PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

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CLINICAL RESEARCH

Sonographic fatty liver and hepatitis B virus carrier status: Synergistic effect on liver damage in Taiwanese adults

Yu-Cheng Lin, Shu-Tin Hsiao, Jong-Dar Chen

Yu-Cheng Lin, Jong-Dar Chen, Department of Family Medicine and Center for Environmental and Occupational Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, China
Shu-Tin Hsiao, Institute of Occupational Medicine Industrial Hygiene, National Taiwan University, Taipei, Taiwan, China
Correspondence to: Dr. Jong-Dar Chen, Department of Family Medicine and Center for Environmental and Occupational Medicine, Shin Kong Wu Ho-Su Memorial Hospital, 95, Wen Chang Road, Shih Lin, Taipei 111, Taiwan, China. jdarchen@ms28.hinet.net
Telephone: +886-2-28332211-2626 Fax: +886-2-28389420
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Abstract

AIM: To examine the epidemiology of hepatitis B virus carrier status (HBVC) and sonographic fatty liver (SFL) in Taiwanese adults, and to evaluate their possible interaction in inducing liver damage (LD). From an epidemiological viewpoint, we analyzed previous studies which indicated that fatty liver sensitizes host immune response to HBV infection and enhances liver damage.

METHODS: A cross-sectional retrospective analysis of health records including medical history, physical examination, abdominal sonogram, blood biochemistry and hepatic virological tests. We utilized the Student's *t*-test, chi-square, multivariate logistic regression and synergy index to assess risks for LD.

RESULTS: Among a total of 5406 Taiwanese adults (mean age 46.2 years, 51.5% males), the prevalence of LD, HBVC and SFL were 12.3%, 15.1% and 33.4%, respectively; 5.1% of participants had SFL plus HBVC. Multivariate logistic regression analysis demonstrated that male gender (odds ratio (OR) = 2.8, 95% confidence interval (CI): 2.3-3.5), overweight state (OR = 1.6, 95% CI: 1.3-2.0), HBVC (OR = 2.5, 95% CI: 2.0-3.1) and SFL (OR = 4.2, 95% CI: 2.2-5.3) were independently associated with LD. Synergism analysis showed that the adjusted OR for LD in adults with HBVC-alone was 3.3 (95% CI: 2.4-4.6), SFL-alone, 4.7 (95% CI: 3.7-6.1) and combined HBVC and SFL, 9.5 (95% CI: 6.8-13.3); the synergy index was 1.4 (95% CI: 1.001-2.0).

CONCLUSION: In Taiwanese adults, SFL plus HBVC have a significant synergistic association with LD.

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INTRODUCTION

Fatty liver and hepatitis B virus (HBV) infection are important causes of liver damage (LD)[1-3]. However, only limited data is available on the interaction of these two risk factors in inducing liver damage.

Fatty liver, termed histologically as hepatosteatosis, refers to an accumulation of fat in the hepatocytes. Fatty liver can be detected non-invasively by sonogram[4]. Several epidemiological studies have shown that sonographic fatty liver (SFL) has a strong positive association with the metabolic syndrome[2,5]. SFL may progress to fibrosis or cirrhosis and is a growing health problem in many developing as well as developed countries[2,5,6]. HBV infection is usually transmitted through blood or sexual contact with an infected person. Chronic HBV infection also results in serious sequelae including hepatocellular carcinoma, and continues to be an important public health problem in hyperendemic areas including several Asian countries[3].

Both SFL and HBV carrier status (HBVC) are commonly encountered by primary health care doctors in Taiwan[4,7]. According to previous epidemiological studies, coexistence of SFL and HBVC is not uncommon in clinical practice[8]. The findings that fatty liver sensitizes the host immune response to the HBV infection had been reported in some studies[9,10]; however, little is known as to whether the damaging effects of SFL and HBVC are enhanced by the co-existence of the two diseases.

We examined the epidemiology of SFL and HBVC in Taiwanese adults by analyzing retrospectively the database of a health care center in Taipei. We focused on whether a combination of these two liver disorders has a deleterious effect on the serum alanine aminotransferase levels, which is a conventional marker of liver damage and is a predictor of advanced liver disease[11,12].

Table 1 Demographic data of the total study population and the subgroups defined by HBVC[1] and SFL[2] positive or negative status mean ± SD

Characteristics	All cases (n = 5406)	All cases classified by HBVC (n = 5406)		All cases classified by SFL (n = 5406)	
		HBVC (-) (n = 4589)	HBVC (+) (n = 817)	SFL (-) (n = 3603)	SFL (+) (n = 1803)
Age (yr)	46.2 ± 9.4	46.3 ± 9.5	45.9 ± 8.8	45.3 ± 9.6	48.0 ± 8.7[d]
BMI (kg/m^2)	23.5 ± 3.3	23.5 ± 3.3	23.7 ± 3.4	22.3 ± 2.7	25.9 ± 3.1[d]
Waist (cm)	82.6 ± 9.2	82.5 ± 9.1	83.2 ± 9.8	79.9 ± 8.5	87.8 ± 8.3[d]
AST (U/L)	22.8 ± 9.6	22.1 ± 8.3	26.9 ± 14.0[b]	21.6 ± 9.1	25.3 ± 10.1[d]
ALT (U/L)	25.8 ± 19.9	24.3 ± 17	34 ± 30.4[b]	21.6 ± 16.5	34.0 ± 23.3[d]
Male, n(%)	2760 (51.1)	2271 (49.5)	489 (59.9)[b]	1598 (44.4)	1162 (64.5)[d]
Overweight, n (%)	2237 (41.4)	1883 (41.0)	354 (43.3)	920 (25.5)	1317 (73.0)[d]
Central obesity, n (%)	1038 (19.2)	883 (19.2)	155 (19.0)	545 (15.1)	493 (27.3)[d]
SFL, n (%)	1803 (33.4)	1526 (33.3)	277 (33.9)		
HBsAg-positive, n (%)	817 (15.1)			540 (15.0)	277 (15.4)
HBsAb-negative, n (%)	1983 (36.7)	1211 (26.4)		1313 (36.4)	670 (37.2)
LD, n (%)	666 (12.3)	472 (10.7)	174 (21.3)[b]	200 (5.6)	466 (25.9)[d]

HBVC: hepatitis B virus carrier status; HBVC (-)/HBVC (+), non-carrier status/hepatitis B virus (HBV) carrier status. SFL: sonographic fatty liver; SFL (-)/SFL (+), subject without SFL/subject with SFL. BMI: body mass index = Weight (kg)/Length (m)^2; ALT: alanine aminotranferease (U/L); AST: aspartate aminotransferase (U/L); HBsAg: HBV surface antigen; HBsAb: anti-HBV surface antibody. BMI > 24. Waist circumference > 90 cm for men; > 80 cm for women. LD: liver damage defined as ALT > 40 (U/L). [b]P < 0.01 *vs* reference subjects HBVC (-); Student's t test for continuous variables; χ^2 tests for categorical variables. [d]P < 0.01 *vs* reference subjects SFL(-); Student's t test for continuous variables; χ^2 tests for categorical variables.

MATERIALS AND METHODS

Subjects

The records of 5899 adult subjects, 18 to 65 years in age who had visited the Shin Kong Wu Ho-Su Memorial Hospital health center between January 2004 and December 2005 for routine periodic checkups, were collected anonymously.

Methods

A questionnaire on personal medical history, including alcohol consumption (usage more than once a week in the recent past 3 mo: yes *vs* no; yes defined as a habitual drinker), medication usage and major operations, was filled out by the examinees. A total of 493 participants were excluded from the final analysis for following reasons: habitual drinking, history of major abdominal surgery, diabetes and long-term use of corticosteroids, hormone replacement therapy, insulin replacement therapy and oral antidiabetic agents.

The physical examination data included anthropometrical evaluation and measurements of systolic and diastolic blood pressure. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured midway between the lowest rib and the iliac crest. Definition of overweight was BMI > 24 kg/m^2, and that of central obesity was waist circumference > 90 cm for men and > 80 cm for women, based on Taiwanese criteria[13].

The biochemical blood tests were obtained using the Hitachi/Roche auto analyzer model 7600 PPEE (Hitachi Corp, Tokyo, Japan). The tests included aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting plasma glucose, serum triglycerides, and total and high-density lipoprotein (HDL) cholesterol. The results of tests for metabolic syndrome (blood glucose and lipids) are not shown in the tables but were adjusted for the multivariate analysis. HBV surface antigen (HBsAg), anti-HBV surface antibody (HBsAb) and anti-HCV antibody were measured by the microparticle enzyme immunoassay (MEIA) using the Abbott Axsym System instrument (Abbott Laboratories Services Corporation, Taipei, Taiwan). LD was defined by cutoff > 40 U/L for ALT[14].

Abdominal sonographic examinations were performed using convex-type real-time electronic scanners (Toshiba SSA-340 with 3.75 MHz convex-type transducer) by four gastrointestinal specialists who were blind to the examinees' medical history and blood test results. The definition of SLF was based on a comparative assessment of image brightness relative to the kidneys, as described previously[4,15-17].

SAS software was used for statistical analysis (Version 8.0; SAS Institute, Cary, NC, USA). Student's t and chi-square tests were used for analyzing continuous variables and categorical variables, respectively. Multivariate logistic regression was utilized to evaluate the relationship between salient risk factors. A program developed in the SAS computer package for the calculation of synergy index (SI) was used[18]. ASI value of > 1.0 indicates that the interaction is more than an additive interaction, i.e. is a synergism.

RESULTS

The records of a total of 5406 Taiwanese adults (2760 males, 2646 females; aged from 18 to 65 years) were used for the analysis.

Table 1 summarizes the findings in the total study population. The mean ± standard deviation of the different characteristics were: age, 46.2 ± 9.4 years; BMI, 23.5 ± 3.3 kg/m^2; waist circumference, 82.6 ± 9.2 cm; AST, 22.8 ± 9.6 U/L and ALT, 25.8 ± 19.9 U/L. Central obesity was seen in 19.2% individuals while 41.15% were overweight. The prevalence rates of LD, HBVC and SFL

Table 2 Results of logistic multivariate regression analysis[1] of LD[2] and tested variables

Risk factors	All cases	
	OR	95% CI
Gender (male *vs* female)	2.8	2.3-3.5
Overweight (yes *vs* no)	1.6	1.3-2.0
Central obesity (yes *vs* no)	1.0	0.8-1.3
SFL (yes *vs* no)	4.2	3.3-5.3
HBVC (yes *vs* no)	2.5	2.0-3.1

[1]Data were adjusted for age, gender, blood pressures, sugar, lipids and hepatitis C virus infection. LD: liver damage defined as ALT > 40; ALT: alanine aminotranferease (U/L). OR: odds ratio; CI: confidence interval. BMI > 24; BMI: body mass index = Weight (kg)/Length (m)^2. Waist circumference > 90 cm for men; > 80 cm for women. SFL: sonographic fatty liver. HBVC: hepatitis B virus carrier status.

were 12.3%, 15.1% and 33.4%, respectively; 5.1% of participants (277 in 5406) were HBV carriers with SFL.

The results obtained in the subgroups categorized by HBVC and SFL are shown in Table 1. HBV carriers had significantly higher levels of AST (26.9 ± 14.0 *vs* 22.1 ± 8.3 U/L, $P < 0.001$) and ALT (34.0 ± 30.4 *vs* 24.3 ± 17.0 U/L, $P < 0.001$) compared to non-carriers. There were no significant differences between HBV carriers and non-carriers with respect to age, BMI, and waist circumference. The proportion of males was higher in HBV carriers compared to non carriers (59.9% *vs* 49.5%). Liver function tests were abnormal significantly more frequently in HBV carriers compared to non-carriers (21.3% *vs* 10.7%). No significant differences were observed between carriers and non-carries with respect to SFL (33.3% *vs* 33.9%), overweight status (41% *vs* 43.3%) and central obesity (19.2% *vs* 19%). The proportion of subjects who were HBsAb negative was 36.7% in the total population and 26.4% in non-HBV carriers.

The results of different parameters based on whether the subjects were positive or negative for SFL are shown in Table 1. The results showed significant ($P < 0.001$) differences between subjects with SFL compared to those without SFL for all the characteristics: age 45.3 ± 9.6 *vs* 48 ± 8.7 years, BMI 22.3 ± 2.7 *vs* 25.9 ± 3.1 kg/m^2, waist circumference 79.9 ± 8.5 *vs* 87.8 ± 8.3 cm, AST 21.6 ± 9.1 *vs* 25.3 ± 10.1 U/L, ALT 21.6 ± 16.5 *vs* 34 ± 23.3 U/L, overweight status 25.5% *vs* 73%, obesity 15.1% *vs* 27.3% and liver damage, 5.6% *vs* 25.9%. There were significantly more males in the subgroup with sonographic fatty liver compared to those without SFL (64.5% *vs* 44.4%; $P < 0.001$). The only exceptions were HBVC (15.0% *vs* 15.4%, $P = 0.72$) and HBsAb-negative rates (36.4% *vs* 37.2%, $P = 0.61$), which were similar in the subgroups without or with SFL.

The results of the following physical findings and metabolic tests have not been shown in the tables but were used as potential confounding factors in the multivariate analysis: systolic blood pressure 15.5 ± 2.4 kPa, diastolic pressure 9.4 ± 1.5 kPa, fasting sugar 4.9 ± 0.5 mmol/L, triglycerides 3.2 ± 2.0 mmol/L and HDL-C 1.4 ± 0.4 mmol/L. The prevalence of elevated blood pressure was 23.6%, hyperglycemia 2.7%, hypertriglyceridemia 24.8%, and hypo-HDL-cholesterolemia 21.1%.

The results of multivariate analysis and adjusted odds ratios for LD of the total population are summarized in Table 2. According to the multiple logistic regression analysis, risks factors such as male gender (OR = 2.8, 95% confidence interval (CI): 2.3-3.5), overweight state (OR = 1.6, 95% CI: 1.3-2.0), SFL (OR = 4.2, 95% CI: 2.2-5.3) and HBVC (OR = 2.5, 95% CI: 2.0-3.1) were independently associated with LD in total study population.

Table 3 displays the results obtained in the four subgroups: SFL plus HBVC, SFL-alone, HBVC-alone and the reference group which consisted of non-carriers without SFL. Adults in the SFL plus HBVC group had significantly ($P < 0.001$) higher values of the following characteristics: age 48.2 ± 8.3 *vs* 45.4 ± 9.7 years, BMI 26.1 ± 3.2 *vs* 22.3 ± 2.7 kg/m^2, waist circumference 88.9 ± 9.4 *vs* 79.9 ± 8.5 cm, AST 29.6 ± 16.4 *vs* 20.9 ± 8.1 U/L, ALT 43.3 ± 39.4 *vs* 20.3 ± 14.6 U/L, overweight state 73.3% *vs* 25.1%, central obesity 31.1% *vs* 15.5% and abnormal liver function 37.2% *vs* 4.2%. Likewise, the SFL-alone subjects, had significantly higher values compared to the reference group with respect to: age 47.9 ± 8.8 years, BMI 25.9 ± 3.0 kg/m^2, waist circumference 87.5 ± 8.0 cm, AST 24.5 ± 8.3 U/L, ALT 32.3 ± 18.5 U/L, overweight state 73.0%, central obesity 26.7% and liver damage 23.8%. Unlike the SFL-alone and SLF plus HBVC groups, the HBVC-alone subjects had significantly higher levels than the reference group only with respect to AST 25.6 ± 12.5 U/L, ALT 29.2 ± 23.3 U/L and liver damage 13.2%, whereas age, BMI, waist circumference, rates of overweight or central obesity were not significant (Table 3). There were significantly more males in the SFL-alone, HBVC-alone and SFL plus HBVC groups: 63.0%, 53.3% and 72.6% respectively, compared to the reference group, 42.8%. The proportion of HBsAb-negative subjects was similar in non-carriers with or without SFL, 26.0% *vs* 27.1%.

Table 4 shows the risk of LD in subjects with SFL or HBVC alone and those with SFL plus HBVC compared to the reference group. The multivariate-adjusted odds ratios of liver damage for adults with HBVC-alone, SFL-alone and combined SFL plus HBVC were 3.3 (95% CI: 2.4-4.6), 4.7 (95% CI: 3.7-6.1) and 9.5 (95% CI: 6.8-13.3) respectively, the synergy index of HBV plus SFL for elevated AST levels was 1.4 (95% CI: 1.006-2.0), indicating a synergist effect[18].

DISCUSSION

In the present study carried out on a Taiwanese adult population, the prevalence rates of HBVC and SFL were 15.1% and 33.4% respectively, which are similar to those reported from other hyperendemic developing and developed Asian countries[3,5,19].

Male gender and an overweight state were independently associated with liver damage as non-modifiable and theoretically modifiable risk factors. Although several workers have shown that males are vulnerable to HBV infection, hepatosteatosis and liver damage[20-24], studies on overweight subjects also show that weight reduction brings about significant improvement in the liver function tests[6]. The importance of weight control in the management of liver damage should be

Table 3 Characteristics of four subgroups classified by HBVC and SFL positive or negative status mean ± SD

Characteristics	Liver status			
	HBVC (-) SFL (-) (*n* = 3063)	HBVC (-) SFL (+) (*n* = 1526)	HBVC (+) SFL (-) (*n* = 540)	HBVC (+)SFL(+) (*n* = 277)
Age (yr)	45.4 ± 9.7	47.9 ± 8.8[b]	44.8 ± 8.8	48.2 ± 8.3[b]
BMI (kg/m^2)	22.3 ± 2.7	25.9 ± 3.0[b]	22.5 ± 2.7	26.1 ± 3.2[b]
Waist (cm)	79.9 ± 8.5	87.5 ± 8.0[b]	79.9 ± 8.5	88.9 ± 9.4[b]
AST (U/L)	20.9 ± 8.1	24.5 ± 8.3[b]	25.6 ± 12.5[b]	29.6 ± 16.4[b]
ALT (U/L)	20.3 ± 14.6	32.3 ± 18.5[b]	29.2 ± 23.3[b]	43.3 ± 39.4[b]
Male, *n*(%)	1310 (42.8)	961 (63.0)[b]	288 (53.3)[b]	201 (72.6)[b]
Overweight, *n* (%)	769 (25.1)	1114 (73.0)[b]	151 (28.0)	203 (73.3)[b]
Central obesity, *n* (%)	476 (15.5)	407 (26.7)[b]	69 (12.8)	86 (31.1)[b]
LD, *n* (%)	129 (4.2)	363 (23.8)[b]	71 (13.2)[a]	103 (37.2)[b]
HBsAb-negative, *n* (%)	797 (26.0)	414 (27.1)		

HBVC, hepatitis B virus carrier status. SFL, sonographic fatty liver. HBVC (-) SFL (-), without SFL nor HBVC; HBVC (-) SFL (+), SFL-alone; HBVC (+) SFL (-), HBVC-alone; HBVC (+) SFL (+), SFL plus HBVC. BMI, body mass index = Weight (kg)/Length (m)^2. 5ALT, alanine aminotranferease (U/L); AST, aspartate aminotransferase (U/L); HBsAb, anti-hepatitis B surface antibody. BMI > 24. Waist circumference > 90 cm for men; > 80 cm for women. LD: liver damage defined as ALT > 40 (U/L). [a]$P < 0.01$ and [b]$P < 0.01$ *vs* reference subjects HBVC (-) SFL (-); Student's t test for continuous variables; χ^2 tests for categorical variables.

Table 4 Prevalence and odds ratio of LD for single or combined states of HBVC and SFL

Liver status		Liver damage rate (%)	OR	95% CI	SI	95% CI
SFL	HBVC					
(-)	(-)	4.2	1.0	Reference	No risk	-
(-)	(+)	13.2[b]	3.3	2.4 - 4.6	One risk only	-
(+)	(-)	23.8[b]	4.7	3.7 - 6.1	One risk only	-
(+)	(+)	37.2[b]	9.5	6.8 - 13.3	1.4	1.001 - 2.0

LD: liver damage defined as ALT > 40 (U/L); ALT: alanine aminotranferease (U/L). HBVC: hepatitis B virus carrier status. SFL: sonographic fatty liver. OR: odds ratio; CI: confidence interval; data were adjusted for age, gender, blood pressures, sugar, lipids and hepatitis C virus infection. SI: synergy index, Ref [18]. [b]$P < 0.01$ *vs* reference subjects; data were analyzed by multivariate logistic regression analysis.

emphasized in Taiwanese adults, especially males.

Our findings support previous observations that both SFL and HBVC have a strong association with liver damage[6,25]. In addition, our study shows that SFL and HBVC produce liver injury by different mechanisms. In hepatosteatosis, the severity of liver injury is closely related to the amount of lipid accumulation in the hepatocytes[15,16]. Fat accumulation can be semi-quantitatively estimated by sonograms[5,16,26,27], thus analysis of hepatosteatosis on sonogram can determine the potential for liver injury[15,16,27-29]. By contrast, the severity of liver injury in HBV carriers depends on several viral factors including virus type and viral load[30-33]. Thus, knowledge of HBsAg carrier status alone, without information on the viral type and number viral copies, provides only limited information on the severity of liver injury[34,35]. In the present multivariable analysis (Tables 2 and 4), HBVC exhibited a significant but weaker association with liver injury than SFL, nevertheless, in future studies the impact of these risk factors on liver damage should be assessed by analysis adjusted for virus type and viral copies.

Our study provides an epidemiological analysis on the influence of combined HBVC and SFL on liver damage, and indicates a synergistic effect (Table 4). According to the widely accepted "two-hit theory" of steatohepatitis, the "first hit" is excess lipid accumulation in hepatocytes; lipids in the liver cells are sensitive to the "second hit" involving factors such as oxidative stress, oxygen-radicals, cytokines, lipid-peroxidation, which result in steatohepatitis[36-40]. It is possible that the two hits can exist simultaneously in lipid-containing hepatocytes infected with HBV.

In the present study, the "first hit", lipid accumulation detected by sonogram, showed no significant difference between HBV carriers and non-carriers (Table 3). These findings are in agreement with previous observations[41] that HBVC prevalence is not influenced by the presence of SFL, and vice versa (Table 1). Despite the insignificant association of the "first hit" regarding the coexistence of HBVC and SFL, the "second hit" should be considered as the candidate causing significant liver injury. Several studies on HBV infection and fatty liver have reported oxidative stress-related events such as the assembly of HBV viral particles[42], the HBV altered lipid peroxidation pathway and hepatocyte electron transport system by charged HBV[43-45]. It is reasonable to theorize that these oxidative stress-related events act together in inducing additional and potent oxidative stress in the hepatocytes, thus enhancing the "second hit", which promotes injury to the vulnerable lipid-containing hepatocytes, resulting in hepatitis.

In addition, from the view point of molecular biology,

both hepatosteatosis and HBV infection are associated with dysfunction of the mitochondria, which are the producers of metabolic energy, biosensor for oxidative stress, and effector for liver cell death through the process of apoptosis[46,47]. Previous studies on hepatitis B virus have shown that a viral protein, HBx protein, is found in the mitochondrion and targets mitochondrial calcium regulation, which results in mitochondrial dysfunction[48,49]. On the other hand, investigations on hepatosteatosis demonstrate that excess lipid peroxidation plays a role in triggering mitochondrial membrane permeabilization and apoptosis[50-53]. Mitochondrial dysfunction caused simultaneously by HVB infection and hepatosteatosis should be considered as an important cause of hepatocellular injury, represented by a significant increase in the frequency of abnormal liver function tests in SFL-affected HBV carriers.

Although our study shows a statistical association between HBVC, SFL and LD, a direct biochemical and biomolecular evidence for the causality and synergism awaits further investigations.

To date, besides weight reduction and physical exercise, there are few recommendations for the management of fatty liver[6,36,39]. At the same time, the use of hepatitis B vaccine has been shown to effectively reduce the incidence of new infections, and vaccination is recommended for at-risk, sexually active adult individuals[54]. In our study, 27.1% of fatty liver-affected non-HBV carriers were HBsAb-negative (Table 1). As SFL is one of the major causes of liver damage, and is an independent risk factor predicting advanced liver disease for HBV carriers[3,7], expanding vaccination recommendations to fatty liver-affected subjects could be an effective preventive strategy against advanced liver disease.

To sum up, sonographic fatty liver and HBV carrier status are the most prevalent liver problems in Taiwanese adults, with male subjects being more vulnerable to fatty liver, HBV infection and liver damage than females. Health promotion strategies such as weight control and use of HBV vaccination should be emphasized in Taiwanese adults, especially males. Since HBVC combined with SFL has a synergistic effect on liver injury, we recommend HBV vaccination for Taiwanese adults with fatty liver who do not have adequate protective antibodies.

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REFERENCES

1 **Limdi JK**, Hyde GM. Evaluation of abnormal liver function tests. *Postgrad Med J* 2003; **79**: 307-312
2 **Gasbarrini G**, Vero V, Miele L, Forgione A, Hernandez AP, Greco AV, Gasbarrini A, Grieco A. Nonalcoholic fatty liver disease: defining a common problem. *Eur Rev Med Pharmacol Sci* 2005; **9**: 253-259
3 **Merican I**, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN, Hasnian SS, Leung N, Lesmana L, Phiet PH, Sjalfoellah Noer HM, Sollano J, Sun HS, Xu DZ. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol* 2000; **15**: 1356-1361
4 **Tam KM**, Wu JS. Ultrasonographic diagnosis of fatty liver. *Taiwan Yixuehui Zazhi* 1986; **85**: 45-53
5 **Fan JG**, Zhu J, Li XJ, Chen L, Lu YS, Li L, Dai F, Li F, Chen SY. Fatty liver and the metabolic syndrome among Shanghai adults. *J Gastroenterol Hepatol* 2005; **20**: 1825-1832
6 **Sass DA**, Chang P, Chopra KB. Nonalcoholic fatty liver disease: a clinical review. *Dig Dis Sci* 2005; **50**: 171-180
7 **Chang MH**. Hepatitis B virus infection in children: epidemiology, natural course and prevention in Taiwan. *J Formos Med Assoc* 1996; **95**: 593-598
8 **Gordon A**, McLean CA, Pedersen JS, Bailey MJ, Roberts SK. Hepatic steatosis in chronic hepatitis B and C: predictors, distribution and effect on fibrosis. *J Hepatol* 2005; **43**: 38-44
9 **Shabot JM**, Jaynes C, Little HM, Alperin JB, Snyder N. Viral hepatitis in pregnancy with disseminated intravascular coagulation and hypoglycemia. *South Med J* 1978; **71**: 479-481
10 **Canbay A**, Bechmann LP, Best J, Jochum C, Treichel U, Gerken G. Crohn's disease-induced non-alcoholic fatty liver disease (NAFLD) sensitizes for severe acute hepatitis B infection and liver failure. *Z Gastroenterol* 2006; **44**: 245-248
11 **Yuen MF**, Yuan HJ, Wong DK, Yuen JC, Wong WM, Chan AO, Wong BC, Lai KC, Lai CL. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005; **54**: 1610-1614
12 **Wong WM**, Ho JC, Ooi GC, Mok T, Chan J, Hung IF, Ng W, Lam YM, Tam WO, Wong BC, Wong PC, Ho PL, Lai CL, Lam WK, Lam SK, Tsang KW. Temporal patterns of hepatic dysfunction and disease severity in patients with SARS. *JAMA* 2003; **290**: 2663-2665
13 **Chu NF**. Prevalence of obesity in Taiwan. *Obes Rev* 2005; **6**: 271-274
14 **Katayama K**, Hayashi N, Takehara T, Towata T, Kasahara A, Fusamoto H, Kamada T. Effects of alpha-interferon on gamma-interferon production of peripheral blood mononuclear cells in hepatitis B virus carriers. *J Clin Immunol* 1992; **12**: 347-352
15 **Saadeh S**, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002; **123**: 745-750
16 **Steinmaurer HJ**, Jirak P, Walchshofer J, Clodi PH. Accuracy of sonography in the diagnosis of diffuse liver parenchymal diseases--comparison of sonography and liver histology. *Ultraschall Med* 1984; **5**: 98-103
17 **Yajima Y**, Ohta K, Narui T, Abe R, Suzuki H, Ohtsuki M. Ultrasonographical diagnosis of fatty liver: significance of the liver-kidney contrast. *Tohoku J Exp Med* 1983; **139**: 43-50
18 **Lundberg M**, Fredlund P, Hallqvist J, Diderichsen F. A SAS program calculating three measures of interaction with confidence intervals. *Epidemiology* 1996; **7**: 655-656
19 **Qu JB**, Zhang ZW, Shimbo S, Watanabe T, Nakatsuka H, Matsuda-Inoguchi N, Higashikawa K, Ikeda M. Urban-rural comparison of HBV and HCV infection prevalence in eastern China. *Biomed Environ Sci* 2000; **13**: 243-253
20 **Lonardo A**, Carani C, Carulli N, Loria P. 'Endocrine NAFLD' a hormonocentric perspective of nonalcoholic fatty liver disease pathogenesis. *J Hepatol* 2006; **44**: 1196-1207
21 **Chowdhury A**, Santra A, Chaudhuri S, Ghosh A, Banerjee P, Mazumder DN. Prevalence of hepatitis B infection in the general population: a rural community based study. *Trop Gastroenterol* 1999; **20**: 75-77
22 **Hopkirk N**, Moyes CD, Lucas CR. Liver function and hepatitis markers in carriers of hepatitis B virus in New Zealand. *N Z Med J* 2000; **113**: 114-116
23 **Tanaka J**, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, Suzuki K, Miyakawa Y, Yoshizawa H. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. *Intervirology* 2004; **47**: 32-40

24 **Wright TL**. Introduction to chronic hepatitis B infection. *Am J Gastroenterol* 2006; **101** Suppl 1: S1-S6
25 **Choi S**, Diehl AM. Role of inflammation in nonalcoholic steatohepatitis. *Curr Opin Gastroenterol* 2005; **21**: 702-707
26 **Joy D**, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? *Eur J Gastroenterol Hepatol* 2003; **15**: 539-543
27 **Riley TR**, Kahn A. Risk factors and ultrasound can predict chronic hepatitis caused by nonalcoholic fatty liver disease. *Dig Dis Sci* 2006; **51**: 41-44
28 **Colicchio P**, Tarantino G, del Genio F, Sorrentino P, Saldalamacchia G, Finelli C, Conca P, Contaldo F, Pasanisi F. Non-alcoholic fatty liver disease in young adult severely obese non-diabetic patients in South Italy. *Ann Nutr Metab* 2005; **49**: 289-295
29 **Angelico F**, Del Ben M, Conti R, Francioso S, Feole K, Maccioni D, Antonini TM, Alessandri C. Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases. *J Gastroenterol Hepatol* 2003; **18**: 588-594
30 **Chan HL**, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, Sung JJ. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut* 2004; **53**: 1494-1498
31 **Seo Y**, Yoon S, Truong BX, Kato H, Hamano K, Kato M, Yano Y, Katayama M, Ninomiya T, Hayashi Y, Kasuga M. Serum hepatitis B virus DNA levels differentiating inactive carriers from patients with chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2005; **17**: 753-757
32 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73
33 **Yu MW**, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005; **97**: 265-272
34 **Iloeje UH**, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**: 678-686
35 **Luo KX**, Zhou R, Liang ZS, Jiang S. Correlation between the prevalence of serum HBV DNA and immunoserologic HBV markers in the subjects with or without hepatitis. *Immunol Invest* 1992; **21**: 275-281
36 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112
37 **Bradbury MW**. Lipid metabolism and liver inflammation. I. Hepatic fatty acid uptake: possible role in steatosis. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G194-G198
38 **Sanyal AJ**. Mechanisms of Disease: pathogenesis of nonalcoholic fatty liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 46-53
39 **Jonas MM**. Nonalcoholic fatty liver disease. *Adolesc Med Clin* 2004; **15**: 159-173, xi
40 **Wanless IR**, Shiota K. The pathogenesis of nonalcoholic steatohepatitis and other fatty liver diseases: a four-step model including the role of lipid release and hepatic venular obstruction in the progression to cirrhosis. *Semin Liver Dis* 2004; **24**: 99-106
41 **Moritani M**, Adachi K, Arima N, Takashima T, Miyaoka Y, Niigaki M, Furuta K, Sato S, Kinoshita Y. A study of arteriosclerosis in healthy subjects with HBV and HCV infection. *J Gastroenterol* 2005; **40**: 1049-1053
42 **Desombere I**, Willems A, Gijbels Y, Leroux-Roels G. Partial delipidation improves the T-cell antigenicity of hepatitis B virus surface antigen. *J Virol* 2006; **80**: 3506-3514
43 **Lee YI**, Hwang JM, Im JH, Lee YI, Kim NS, Kim DG, Yu DY, Moon HB, Park SK. Human hepatitis B virus-X protein alters mitochondrial function and physiology in human liver cells. *J Biol Chem* 2004; **279**: 15460-15471
44 **Huang CF**, Lin SS, Ho YC, Chen FL, Yang CC. The immune response induced by hepatitis B virus principal antigens. *Cell Mol Immunol* 2006; **3**: 97-106
45 **Waris G**, Huh KW, Siddiqui A. Mitochondrially associated hepatitis B virus X protein constitutively activates transcription factors STAT-3 and NF-kappa B via oxidative stress. *Mol Cell Biol* 2001; **21**: 7721-7730
46 **Cottrell DA**, Turnbull DM. Mitochondria and ageing. *Curr Opin Clin Nutr Metab Care* 2000; **3**: 473-478
47 **Medina J**, Fernández-Salazar LI, García-Buey L, Moreno-Otero R. Approach to the pathogenesis and treatment of nonalcoholic steatohepatitis. *Diabetes Care* 2004; **27**: 2057-2066
48 **Zhang X**, Zhang H, Ye L. Effects of hepatitis B virus X protein on the development of liver cancer. *J Lab Clin Med* 2006; **147**: 58-66
49 **Bouchard MJ**, Wang LH, Schneider RJ. Calcium signaling by HBx protein in hepatitis B virus DNA replication. *Science* 2001; **294**: 2376-2378
50 **Reddy JK**. Nonalcoholic steatosis and steatohepatitis. III. Peroxisomal beta-oxidation, PPAR alpha, and steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G1333-G1339
51 **Pessayre D**, Berson A, Fromenty B, Mansouri A. Mitochondria in steatohepatitis. *Semin Liver Dis* 2001; **21**: 57-69
52 **Pessayre D**, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol* 2004; **16**: 1095-1105
53 **Rao MS**, Reddy JK. Peroxisomal beta-oxidation and steatohepatitis. *Semin Liver Dis* 2001; **21**: 43-55
54 **Mahoney FJ**. Update on diagnosis, management, and prevention of hepatitis B virus infection. *Clin Microbiol Rev* 1999; **12**: 351-366

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