NAFLD: epidemiology of NAFLD. Nat Clin Pract Gastroenterol Hepatol 2007; 4(8): 432-41.
34. Harrison SA. Liver disease in patients with diabetes mellitus. *J Clin Gastroenterol* 2006; 40: 68-76.
35. Choudhuri G, Somani SK, Baba CS, Alexander G. Autoimmune hepatitis in India: profile of an uncommon disease. *BMC Gastroenterology* 2005; 5: 27-35.
36. Jalihal A, Upali-Telisinghe P, Heng-Chong V. Profiles of autoimmune hepatitis in Brunei Darussalam. *Hepatobiliary Pancreat Dis Int* 2009; 8(6): 602-7.
37. Sampson MJ, Williams T, Heyburn PJ, et al. Prevalence of HFE (hemochromatosis gene) mutations in unselected male patients with type 2 diabetes. *J Lab Clin Med* 2000; 135(2): 170-3.
38. Conte D, Manachino D, Colli A, et al. Prevalence of genetic hemochromatosis in a cohort of Italian patients with diabetes mellitus. *Ann Intern Med* 1998; 128(5): 370-3.
39. Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: A changing scene. *Am J Med* 1991; 90: 445-9.
40. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schatner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic patients with chronic hepatitis C virus infections. *Mayo Clinic Proc* 2000; 75(4): 355-9.
41. Garcia-Compean D, Jaquez-Quintana JO, González-González JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World J Gastroenterol* 2009; 15(3): 280-8.
42. Data from the Dirección General de Epidemiología; available at http://sinais.salud.gob.mx/mortalidad/
43. Taura N, Ichikawa T, Hamasaki K, et al. Association between liver fibrosis and insulin sensitivity in chronic hepatitis C patients. *Am J Gastroenterol* 2006; 101: 2752-9.
44. Bianchi G, Marchesini G, Zoli M, et al. Prognostic significance of diabetes in patients with cirrhosis. *Hepatology* 1994; 20: 119-25.
45. Negro F, Alaei M. Hepatitis C and type 2 diabetes. *World J Gastroenterol* 2009; 15(13): 1537-47.
46. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; 126: 460-8.