

The Relationship of Overweight and Obesity to High Mortality Rates from Liver Cirrhosis in Mexico

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Abstract

Background & Aim: Liver cirrhosis continues to be an important cause of death in Mexico. Some data suggest that being overweight is a risk factor for chronic liver disease. The aim of this study was to assess the link between the incidences of being overweight or obese and mortality from liver cirrhosis in Mexico during the period 1990-2001. **Methods:** We designed and conducted an ecological study of trends with multiple comparisons of regions of Mexico (North, Central, Mexico City, and South). We built the time trends according to the mortality rates of liver cirrhosis reported by the System of Vital Statistics (Health Ministry) in each state for each year from 1990 to 2001. The information on prevalences of overweight (body mass index (BMI) = 25-29.9) and obesity (BMI $\geq$ 30) was from two national surveys (1993 and 2000). **Results:** The analysis of mortality trends in liver cirrhosis by region showed an increase in the risk of death across time. This risk was considerably higher for the South Region ($\beta = 1.03$, $p < 0.0001$). The mortality rates remained higher than 30 per 100,000 inhabitants. When we selected the three states with the highest mortality rates for each region, the most significant changes in the trends were in the North and South regions ($\beta = 0.75$, $p < 0.0001$ and $\beta = 1.29$, $p < 0.0001$, respectively). In addition, the prevalence of overweight in the four regions increased from 1993 to 2000 (percentage

change, 10.2-48.2). Obesity was most prevalent in the North and South regions in 1993. **Conclusion:** Our observations support the hypothesis that obesity might play an important role in the risk of developing liver cirrhosis.

Key words: Obesity, liver cirrhosis, non alcoholic steatohepatitis, mortality, cryptogenic, Mexico.

Introduction

In 2000, liver cirrhosis was the fourth leading cause of death in Mexico. More importantly, it was the second leading cause of death in 35-55 year olds.¹ Alcohol and hepatitis C (HCV) infection are the most frequent causes of liver cirrhosis in Mexico.² In addition, it has been suggested that cryptogenic cirrhosis is the second major cause of liver disease. The prevalence of cryptogenic cirrhosis ranged from 5 to 30% of cirrhotic patients in previous studies.^{3,4} A diagnosis of cryptogenic cirrhosis is usually accepted after an extensive evaluation has excluded recognizable etiologies such as occult alcohol abuse, occult viral (non-B, non-C) hepatitis, silent autoimmune hepatitis, or progression of nonalcoholic steatohepatitis (NASH).⁵

Obesity is described in 40-100% of patients with NASH, depending on the definition of obesity that is used.^{6,7} In Mexico, a high prevalence of obesity (body mass index (BMI) of ≥ 30.0) was noted in both men (14.9%) and women (25.1%) in the last Mexican National Health Survey 2000 (Health Ministry – ENSA 2000).^{8,9}

In addition, NASH has been reported worldwide, although geographic variations in prevalence are evident. NASH is the histological diagnosis in 7-11% of patients undergoing liver biopsy in the United States and Canada,^{10,11} but is found in only 1.2% of patients undergoing liver biopsy in Japan.¹² In a recent histological study, NASH was documented in 26% of 81 nonalcoholic patients with marker-negative abnormal liver function test results.¹³ NASH may be even more prevalent among asymptomatic patients with elevated liver function test results, negative viral markers, and negligible alcohol intake because many of these patients do not undergo liver

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biopsy. The prevalence of NASH in the general population has not been defined. In a large autopsy series of 351 unselected nonalcoholic obese and nonobese patients, the prevalence of NASH was 6.3%.¹⁴ On the other hand, in the last National Survey of chronic diseases in Mexico (1993), the five Mexican States with high rates of liver cirrhosis were Campeche, Hidalgo, Estado de Mexico, Puebla and Yucatan (Encuesta Nacional de Enfermedades Crónicas (ENEC), Epidemiología, Secretaría de Salud, México 1993). (National Survey on Chronic Diseases. Epidemiology, Ministry of Health, Mexico 1993).¹ The question arises as to whether the increase in overweight and obesity prevalence seen in Mexico may be related to the high mortality rates of liver cirrhosis reported in the five Mexican states. The main aim of this study was to assess the relationship between the prevalences of overweight and obesity and the trends in mortality by liver cirrhosis in Mexico in the period 1990-2001.

Methods

We conducted an ecological study of trends for multiple comparison groups.¹⁵ The groups were geographically defined according to the following division by states of Mexico. **North Region:** Baja California (BC), Baja California Sur (BCS), Coahuila (Coah), Chihuahua (Chih), Durango (Dgo), Nuevo León (NL), Sinaloa (Sin), Sonora (Son), Tamaulipas (Tams), and Zacatecas (Zac); **Central Region:** Aguascalientes (Ags), Colima (Col), Guanajuato (Gto), Hidalgo (Hgo), Jalisco (Jal), México (Mex), Michoacán (Mich), Nayarit (Nay), Querétaro (Qro), San Luis Potosí (SLP), and Tlaxcala (Tlax); **South Region:** Campeche (Camp), Chiapas (Chis), Guerrero (Gro), Morelos (Mor), Oaxaca (Oax), Puebla (Pue), Quintana Roo (QRoo), Tabasco (Tab), Veracruz (Ver), and Yucatán (Yuc); and **Mexico City Region:** Distrito Federal (DF).

The time trends were built in accordance with the mortality rates of liver cirrhosis reported by the System of Vital Statistics (Health Ministry) by each state and for each year during the period 1990-2001. The codes of the International Classification of Diseases (ICD - World Health Organization) that were taken to group liver cirrhosis are: 9th revision: 571-573 (years 1990-1997), and 10th revision: K70-K77 (years 1998-2001).

The information on prevalences of overweight and obesity was based on data from two national surveys. The first is the National Survey of Chronic Diseases that was conducted by the Health Ministry during 1993.¹ This survey reports such prevalences only by region (as previously mentioned). The second survey is the Mexican National Health Survey 2000 (Health Ministry – ENSA 2000).⁸ Because this survey contains information about the prevalence of overweight and obesity by state, in order to establish comparisons, we grouped the state information into regions. Both surveys define overweight as a BMI of between 25 and 29.9, and obesity as a BMI equal to or higher than 30.

Consequently, because the available information about overweight and obesity only corresponded to two time points, we only compared the percentage change in the prevalence (increase or decrease) between 1993 and 2000.

Statistical analyses

The mortality rates are expressed per 100,000 inhabitants. Scatterplots of mortality rates by year were built for each region. Adjusted lines were derived by simple linear regression analysis and the β coefficients (slopes) and their statistical significance are presented.¹⁶ The statistical significance of the change in prevalences of overweight and obesity was established by means of the χ^2 test. A p -value of < 0.05 was considered statistically significant. All statistical analyses were conducted using the software program SPSS/PC v 10.0 (Chicago, IL).

Results

The analysis of mortality trends by liver cirrhosis divided by region yielded interesting results. Except for Mexico City, all regions showed an increase in the risk of death across the time span (*Figures 1-4*). This risk was considerably higher in the South Region ($\beta = 1.03$, $p < 0.0001$). Although the mortality rates for Mexico City Region remained higher than 30 per 100,000 inhabitants, the trend showed almost no variation during the period ($\beta = -0.19$, $p = 0.11$). The lowest mortality rates (mainly less than 20 per 100,000 inhabitants) were observed in the North Region. Nevertheless, the trend had a statistically significant increase ($\beta = 0.55$, $p < 0.0001$). The Central Region also showed a moderate increase ($\beta = 0.45$, $p = 0.09$). Together with the South Region, it was characterized by states with mortality rates ranging from low (< 10 per 100,000 inhabitants) to high (> 40 per 100,000 inhabitants).

When we selected the three states with the highest mortality rates by each region (except Mexico City, which includes only one state), we observed the most significant changes in the trends in the North and South regions ($\beta = 0.75$, $p < 0.0001$ and $\beta = 1.29$, $p < 0.0001$, respectively). These analyses are presented in *Figures 5-7*.

Practically all four regions showed an increase in the prevalence of overweight from 1993 to 2000 (percentage change between 10.2 and 48.2) (*Table I*). On the other hand, the prevalence of obesity slightly increased in Mexico City and Central regions (1.5 and 2.1% respectively), and decreased by 1.6% in the North Region and 19.4% in the South Region (*Table I*). The changes were statistically significant only for South Region.

Discussion

In this study, we assessed the role of the prevalences of overweight and obesity on the trends in mortality

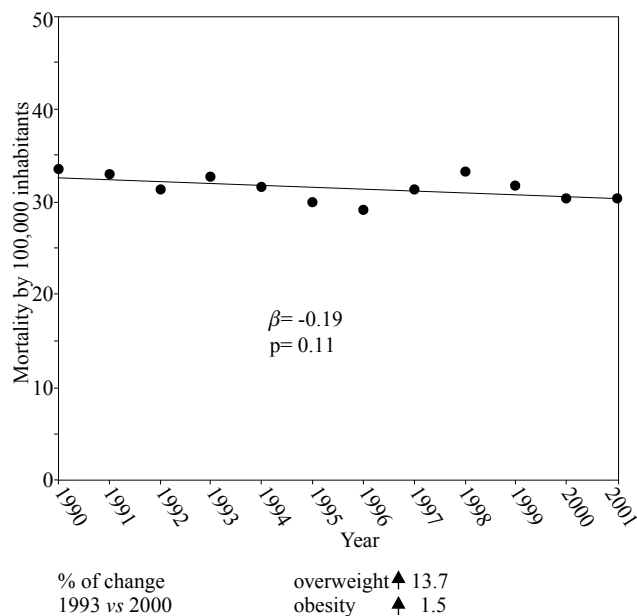


Figure 1. Mortality trend by liver cirrhosis. Mexico City Region.

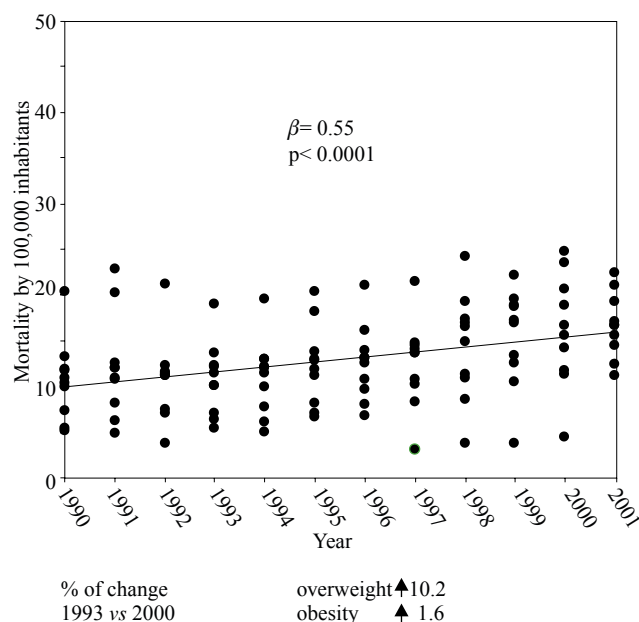


Figure 3. Mortality trend by liver cirrhosis. North Region.

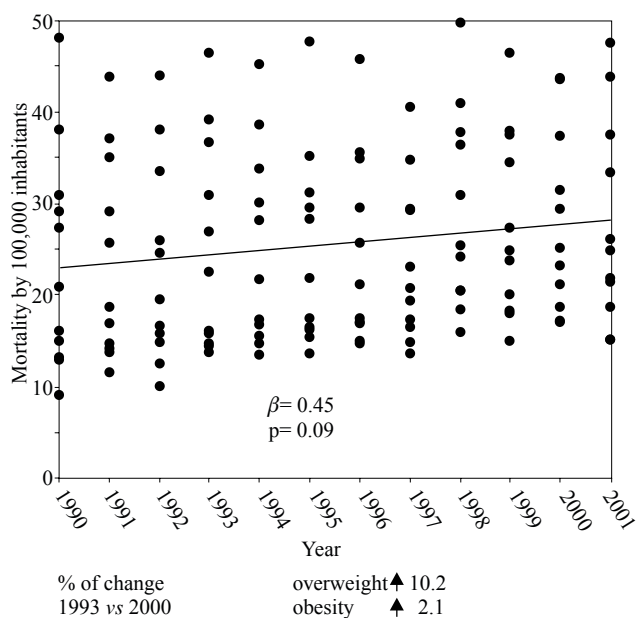


Figure 2. Mortality trend by liver cirrhosis. Central Region.

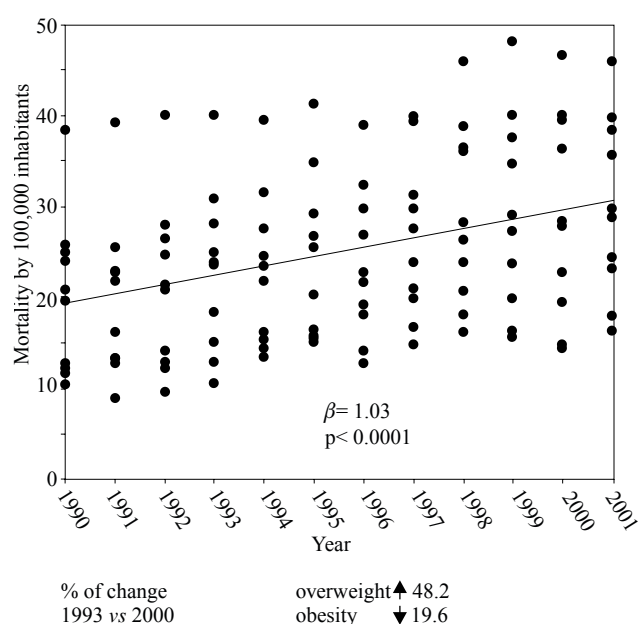


Figure 4. Mortality trend by liver cirrhosis. South Region.

from liver cirrhosis in Mexico in the period 1990-2001. There was an increase in the prevalence of overweight, practically in all the four regions of Mexico between 1993 and 2000. The highest prevalences of obesity, observed in the North and South regions in 1993, had reduced by the year 2000. In addition, we observed the most significant changes in the trends of mortality rates by liver cirrhosis in the North and South regions. Our observations support the hypothesis that obesity might play a significant role in the risk of developing liver cirrhosis in Mexico.

The results of the present study are important because of the emergent epidemic of overweight and obesity in the developed and developing world.^{17,18} Thus, the clinician is increasingly confronted with the problems and dilemmas associated with nonalcoholic fatty liver disease (NAFLD). After excluding other forms of liver disease, the clinician needs to be able to select patients at risk of progressive disease, investigate them appropriately, and develop management strategies.

How can we explain the present observations? Firstly, it has been suggested that obesity is the condition most

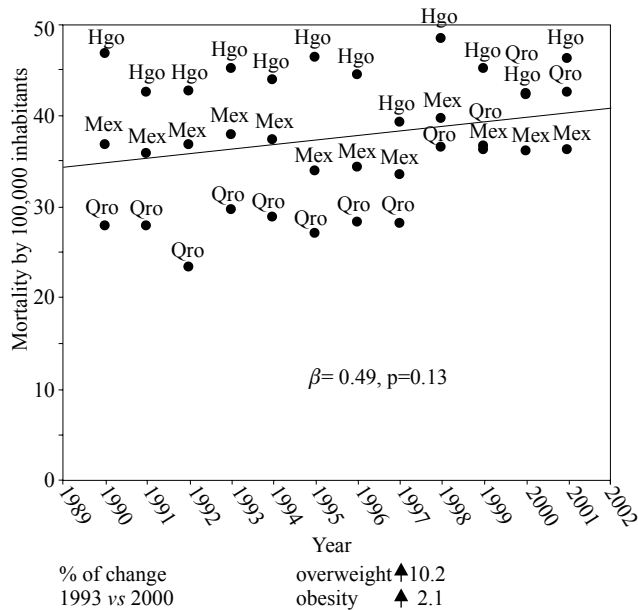


Figure 5. Mortality trend by liver cirrhosis. Selected states of Central Region.

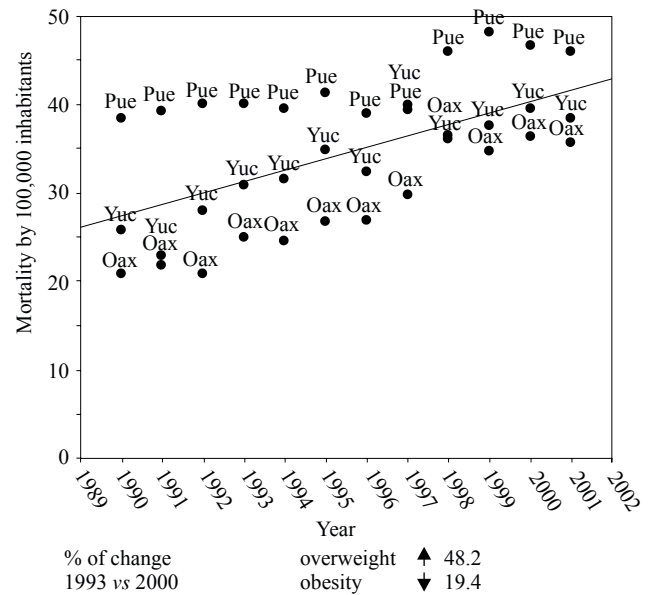


Figure 7. Mortality trend by liver cirrhosis. Selected states of South Region.

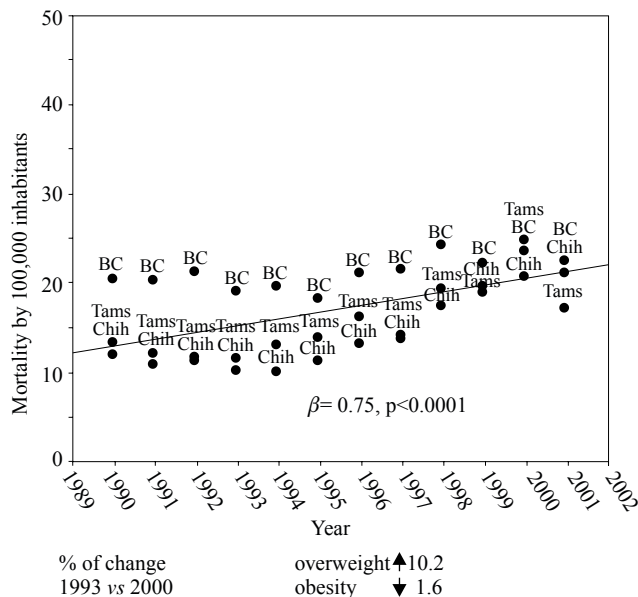


Figure 6. Mortality trend by liver cirrhosis. Selected states of North Region.

often reported in association with NAFLD.¹⁹ Secondly, there is a direct correlation between BMI and the prevalence and severity of NAFLD. Thirdly, the prevalence of NAFLD increases by 4.6-fold in obese people. About two to three fourths of obese (BMI ≥ 30 kg/m²) individuals have NAFLD, whereas more than 90% of severely obese (BMI > 35 kg/m²) people have NAFLD.²⁰ The spectrum of NAFLD is wide and ranges from simple fat accumulation in hepatocytes (steatosis) without biochemical or histological evidence of inflammation or fibrosis, through to fat accumulation plus necroinflammatory activity with or without fibrosis (steatohepatitis), to the development of advanced liver fibrosis or cirrhosis (cirrhotic stage).²⁰ All these stages are histologically indistinguishable from those produced by excessive alcohol consumption, but occur in patients who do not abuse alcohol. Nonalcoholic steatohepatitis (NASH) represents only a stage within the spectrum of NAFLD.

On the other hand, the role of obesity compared with that of alcohol in inducing liver diseases or abnormal results on liver function tests is still controversial. Although

Table I. Prevalences (%) of overweight and obesity, according to two national surveys (1993 and 2000).

Region	Year: 1993			2000			1993 vs 2000 % change		p-value
	BMI: < 25	25-29.9	≥ 30	< 25	25-29.9	≥ 30	25-29.9	≥ 30	
North	37.8	37.4	24.7	34.5	41.2	24.3	↑ 10.2	↓ 1.6	0.71
Central	44.3	36.1	19.5	40.3	39.8	19.9	↑ 10.2	↑ 2.1	0.83
South	39.7	38.6	21.7	25.3	57.2	17.5	↑ 48.2	↓ 19.4	0.03
Mexico City	40.5	40.1	19.4	34.7	45.6	19.7	↑ 13.7	↑ 1.5	0.67

the presence of excess weight for at least 10 years has been claimed to be a potential additional risk factor for acute alcoholic hepatitis and cirrhosis,²¹ most data have been collected from selected series or retrospectively. Naveau *et al.*²¹ showed that the presence of excess weight for at least 10 years is a risk factor for cirrhosis, acute alcohol hepatitis, and steatosis. Further, those investigators suggested that there is a possible potential for the metabolic effects of ethanol ingestion caused by excess weight in patients with alcoholic liver disease.

Interestingly in the present study, the highest prevalence of obesity in 1993 was reported in the South and North regions of Mexico, and this result may be explained in part by those regions having the highest mortality rates for liver cirrhosis in Mexico.

Currently the pathogenesis of NASH involves a "two-hit" hypothesis in which an initial metabolic disturbance causes steatosis and a second pathogenic stimulus causes oxidative stress, reactive oxygen species, lipid peroxidation, and a resultant steatohepatitis.^{22,23} Moreover, experimental studies have shown that, under certain circumstances, obese animals might develop steatohepatitis,^{24,25} which could result in a fibrogenic response. In a longitudinal study of obese patients with repeated liver biopsies, Ratzu *et al.*²⁶ found an association between necroinflammatory activity and septal fibrosis, because patients without necroinflammatory activity on the initial biopsy did not progress to septal fibrosis within as many as 15 years of follow-up. However, it is not known if the development of steatohepatitis in obesity is genetically determined. In this series, when necroinflammatory activity was absent on the initial biopsy, it did not subsequently develop, whereas it persisted when it was present. This suggests that two different populations of overweight patients might exist according to whether necroinflammatory activity is present, which might, in turn, condition the subsequent development of septal fibrosis.²⁶

Furthermore, Angulo *et al.*²⁷ found in 144 obese patients who underwent liver biopsy that older age, obesity, and the presence of diabetes mellitus as an independent predictor, help identify those NASH patients who might have severe liver fibrosis.

Finally, we have to recognize the limitations of this ecological study because of its incomplete design.¹⁵ The information on which this design is based is aggregated (mortality rate by state on one side, and prevalence of overweight and obesity on the other). Thus, it is not possible to reach individual inferences from these data without falling into an ecological fallacy. However, this type of study might be useful for estimating risks from data aggregated on a geographical basis. Further, these studies might address specific questions concerning health in relation to investigating clustering of disease, or for hypothesis generation such as the association between obesity and liver cirrhosis.

In conclusion, the high prevalence of obesity and overweight seen in the North and South regions of Mexico in the 1990s could be associated with the high mortality rates from liver cirrhosis observed in those regions. Our observations support the hypothesis that obesity plays a significant role in the risk of liver cirrhosis in Mexico.

References

1. Secretaría de Salud. *Mortalidad 1999*, México, DF: SSA, 1999.
2. Méndez-Sánchez N, Aguilar-Ramírez JR, Aguirre J, Bosques-Padilla F, Contreras AM, Dehesa M, et al. Etiología de la Cirrosis en México. *Rev Gastroenterol Méx* 2002;
3. Kodali VP, Gordon SC, Silverman AL, McCray DG. Cryptogenic liver disease in the United States: further evidence for non-A, non-B, non-C hepatitis. *Am J Gastroenterol* 1994; 89: 1836-1839.
4. Saunders JB, Walters JR, Davies AP, Paton A. A twenty year prospective study of cirrhosis. *Br Med J* 1981; 282: 263-266.
5. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990; 11: 74-80.
6. Bonkovsky H, Jawaideh Q, Tortorelli K, LeClair P, Cobb J, Lambrecht R, Banner B. Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFE gene in non-alcoholic steatohepatitis. *J Hepatol* 1999; 31: 421-429.
7. Weltman M, Farrell G, Hall P, Ingelman-Sundberg M, Liddle C. Hepatic cytochrome P450 2E1 is increased in patients with nonalcoholic steatohepatitis. *Hepatology* 1998; 27: 128-133.
8. Sanchez-Castillo CP, Velazquez-Monroy O, Berber A, Lara-Esqueda A, Tapia-Conyer R, James WP; Encuesta Nacional de Salud (ENSA) 2000 Working Group. Anthropometric cutoff points for predicting chronic diseases in the Mexican National Health Survey 2000. *Obes Res* 2003; 11: 442-51.
9. Méndez-Sánchez N, Uribe M. *OBEESIDAD. Epidemiología, Fisiopatología y Manifestaciones Clínicas*. El Manual Moderno, México 2002.
10. Ludwig J, Viggiano T, McGill D, Ott B. Nonalcoholic steatohepatitis. Mayo clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; 55: 434-438.
11. Byron D, Minuk G. Clinical hepatology: profile of an urban, hospital-based practice. *Hepatology* 1996; 24: 813-815.
12. Nonomura A, Mizukami Y, Unoura M, Kobayashi K, Takeda Y, Takeda R. Clinicopathologic study of alcohol-like liver disease in non-alcoholics; non-alcoholic steatohepatitis and fibrosis. *Gastroenterol Jpn* 1992; 27: 521-528.
13. Daniel S, Ben-Menachem T, Vasudevan G, Ma C, Blumenkehl M. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol* 1999; 94: 3010-3014.
14. Wanless I, Lentz J. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990; 12: 1106-1110.
15. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research. Principles and Quantitative Methods*. Lifetime Learning Publications. New York, 1982. pp 78-81.
16. Kleinbaum DG, Kupper LL, Muller KE, Nizam A. *Applied Regression Analysis and Other Multivariable Methods*. 3rd ed. Duxbury Press. New York, 1998. pp 39-60.
17. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. *JAMA* 1999; 282: 1519-1522.
18. Obesity: preventing and managing the global epidemic. *Report of the WHO Consultation on Obesity*. Geneva, Switzerland: WHO, 1997.
19. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; 346: 1221-1231.
20. Angulo P. Treatment of nonalcoholic fatty liver disease. *Ann Hepatol* 2001; 1: 12-19.

21. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology* 1997; 25: 108-11.
22. Day CP. Pathogenesis of steatohepatitis. *Best Pract Res Clin Gastroenterol* 2002; 16: 663-78.
23. Teish A, Mae Diehl A. Animal models of steatohepatitis. *Best Pract Res Clin Gastroenterol* 2002; 16: 679-90.
24. Yang SQ, Lin HZ, Lane MD, Clemens M, Diehl AM. Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis. *Proc Natl Acad Sci USA* 1997; 94: 2557-2562.
25. Chavin KD, Yang S, Lin HZ, Chatham J, Chacko VP, Hoeck JB, Walajtys-Rode E, Rashid A, Chen CH, Huang CC, Wu TC, Lane MD, Diehl AM. Obesity induces expression of uncoupling protein-2 in hepatocytes and promotes liver ATP depletion. *J Biol Chem* 1999; 274: 5692-5700.
26. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, Khalil L, Turpin G, Opolon P, Poynard T. Liver fibrosis in overweight patients. *Gastroenterology* 2000; 118: 1117-23.
27. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999; 30: 1356-62.