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RAPID COMMUNICATION

Prevalence of metabolic syndrome, obesity and diabetes type 2 in cryptogenic cirrhosis

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Abstract

AIM: To evaluate the prevalence of metabolic syndrome (MS), obesity and type 2 diabetes mellitus (T2DM) in a group of Mexican Mestizo patients with cryptogenic cirrhosis (CC) and to compare this group with patients with cirrhosis secondary to other causes (disease controls).

METHODS: Patients with CC, diagnosed between January, 1990 and April, 2005, were included in a retrospective study. Patients with cirrhosis caused by chronic hepatitis C, alcohol abuse or autoimmune hepatitis (AIH) served as disease controls.

RESULTS: A total of 134 patients with CC were analyzed. Disease controls consisted of 81 patients with chronic hepatitis C, 33 with alcohol abuse and 20 with AIH. The median age of patients with CC was 57 years (range, 16-87); 83 (61.9%) patients were female; 53 (39.6%) were Child A, 65 (48.5%) Child B, and 16 (11.9%) were Child C cirrhosis. The prevalence of MS (29.1% *vs* 6%; $P < 0.001$), obesity (16.4% *vs* 8.2%; $P = 0.04$) and T2DM (40% *vs* 22.4%; $P = 0.013$) was higher in CC patients than in disease controls. There were no differences in sex, age or liver function tests between the two groups.

CONCLUSION: The prevalence of MS, obesity and T2DM were higher in patients with CC than in patients with cirrhosis secondary to others causes. Our findings support the hypothesis that non-alcoholic steatohepatitis (NASH) plays an under-recognized role in CC.

Key words: Cryptogenic chronic hepatitis; Metabolic syndrome; Obesity; Diabetes mellitus

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INTRODUCTION

The diagnosis of "cryptogenic" cirrhosis is made after an extensive evaluation has excluded recognizable etiologies[1]. The prevalence of cryptogenic cirrhosis (CC) ranges from 5% to 30% in cirrhotic patients[1]. In Mexico, the etiology of cirrhosis remains unclear in 10% patients despite an extensive evaluation[2]. Several etiological possibilities are offered in such patients. These include occult alcohol abuse, silent autoimmune hepatitis (AIH), occult viral (non-B, non-C) hepatitis, and progression of nonalcoholic steatohepatitis (NASH)[3].

The prevalence of clinically silent autoimmune hepatitis in patients with CC is unknown; however, several studies have suggested that a significant number of patients with CC may have burnt-out AIH[4-6]. Occult virus disease (Non-B, non-C hepatitis) is considered to account for about 15% of post-transfusion hepatitis[7] and may exist in a silent form for several years[8]. Obesity and non-insulin dependent diabetes mellitus are the

two most common conditions associated with NASH[9], which is frequently asymptomatic[10] and can progress silently to cirrhosis with definitive histological features[10].

The aim of the present study was to characterize the metabolic disturbances [prevalence of metabolic syndrome (MS), obesity and type 2 diabetes mellitus (T2DM)] in a group of Mexican Mestizo patients with CC. In particular, we compared the prevalence of metabolic disturbances in the cryptogenic group with patients with cirrhosis due to other causes: hepatitis C without prior alcoholism, alcohol abuse and AIH.

MATERIALS AND METHODS

In a retrospective manner, we examined the medical records (paper and electronic-based records) of all patients with CC diagnosed from January, 1990 to April, 2005. We also included in a random fashion, disease controls consisting of patients with cirrhosis caused by chronic hepatitis C, alcohol abuse and AIH.

Diagnosis of CC was made after an exhaustive evaluation failed to provide a specific etiology. The data collected included the hepatologic diagnosis, co-morbid conditions, complications of portal hypertension if present, and major forms of treatment. Additional information was obtained from clinical charts, hospital records, the clinic and hospital laboratory databases, and by personal or telephone interview. Patients were included in the study if sufficient data was available and if the diagnosis was confirmed on review of all the available information.

The diagnosis of cirrhosis was made on the basis of clinical, laboratory and imaging data. In addition, histological findings were available in 56 (42%) CC patients. Biopsy was not performed in 78 patients, either because of refusal by the patient or their in-charge physician. Data collected included gender, age at diagnosis of cirrhosis, presenting symptoms, potential occupational exposure to hepatotoxins, family history of liver disease, and family or personal history of autoimmune diseases. Risk assessment for viral hepatitis included history of exposure to intravenous drugs, blood transfusions, tattoos, other known percutaneous needle exposures, and high-risk sexual behavior. All patients underwent extensive serological testing including hepatitis B and C screening [hepatitis B surface antibody, surface antigen, and anticore antibody, and hepatitis C enzyme-linked immunosorbent assay (Abbott Laboratories, Abbott Park, IL)], iron studies (ferritin, iron, iron binding capacity, and tissue assessment if the diagnosis was questionable), ceruloplasmin, antinuclear antibody (ANA), antimitochondrial antibody, and α1-antitrypsin. Quantitative immunoglobulin levels (IgG, IgM, IgA) were obtained in all patients. Assessment of α1-antitrypsin level was performed using isoelectric focusing (pH range, 4.0-5.0).

Patients with CC who had a positive antinuclear antibody (positive > 1:80) test, an index of autoimmune hepatitis, were evaluated by the International Autoimmune Hepatitis (IAH) score, based on clinical and laboratory parameters as previously described[11]. None of the patients received steroid therapy, and thus the IAH score was calculated using the Minimal Required Parameters, wherein a score of 10 to 15 is suggestive of autoimmune hepatitis, and a score of greater than 15 is considered definitive. The term overweight was defined as body mass index (BMI) greater than 25, while obesity was defined as a BMI greater than 30. BMI was calculated by dividing the patients' body weight by the square of their height expressed as kg/m^2. BMI was calculated using the average adult weight reported by the patient and the patient's height. In all cases, type 2 DM was diagnosed by the presence of recurrent fasting hyperglycemia ($\geq$ 126 mg/dL), requiring treatment with dietary management, oral hypoglycemic agents, or insulin therapy. Dyslipidemia was considered in the presence of high serum triglycerides (> 150 mg/dL) and/or low high-density lipoproteins (< 50 mg/dL in women and < 40 mg/dL in men). The diagnosis of MS was made according to the NCEP (ATP) Ⅲ consensus[12,13].

The absolute and relative frequencies were used for summary. The data is presented as mean ± SD. The one-way ANOVA test or Kruskal-Wallis was used to compare parametric or nonparametric variables, respectively. The χ^2 test was used for categorical variables. A P value (α) of < 0.05 was considered significant. Bonferroni correction for P-value was applied for multiple comparisons, calculated as α/n. For multiple comparisons a P value of < 0.016 was considered significant. All statistical analyses were conducted using the statistics program SPSS/PC version 12.0 (Chicago, IL, USA).

RESULTS

After careful review of the medical records, 50 patients who were originally classified as CC in the hospital registry were found to have other causes of liver disease. The main reason for this discrepancy was incomplete investigation or erroneous interpretation of the test results when the patients were referred to our center. These patients were initially listed as CC, but the diagnosis was not corrected in the registry when the new information became available. Other less common reasons for patient exclusion were incomplete medical information and indeterminate test results. For the final analysis, a total of 134 patients with CC were included in the study. In addition, EIGHTY ONE patients with chronic hepatitis C, thirty-three with alcohol abuse and twenty with AIH were evaluated as disease controls. The demographic, clinical, and laboratory characteristics of the study subjects are summarized in Table 1. In patients with CC, the median age was 57 years (range 16-87); 83 (61.9%) were female; and 53 (39.6%) had Child A cirrhosis, 65 (48.5%) were Child B and 16 (11.9%) were Child C.

Five patients were determined to have moderate alcohol consumption (< 2 drinks/d), but this was not considered to be the cause of their liver disease, either by the hepatologist or their primary care physician. None of the patients had a history of intravenous drug

Table 1 Demographic, clinical and laboratory parameters of patients with cryptogenic cirrhosis and non-cryptogenic cirrhosis

Variable	Cryptogenic (*n* = 134, %)	Non-cryptogenic (*n* = 134, %)	*P*
Sex (female)	83 (62)	75 (56)	0.32
DM	53 (40)	30 (22.4)	0.013
HBP	24 (18)	14 (10.4)	0.08
Hyperuricemia	13 (10)	2 (1.5)	0.003
Dyslipidemia	72 (54)	8 (6)	< 0.001
Overweight (BMI > 25)	103 (77)	106 (79)	0.65
Obesity (BMI > 30)	22 (16.4)	11 (8.2)	0.04
MS	39 (29.1)	8 (6)	< 0.001
Age (yr, mean ± SD)	54.6 ± 14.3	56.8 ± 11.4	0.15
BMI (mean ± SD)	27 ± 4.6	26 ± 4	0.22
ALT (U/L, mean ± SD)	52.5 ± 59	57.5 ± 33	0.72
AST (U/L, mean ± SD)	67.1 ± 60	77.8 ± 46	0.19

DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patient's body weight divided by the square of the height expressed in kg/m^2); MS: Metabolic syndrome.

Table 2 Comparison of patients with cryptogenic cirrhosis with and without liver tissue examination

Variable	Liver biopsy (*n* = 56, %)	No liver biopsy (*n* = 78, %)	*P*
Sex (female)	37 (66)	46 (59)	0.47
DM	13 (23)	40 (51)	0.001
HBP	7 (13)	17 (22)	0.18
Hyperuricemia	3 (5)	10 (13)	0.03
Dyslipidemia	21 (38)	51 (65)	0.002
Overweight (BMI > 25)	46 (82)	57 (73)	0.29
Obesity (BMI > 30)	4 (7)	18 (23)	0.017
MS	10 (18)	29 (37)	0.02
Child-Pugh A	29 (52)	24 (31)	0.02
Age (yr, mean ± SD)	55.8 ± 14.5	53.7 ± 14	0.42
BMI (mean ± SD)	26.2 ± 4.6	27.3 ± 4.6	0.28
ALT (U/L, mean ± SD)	51.8 ± 38	52.9 ± 70	0.91
AST (U/L, mean ± SD)	66 ± 48	68 ± 69	0.86
Albumin (g/dL, mean ± SD)	3.3 ± 0.7	2.9 ± 0.6	0.01
Alkaline Phosphatase (U/L, mean ± SD)	150 ± 72	154 ± 74	0.7
Child-Pugh score (mean ± SD)	6.9 ± 2.7	7.7 ± 1.8	0.06

DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patient's body weight divided by the square of the height expressed in kg/m^2); MS: Metabolic syndrome.

use. Seven patients had a history of blood transfusions, but none of them had hepatitis C or hepatitis B virus infections. Seven patients had a positive family history of liver disease. A positive antinuclear antibody test was present in 13 patients (10%), but a definite score for autoimmune hepatitis was not present in any patient. Serum α1-antitrypsin deficiency was assessed in 6 patients. However, none of the patients had biochemical or histological evidence of α1-antitrypsin deficiency. Serum ferritin and iron saturation tests were measured in all patients and were within normal/non-diagnostic limits. Genetic testing for hemochromatosis was not performed, and thus carriage of abnormal alleles cannot be excluded. There was no difference in the liver function tests or the Child Pugh score between patients with CC who had a liver biopsy (*n* = 56, 42%) and those did not (*n* = 78, 58%). However, patients without liver tissue examination had higher prevalence of metabolic disturbances (Table 2).

The prevalence of MS, obesity and T2DM were greater in CC patients compared to patients without CC (Table 1). When patients without CC were classified by etiology (hepatitis C, alcohol, and AIH), significant differences in MS prevalence were observed: 6.2% in hepatitis C, 6% in patients with alcohol abuse, and 5% in AIH *vs* 29.1% in CC patients ($P < 0.001$). The differences in the prevalence of T2DM persisted, but when Bonferroni correction for multiple-comparison was used, only obesity showed a statistical trend (Table 3). The prevalence of the different components of MS were analyzed separately; Dyslipidemia ($P < 0.001$) and abnormal glucose ($P = 0.01$) were more common in CC patients than in disease controls, while high blood pressure (HBP) showed a trend towards significance ($P = 0.08$). Hyperuricemia was more frequent in CC patients (10% *vs* 1.5%, $P = 0.003$).

DISCUSSION

The present study shows a high prevalence of MS, obesity, and T2DM in Mexican Mestizo population with CC. The relationship between T2DM, obesity, and cirrhosis has been much debated[14-17]. To our knowledge, this is the first study that shows an association between MS and CC. There is less controversy regarding an association between MS, obesity, T2DM, and NASH[18], and several previous studies have shown a relationship between components of MS and NASH as well as the severity of liver fibrosis[19-21]. MS is a worldwide problem with a high prevalence rate[22], and in agreement with our data this abnormality, along with some of its components, is more frequent in CC than in patients with cirrhosis caused by other etiologies. This finding is very important because it provides further evidence to support the theory that NAFLD/NASH can progress to cirrhosis in some patients.

The prevalence of MS was 500% higher in patients with CC compared to patients without CC. When the prevalence of each of the MS components in patients with and without CC was analyzed, only abnormal glucose values and Dyslipidemia showed statistically significant differences between the two groups (Table 1). There was no difference between the two groups with respect to the prevalence of HBP and being overweight. This may be related to the hemodynamic changes and malnutrition, seen commonly in cirrhotic patients. The mean ± SD of HDL and triglyceride levels in CC patients were similar in women (43.4 ± 10.9 mg/dL and 92.4 ± 49 mg/dL) and men (39.5 ± 8.5 mg/dL and 111.3 ± 59 mg/dL). Both of these test values were abnormal when the NCEP guidelines were taken into consideration (abnormal HDL serum levels < 50 mg/dL for women and < 40 mg/dL for men); prevalence of low HDL levels was seen in 76.7% women and 41.5% men. An observation not previously reported is the finding of higher prevalence (statistically significant) of hyperuricemia in CC compared to disease controls. Hyperuricemia is not accepted as

Table 3 Comparison of patients with cryptogenic cirrhosis and disease controls separated by the etiology of cirrhosis

Variable	Cryptogenic (*n* = 134, %)	CHC (*n* = 81, %)	Alcohol (*n* = 33, %)	AIH (*n* = 20, %)	*P*
Sex (female)	83 (62)	54 (66.7)	7 (21.2)	14 (70)	< 0.001
DM	53 (40)	17 (21)	10 (30.3)	3 (15)	0.013
HBP	24 (18)	8 (10)	4 (12.1)	2 (10)	0.36
Hyperuricemia	13 (10)	1 (1.2)	0 (0)	1 (5)	0.027
Dyslipidemia	72 (54)	5 (6)	1 (3)	2 (10)	< 0.001
Overweight (BMI > 25)	103 (77)	63 (78)	27 (81.8)	16 (80)	0.93
Obesity (BMI > 30)	22 (16.4)	5 (6.2)	5 (15.2)	1 (5)	0.10
MS	39 (29.1)	5 (6.2)	2 (6)	1 (5)	< 0.001
Age (yr, mean ± SD)	54.6 ± 14.3	56.8 ± 11.4	58 ± 12.6	55.6 ± 14.1	0.48
BMI (mean ± SD)	27 ± 4.6	26 ± 4	26.4 ± 3.5	26.1 ± 5.1	0.65
ALT (U/L, mean ± SD)	52.5 ± 59	57.5 ± 33	52.6 ± 47.9	46.2 ± 27.7	0.79
AST (U/L, mean ± SD)	67.1 ± 60	77.8 ± 46	73.1 ± 52	73.5 ± 69	0.59

CHC: Cirrhosis by hepatitis C virus; AIH: Autoimmune hepatitis; DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patients' body weight divided by the square of the height expressed in kg/m^2); MS: Metabolic syndrome.

a criterion of MS; however, it is a common metabolic disturbance in this group of patients. We believe that the higher prevalence of hyperuricemia in CC may be another piece in the puzzle in the relationship between MS, NASH and cirrhosis.

In 1999, Caldwell *et al*[17] described the prevalence of obesity and T2DM in 70 patients with CC, and compared the findings with three patient groups: NASH, cirrhosis with hepatitis C, and primary biliary cirrhosis (PBC). The prevalence of these risks factors (obesity and T2DM) were similar between patients with NASH and patients with CC, both of which had a higher prevalence compared to patients with hepatitis C and PBC. In another study by Poonawala *et al*[16], the prevalence of obesity and T2DM in patients with CC was compared with the prevalence in control patients. The various causes of cirrhosis in the control group were alcohol, chronic viral hepatitis, AIH, PBC and primary sclerosing cholangitis. Similar to the findings by Caldwell *et al*[17], the prevalence of obesity (55% *vs* 24%) and T2DM (47% *vs* 22%) were significantly higher in patients with CC compared with disease controls. Both authors concluded that their data supported the hypothesis that NASH may be an etiological factor in some of the patients with CC[16,17]. We obtained similar results, but in a different population (Mexican Mestizo) and with a bigger sample size. When we classified the patients as CC *vs* no CC, important differences in the prevalence of obesity and T2DM were observed (16.4% *vs* 8.2% and 40% *vs* 22.4%, respectively). However, when patients without CC were classified by etiology, only the prevalence of T2DM was statistically significant (Table 3). With respect to obesity, the prevalence between CC and patients with cirrhosis secondary to alcohol abuse was similar, and both showed a higher frequency than patients with cirrhosis due to hepatitis C and AIH.

An interesting finding in the present study was that patients with CC without a liver biopsy had greater prevalence of MS, obesity and T2DM compared with patients with CC who had a liver biopsy, despite similar liver function tests. This finding may be related to the presence of metabolic disturbances, suggesting to the physician the diagnosis of CC secondary to NASH; thus creating a different situation from patients with CC without metabolic disturbances.

The present study suffered from some limitations. First, the study design. Second, we did not record the waist circumference for the diagnosis of MS, but used BMI as a substitute for waist circumference. The use of BMI may have had a small impact on the number of cases diagnosed with MS, since there is a strong correlation between these parameters ($r = 0.8$)[23,24]. We recognize that this may have resulted in underestimating the number of cases that fulfilled the NCEP definition.

In conclusion, the prevalence of MS, obesity and T2DM in patients with CC is higher than that seen in patients with cirrhosis secondary to others causes. Moreover, the prevalence of hyperuricemia was higher in patients with CC compared to patients with cirrhosis secondary to others causes, a finding not reported previously. Our results support the hypothesis that NASH plays an under-recognized role in some patients with CC.

COMMENTS

Background

Nonalcoholic steatohepatitis (NASH) is the main etiology suspected in patients with Cryptogenic Cirrhosis (CC). The association of NASH with Metabolic Syndrome (MS) is well-known; however, the association of CC with MS has not been well examined.

Research frontiers

The possible association of MS and CC remains unknown.

Innovations and breakthroughs

This study shows an association between MS with CC, and raises the possibility of an under-recognized role of NASH in CC.

Applications

Further prospective studies may clarify the association between MS and CC.

Peer review

The findings in the present study imply that non-alcoholic steatohepatitis is frequently associated with cryptogenic cirrhosis. This paper is well written and the results suggest an under-recognized role of NASH in patients with cryptogenic cirrhosis.

REFERENCES

1 **Lizardi-Cervera J**, Motola-Kuba D, Guevara-Gonzalez L. [Obesity and its association with cryptogenic cirrhosis and hepatocarcinoma] *Gac Med Mex* 2004; **140** Suppl 2: S77-S83

2 **Mendez-Sanchez N**, Aguilar-Ramirez JR, Reyes A, Dehesa M, Juorez A, Castneda B, Sanchez-Avila F, Poo JL, Guevara Gonzalez L, Lizardi J, Valdovinos MA, Uribe M, Contreras AM, Tirado P, Aguirre J, Rivera-Benitez C, Santiago-Santiago R, Bosques-Padilla F, Munoz L, Guerroro A, Ramos M, Rodriguez-Hernandez H, Jacobo-Karam J, Grupo de Estudio, Asociacion Mexicana de Hepatologia. Etiology of liver cirrhosis in Mexico. *Ann Hepatol* 2004; **3**: 30-33

3 **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

4 **Kaymakoglu S**, Cakaloglu Y, Demir K, Turkoglu S, Badur S, Gurel S, Besisik F, Cevikbas U, Okten A. Is severe cryptogenic chronic hepatitis similar to autoimmune hepatitis? *J Hepatol* 1998; **28**: 78-83

5 **Ayata G**, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, Khettry U. Cryptogenic cirrhosis: clinicopathologic findings at and after liver transplantation. *Hum Pathol* 2002; **33**: 1098-1104

6 **Berg T**, Neuhaus R, Klein R, Leder K, Lobeck H, Bechstein WO, Muller AR, Wiedenmann B, Hopf U, Berg PA, Neuhaus P. Distinct enzyme profiles in patients with cryptogenic cirrhosis reflect heterogeneous causes with different outcomes after liver transplantation (OLT): a long-term documentation before and after OLT. *Transplantation* 2002; **74**: 792-798

7 **Alter MJ**, Hadler SC, Judson FN, Mares A, Alexander WJ, Hu PY, Miller JK, Moyer LA, Fields HA, Bradley DW. Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. *JAMA* 1990; **264**: 2231-2235

8 **Koretz RL**, Abbey H, Coleman E, Gitnick G. Non-A, non-B post-transfusion hepatitis. Looking back in the second decade. *Ann Intern Med* 1993; **119**: 110-115

9 **Sheth SG**, Gordon FD, Chopra S. Nonalcoholic steatohepatitis. *Ann Intern Med* 1997; **126**: 137-145

10 **Bacon BR**, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994; **107**: 1103-1109

11 **Johnson PJ**, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatology* 1993; **18**: 998-1005

12 **Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).** *JAMA* 2001; **285**: 2486-2497

13 **Lerman GI**, Aguilar-Salinas CA, Gomez-Perez FJ, Reza AA, Hernandez JS, Vazquez CC, Rull JA. El Síndrome Metabólico. Posición de la Sociedad Mexicana de Nutrición y Endocrinología, sobre la definición, fisiopatología y diagnóstico. Características del síndrome metabólico en México. *Rev Edocrinol Nutr* 2004; **12**: 109-122

14 **Bloodworth JM Jr**. Diabetes mellitus and cirrhosis of the liver. *Arch Intern Med* 1961; **108**: 695-701

15 **Leevy CM**. Fatty liver: a study of 270 patients with biopsy proven fatty liver and review of the literature. *Medicine* (Baltimore) 1962; **41**: 249-276

16 **Poonawala A**, Nair SP, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. *Hepatology* 2000; **32**: 689-692

17 **Caldwell SH**, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; **29**: 664-669

18 **Angulo P**. Nonalcoholic fatty liver disease. *Rev Gastroenterol Mex* 2005; **70** Suppl 3: 52-56

19 **Dixon JB**, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001; **121**: 91-100

20 **Angulo P**, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999; **30**: 1356-1362

21 **Harrison SA**, Torgerson S, Hayashi PH. The natural history of nonalcoholic fatty liver disease: a clinical histopathological study. *Am J Gastroenterol* 2003; **98**: 2042-2047

22 **Aguilar-Salinas CA**, Rojas R, Gomez-Perez FJ, Valles V, Rios-Torres JM, Franco A, Olaiz G, Rull JA, Sepulveda J. High prevalence of metabolic syndrome in Mexico. *Arch Med Res* 2004; **35**: 76-81

23 **Seidell JC**, Perusse L, Despres JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 2001; **74**: 315-321

24 **Ellis KJ**. Human body composition: in vivo methods. *Physiol Rev* 2000; **80**: 649-680

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