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

ELSEVIER

World J Gastroenterol 2005;11(22):3357-3362
World Journal of Gastroenterology ISSN 1007-9327
© 2005 The WJG Press and Elsevier Inc. All rights reserved.

Correlation of serum leptin levels with anthropometric and metabolic parameters and biochemical liver function in Chinese patients with chronic hepatitis C virus infection

Zheng-Wen Liu, Ni Zhang, Qun-Ying Han, Jun-Tao Zeng, Yong-Lie Chu, Jian-Ming Qiu, Ya-Wen Wang, Lie-Ting Ma, Xiao-Qin Wang

Zheng-Wen Liu, Ni Zhang, Qun-Ying Han, Jun-Tao Zeng, Yong-Lie Chu, Jian-Ming Qiu, Department of Infectious Diseases, First Hospital, Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
Ya-Wen Wang, Lie-Ting Ma, Xiao-Qin Wang, Central Medical Laboratory, First Hospital, Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
Supported by the National Natural Science Foundation of China, No. 30170842
Correspondence to: Professor Zheng-Wen Liu, Department of Infectious Diseases, First Hospital, Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China. zhengwenl@sohu.com
Telephone: +86-29-5324066 Fax: +86-29-5226360
Received: 2004-06-16 Accepted: 2004-07-22

Abstract

AIM: To determine serum leptin levels and investigate their correlations with anthropometric and metabolic parameters and biochemical liver function in patients with chronic hepatitis C virus (HCV) infection and their potential clinical implications.

METHODS: Forty-two chronic HCV-infected patients without anti-viral treatment were enrolled in this study, 30 patients had chronic hepatitis C, 10 had cirrhosis, and 2 had hepatocellular carcinoma (HCC). Thirty age- and sex-matched healthy individuals served as controls. Serum leptin levels were determined by ELISA. The biochemical liver function and serum lipids were determined at the same time. The height and body weight of patients and controls were measured, and body mass index (BMI) and body fat were calculated simultaneously. The correlations of serum leptin levels with anthropometric and metabolic parameters and biochemical liver function were assessed statistically.

RESULTS: The mean of serum leptin levels in patients with chronic hepatitis C, HCV-associated cirrhosis, HCV-associated HCC and control groups was (6.13±3.94), (5.25±4.21), (4.17±0.28), and (3.59±3.44) ng/mL, respectively. The serum leptin level in patients with chronic hepatitis C was significantly higher than that in controls. The serum leptin levels between cirrhotic patients and controls and between male and female cirrhotic patients had no significant difference. Serum leptin levels were positively-correlated with body fat, BMI, and apolipoprotein B (Apo B) in patients with chronic HCV infection. The serum alanine aminotransferase (ALT) levels were closely-correlated with BMI in patients with chronic hepatitis C.

CONCLUSION: HCV infection interferes with fat and lipid metabolism in patients with chronic HCV infection and leptin may play a role in hepatosteatosis.

© 2005 The WJG Press and Elsevier Inc. All rights reserved.

Key words: Chronic hepatitis C; Leptin; Anthropometric parameter; Lipid metabolism

Liu ZW, Zhang N, Han QY, Zeng JT, Chu YL, Qiu JM, Wang YW, Ma LT, Wang XQ. Correlation of serum leptin levels with anthropometric and metabolic parameters and biochemical liver function in Chinese patients with chronic hepatitis C virus infection. *World J Gastroenterol* 2005; 11(22): 3357-3362
http://www.wjgnet.com/1007-9327/11/3357.asp

INTRODUCTION

Hepatitis C virus (HCV) infection is a worldwide public health problem[1,2]. HCV infection frequently leads to chronic hepatitis, which may progress to cirrhosis and even to hepatocellular carcinoma (HCC)[3]. The mechanisms responsible for the pathogenesis of chronic HCV infection are not well known. One of the common and prominent histopathologic features in patients with chronic HCV infection is the presence of hepatic steatosis, which is believed to be an important co-factor in accelerating the development of liver fibrosis[4-7]. Previous studies demonstrated that chronic HCV infection has close correlations with fat and lipid metabolism[8,9] and that there is a significant relationship between hepatic steatosis and fibrosis in chronic hepatitis C[10-12]. The relationship between body mass index (BMI), steatosis, and fibrosis in chronic HCV-infected patients suggests a role of steatosis in the progression of hepatitis C[13]. Recent attention has been focused on the liver profibrogenic role of leptin in animal models[14] and serum leptin levels have been investigated in European and North American patients with chronic HCV infection in terms of the important role of leptin in the regulation of body fat and lipid metabolism. These studies demonstrated that serum leptin levels correlate with hepatic steatosis in chronic hepatitis C[15], the levels of leptin increase according to the progression of the stage of fibrosis in chronic HCV-infected patients and the severity of liver fibrosis is

associated with high leptin levels in chronic hepatitis C[16]. Furthermore, clinical observations showed that fatigue, a common symptom in hepatitis patients, is associated with high circulating leptin levels in chronic hepatitis C[17] and interferon-alpha antiviral therapy can decrease and suppress leptin levels in chronic hepatitis C patients[18,19]. These data suggest that leptin may play a role in the regulation of hepatic fibrosis in patients with chronic HCV infection[20] although it is controversial[21].

There are differences in the relationship between body fat and BMI among different ethnicities[22] and comparisons of anthropometric measurements showed that Asians have lower BMI but higher body fat than whites[23]. Leptin levels have been shown to be associated with anthropometric parameters such as BMI, total body fat, and subcutaneous fat. Moreover, gender, ethnicity, body composition, and fat distribution have effects on serum leptin concentrations[24,25]. However, no report has documented the role of leptin in Chinese patients with chronic HCV infection so far.

In this study, serum leptin levels in Chinese patients with chronic HCV infection without antiviral treatment were investigated, and their relationships with simultaneously determined anthropometric measurements, metabolic parameters, and biochemical liver function were analyzed to elucidate the role of leptin in Chinese patients with chronic HCV infection and the potential clinical significance.

MATERIALS AND METHODS

Patients

Forty-two HCV-infected patients were studied. All patients were anti-HCV positive and had detectable serum HCV RNA except for two HCC patients. Thirty of them were clinically diagnosed with chronic hepatitis C, 10 with HCV-associated cirrhosis, and two with HCV-associated HCC. All patients had at least two documented occasions of increased serum alanine aminotransferase (ALT) levels 6 mo prior to enrollment, which were higher than the upper normal limit measured at intervals of more than 2 mo. Alcoholics and intravenous drug users or homosexual persons and patients with usage of hepatotoxic drugs, herbal medicine or immuno-suppressive therapy within the past 6 mo were excluded, and none of these patients had chronic renal failure, clotting abnormalities, hemophilia, serious neurological disorders, obesity, chronic viral hepatitis B or delta, HIV infection, autoimmune disease (anti-nuclear antibody titer >1:40), and/or inheritable disorders such as hemochromatosis, alpha-1-antitrypsin deficiency or Wilson's disease, and other metabolic disorders such as diabetes and thyroidism. None of the patients had any antiviral therapies before recruitment and all of them had stable body weight for at least 4 wk before enrollment. All the cirrhotic and HCC patients had no ascites. Informed consent was obtained from all patients. Thirty healthy age- and gender-comparable blood donors served as controls.

Methods

Blood samples were obtained from all subjects after overnight fasting. Samples were centrifuged and sera were stored at -25 ℃. Body height (m) and weight (kg), waist and hip circumference (cm) were taken with standard methods. BMI was calculated by weight/height^2. Fat distribution in abdomen (waist-to-hip ratio, WHR) was calculated by waist circumference/hip circumference. Body fat was calculated according to the formulae 1.2×BMI+0.23×age-16.2 and 1.2×BMI+0.23×age-5.4 for male and female subjects, respectively.

Serum anti-HCV was detected by ELISA using commercially available diagnostic kits for antibody to HCV from Sino-American Biotechnology Company (Zhengzhou, China). Quantification of serum HCV RNA was performed using commercial HCV fluorescence PCR diagnostic kits manufactured by Daan Gene Co., Ltd. (Zhongshan University, Shenzhen, China). The sensitivity of this HCV RNA assay was 80 copies/mL. Serum-soluble leptin levels were determined by commercial ELISA kits (R&D Systems Inc., Minneapolis, MN, USA). The sensitivity was 0.02 ng/mL. It had no cross reaction with interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, tumor necrosis factor (TNF), soluble TNF-receptor II, and interferon. Intra- and inter-assay variabilities were <10.5%. Serum total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, Apo AI, Apo B, and biochemical liver function were assayed on an automatic analyzer (HITACHI 7170A, Hitachi Koki Co., Ltd., Hitachinaka City, Japan).

Statistical analysis

Data were expressed as mean±SD and analyzed with SPSS 11.0 software. Statistical analysis was performed using two-tailed Fisher's exact test, two-tailed Student's *t*-test, χ^2 test, and analysis of covariance wherever appropriate. Correlation tests between parameters were performed by multiple linear regression and multiple correlation analysis. A P value less than 0.05 was considered statistically significant.

RESULTS

Comparison of serum leptin levels between patients with chronic HCV infection and controls

The demographic and anthropometric characteristics in patients with chronic HCV infection and controls are shown in Table 1. The age, body height and weight, waist and hip circumference, BMI, WHR, and body fat were not statistically different between patients with HCV infection and controls (Table 1).

Table 1 Demographic characteristics in patients with HCV infection and controls (mean±SD)

	Patients	Controls	t	P
Number (male/female)	25/17	18/12	0.002[1]	0.968
Age (yr)	44.93±14.35	39.43±12.33	1.696	0.094
Height (m)	1.67±0.08	1.66±0.07	0.925	0.358
Weight (kg)	64.86±15.08	64.00±9.18	0.312	0.756
WC (cm)	81.88±9.59	81.45±12.97	0.137	0.892
HC (cm)	94.25±8.46	94.00±7.92	0.084	0.933
BMI (kg/m^2)	22.94±4.59	23.14±3.09	0.225	0.822
WHR	0.87±0.74	0.87±0.11	0.220	0.827
Body fat (%)	26.21±7.63	24.96±7.25	0.714	0.478

WC: waist circumference, HC: hip circumference, BMI: body mass index, WHR: waist-to-hip circumference ratio, body fat (%): percent of body fat, [1]χ^2 test.

Considering the possible effects of BMI, WHR, and body fat on the levels of serum leptin, analysis of covariance was performed using BMI and body fat as covariate as determined by pre-analysis. The serum leptin level in patients with chronic HCV infection was significantly higher than that in controls ($F = 5.610$, $P = 0.021$, Table 2). Comparisons of serum leptin levels were further performed according to gender in term of the effects of gender on leptin concentrations due to differences in body composition and body fat distribution between male and female patients[26,27]. The results showed that serum leptin level in male and female patients was significantly higher than that in male and female controls ($F = 17.269$, $P<0.001$; $F = 4.002$, $P = 0.056$, Table 2). Serum leptin levels in female individuals were significantly elevated compared with those in male individuals ($F = 9.341$, $P = 0.005$ for patients and $F = 16.080$, $P<0.001$ for controls, Table 2).

Table 2 Comparison of serum leptin levels between patients with HCV infection and controls (mean±SD)

	Patients[2]	Controls[3]	*F*	*P*
No. (male/female)	25/17	18/12	0.002[1]	0.968
Male	3.58±2.06	1.44±1.06	17.269	<0.001
Female	9.13±3.59	6.83±3.23	4.002	0.056
Total	5.83±3.89	3.59±3.44	5.610	0.021

[1]χ^2 test, [2]$F = 9.341$, $P = 0.005$, male *vs* female; [3]$F = 16.080$, $P<0.001$, male *vs* female.

Comparisons of serum leptin levels between chronic HCV-infected patients at different clinical stages and controls

The demographic, anthropometric, biochemical, and virological characteristics in HCV-infected patients at different clinical stages are shown in Table 3.

The serum leptin levels in patients with chronic hepatitis C, HCV-associated cirrhosis, HCV-associated HCC and controls were compared by analysis of covariance. The serum leptin levels in patients with chronic hepatitis C were significantly higher than those in controls ($P = 0.003$). The serum leptin levels in patients with HCV-associated cirrhosis and HCV-associated HCC were not significantly increased as compared with controls ($P = 0.752$ and $P = 0.822$, respectively). The serum leptin levels in patients with chronic hepatitis C were not statistically different from those in patients with HCV-associated cirrhosis ($P = 0.074$) and HCV-associated HCC ($P = 0.397$). The serum leptin levels between patients with HCV-associated cirrhosis and HCV-associated HCC had no significant difference ($P = 0.952$). The serum leptin level in male patients with chronic hepatitis C were obviously different ($F = 12.454$, $P = 0.002$) from that in female patients. However, the serum leptin levels between male and female patients with HCV-associated cirrhosis were not statistically different ($F = 0.054$, $P = 0.823$, Table 4).

Correlation analysis of factors associated with serum leptin and ALT levels

Factors possibly-associated with serum leptin levels in patients

Table 3 Demographic, anthropometric, biochemical, and virological characteristics in chronic HCV-infected patients at different clinical stages (mean±SD)

	Chronic hepatitis C	HCV-associated cirrhosis	HCV-associated HCC
No. (male/female)	17/13	6/4	2/0
Age (yr)	41.03±14.10	53.70±9.93	59.5±12.02
Height (m)	1.68±0.09	1.66±0.05	1.69±0.04
BMI (kg/m^2)	23.01±3.39	22.71±7.59	22.97±4.53
WHR	0.86±0.07	0.87±0.08	0.95±0.02
Body fat (%)	25.79±6.52	27.72±11.23	25.05±2.67
LDL (mmol/L)	2.05±1.01	1.41±0.82	2.24±0.19
CHO (mmol/L)	4.09±2.05	3.22±1.08	5.55±1.06
TG (mmol/L)	1.51±1.03	0.81±0.45	1.52±0.47
HDL (mmol/L)	1.13±0.43	1.07±0.40	1.34±0.74
Apo AI (mg/L)	1.36±0.40	1.17±0.44	1.45±0.72
Apo B (mg/L)	0.55±0.27	0.39±0.19	0.71±0.13
ALT (U/L)	93.19±83.08	45.4±35.86	20.5±0.71
AST (U/L)	67.96±50.65	77.70±62.11	48.50±20.51
GGT (U/L)	50.27±41.22	49.80±53.79	92.00±18.38
HCV RNA (copies/mL)	(6.4±12)×10^4	(6.2±8.9)×10^4	<80

BMI: body mass index, WHR: waist-to-hip circumference ratio, body fat (%): percent of body fat, LDL: low density lipoprotein, CHO: cholesterol, TG: triglycerides, HDL: high density lipoprotein, Apo AI: apolipoprotein AI, Apo B: apolipoprotein B, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyltransferase, HCV RNA: hepatitis C virus ribonucleic acid.

Table 4 Comparisons of serum leptin levels between HCV-infected patients at different clinical stages and controls (mean±SD)

	Chronic hepatitis C	HCV-associated cirrhosis	HCV-associated HCC	Controls
No. (M/F)	17/13	6/4	2/0	18/12
Male	3.75±2.11	2.90±2.33	4.17±0.28	1.44±1.06
Female	9.25±3.61	8.77±4.07		6.83±3.23
Total	6.13±3.94[1]	5.25±4.21[2]	4.17±0.28[3]	3.59±3.44

[1]$P = 0.003$, [2]$P = 0.752$ and [3]$P = 0.822$ compared with controls, respectively. $F = 12.454$, $P = 0.002$, $F = 0.054$, $P = 0.823$ and $F = 6.365$, $P = 0.018$ when comparisons were performed between male and female patients with chronic hepatitis C, HCV-associated cirrhosis and controls.

with chronic HCV infection were analyzed. Multiple linear regression was performed using the leptin levels as a dependent variable and ALT, AST, CHO, HDL, TG, Apo AI, Apo B, LDL, HCV RNA, BMI, body fat, and WHR as independent variables. The results showed that the serum leptin levels were associated with body fat, BMI, and Apo B but not with liver function and serum HCV RNA levels (Table 5).

Table 5 Factors possibly associated with serum leptin levels in patients with chronic HCV infection

Dependent variable	Independent variables	Standardized coefficients (Beta model)	*P*
Leptin	Body fat (%)	1.630	<0.001
Leptin	BMI	1.050	0.003
Leptin	Apo B	0.342	0.008

Body fat (%): percent of body fat, BMI: body mass index, Apo B: apolipoprotein B.

The possibly-associated factors with serum leptin and ALT levels in patients with chronic HCV infection were also analyzed using the ALT levels as a dependent variable and CHO, HDL, TG, Apo AI, Apo B, LDL, HCV RNA, BMI, body fat, and WHR as independent variables. The results showed that serum leptin levels were positively-correlated with body fat ($r = 0.520$, $P = 0.003$) and ALT levels were positively-correlated with Apo B ($r = 0.400$, $P = 0.032$) and BMI ($r = 0.389$, $P = 0.034$). No correlation between serum leptin and ALT levels in patients with HCV-associated cirrhosis was found.

DISCUSSION

Hepatic steatosis is a common histopathologic feature in patients with chronic HCV infection[4,5]. HCV-core-protein expression can induce steatosis in transgenic mouse model[28]. The possible role of leptin in the pathogenesis of hepatic steatosis and fibrosis has been studied[29]. It was found that leptin has a close relationship with the hepatic steatosis in alcoholic steatohepatitis[30]. The role of leptin is also a focus of study due to the high incidence of hepatic steatosis in chronic hepatitis C patients. Leptin levels in patients with chronic HCV infection are increased, suggesting that HCV infection interferes with fat metabolism and leptin levels. However, it is not clear whether there are also some differences in leptin levels in chronic hepatitis C patients because of the difference in body composition and fat distribution between Chinese and Western people. Therefore, the serum leptin levels in Chinese patients with chronic HCV infection and normal healthy controls were determined and analyzed to address these issues in our study.

The subjects studied were strictly and accurately selected to rule out or minimize the possible influences of other factors, such as diabetes mellitus, alcohol, and antiviral therapy on leptin levels. Our results showed that the leptin levels in patients with chronic HCV infection were obviously increased as compared with normal controls. The serum leptin levels in both male and female patients with chronic HCV infection are increased as compared with controls although the leptin levels are generally higher in females than in males. Our results are in accordance with previous reports[31-35]. The precise mechanisms, by which chronic HCV infection causes elevated serum leptin levels, are not completely known. Factors such as inflammation, abnormal fat metabolism, and hepatic steatosis in patients with chronic HCV infection, might be involved.

Findings in this study may mainly represent the expression of reduced fat mass in cirrhotic patients[36] and the abnormalities of sexual hormone metabolism in male cirrhotic patients[37].

Our analyses showed that the serum leptin levels were correlated with body fat, BMI, and Apo B but not with liver function and serum HCV RNA levels. These results suggest that leptin levels in chronic HCV infection are preferentially affected by fat and lipid metabolisms. Giannini *et al*[38], demonstrated that serum leptin levels in nonalcoholic steatohepatitis (NASH) and chronic hepatitis C increase, although the differences are not statistically significant. Therefore, it seems that the extents of leptin elevation are closely related with the severity of abnormal fat metabolism and hepatic steatosis in chronic HCV-infected patients.

Our further analyses showed that ALT levels were positively correlated with BMI ($r = 0.410$, $P = 0.030$), body fat ($r = 0.520$, $P = 0.003$), Apo B ($r = 0.400$, $P = 0.032$) and BMI ($r = 0.389$, $P = 0.034$). However, the serum leptin and ALT levels in patients with HCV-associated cirrhosis had no correlation with any other variable. These results further demonstrate the close relationships between leptin levels and fat metabolism and between hepatic necroinflammation and lipid and fat metabolisms in patients with chronic hepatitis C. A possible link between leptin and decreased lipid levels and interaction between HCV and Apo B have been elucidated[39-41]. Disappearance of these correlations in patients with HCV-associated cirrhosis may be a reflection of reduced fat mass in cirrhotic patients[36,42] and the abnormalities of sexual hormone metabolism in male cirrhotic patients[37]. Taken together, serum leptin levels in patients with chronic HCV infection appear to be controlled by multiple factors such as body composition, gender, abnormalities of fat and lipid metabolism, and hepatic steatosis resulting from chronic HCV infection. The stages of liver diseases also affect leptin levels in patients with chronic HCV infection.

Another major focus of recent studies is the role of leptin in the modulation of immune response and inflammation. The increase in leptin production that occurs during infection and inflammation strongly suggests that leptin is a part of cytokine cascade, which regulates the innate immune response and host defense mechanisms although both proinflammatory and anti-inflammatory effects have been documented for leptin[43]. Leptin plays an important role in T-cell-mediated immune responses and stimulates proliferation of CD4+ T cells and promotes Th1 responses[44-46]. Moreover, congenital leptin deficiency in humans is found to be associated with a decreased number of circulating CD4+T cells, impaired T-cell proliferation and cytokine release, all of which could be reversed by administration of recombinant leptin[47]. Observations in alcoholics showed that circulating levels of leptin are associated with NK activity in humans, suggesting that abnormal *in vivo* concentrations of leptin may contribute to the decline of NK activity in alcoholics[48]. The results of experiments in animals showed that leptin represents a

functional link between endocrine and immune systems[49]. On the other hand, considerable evidence suggests that immune mechanisms are involved in the pathogenesis of HCV infection. Both humoral and cell-mediated immune responses are believed to participate in the host defense against HCV infection. In particular, cell-mediated response plays a role in the immunopathogenesis of chronic hepatitis C[50]. An enhanced Th2 response is present in HCV infection, which may be responsible for the chronicity of HCV infection[51]. Both class I-restricted CD8+T cell and class II-restricted CD4+T cell responses to viral antigens are an important pathway responsible for hepatocyte damage in hepatitis C[52]. Lack of correlation between intrahepatic HCV RNA level and microinflammation in chronic hepatitis C also suggests that HCV-associated liver damage is mostly immunomediated[53]. T cells infiltrate into the liver of patients with chronic hepatitis C, which is believed to play a crucial role in the immunopathogenesis of hepatic inflammation[54]. Therefore, whether the immunoregulatory functions of leptin have relevance to the immunopathogenesis of chronic HCV infection needs to be further investigated.

Studies and observations showed that in hypoleptinemic patients with extreme insulin resistance and lipodystrophy, leptin can ameliorate insulin resistance, hyperglycemia, hyperinsulinemia, dyslipidemia, and hepatic steatosis. In leptin-deficient states, leptin therapy can restore gonadotrophin secretion, luteinizing hormone, and thyroid-stimulating hormone pulsitility[55]. In addition, leptin has been suggested as a novel strategy for immune intervention in pathologic conditions[56]. Most of the above abnormal conditions exist in patients with chronic hepatitis or cirrhosis. Therefore, whether enhancing or inhibiting leptin's activities plays a therapeutic role in these conditions also needs to be investigated[57].

In conclusion, patients with chronic hepatitis C have increased serum leptin levels. However, serum leptin levels in HCV-associated cirrhotic patients have no significant difference compared with controls. Serum leptin levels in patients with chronic hepatitis C are positively-correlated with body fat, BMI, and Apo B. Serum ALT levels are closely-correlated with BMI. These findings suggest that HCV infection interferes with fat and lipid metabolism in patients with chronic HCV infection, and the serum leptin levels might be a reflection of the abnormalities in fat and lipid metabolism resulted from viral infection and related hepatic necroinflammation. Further studies are warranted to elucidate the possible immunoregulatory role and potential therapeutic role of leptin in chronic HCV infection.

ACKNOWLEDGMENTS

We thank Dr. Jian-Ming Qiu from Department of Molecular Microbiology and Immunology, School of Medicine, University of Missouri, Columbia for his support and helpful reading of the manuscript.

REFERENCES

1 **Ebeling F.** Epidemiology of the hepatitis C virus. *Vox Sang* 1998; **74 Suppl 2**: 143-146
2 **Memon MI,** Memon MA. Hepatitis C: an epidemiological review. *J Viral Hepat* 2002; **9**: 84-100
3 **Niederau C,** Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, Nawrocki M, Kruska L, Hensel F, Petry W, Haussinger D. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998; **28**: 1687-1695
4 **Goodman ZD,** Ishak KG. Histopathology of hepatitis C virus infection. *Semin Liver Dis* 1995; **15**: 70-81
5 **Fischer HP,** Willsch E, Bierhoff E, Pfeifer U. Histopathologic findings in chronic hepatitis C. *J Hepatol* 1996; **24**: 35-42
6 **Ramalho F.** Hepatitis C virus infection and liver steatosis. *Antiviral Res* 2003; **60**: 125-127
7 **Walsh MJ,** Vanags DM, Clouston AD, Richardson MM, Purdie DM, Jonsson JR, Powell EE. Steatosis and liver cell apoptosis in chronic hepatitis C: a mechanism for increased liver injury. *Hepatology* 2004; **39**: 1230-1238
8 **Serfaty L,** Andreani T, Giral P, Carbonell N, Chazouilleres O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001; **34**: 428-434
9 **Sabile A,** Perlemuter G, Bono F, Kohara K, Demaugre F, Kohara M, Matsuura Y, Miyamura T, Brechot C, Barba G. Hepatitis C virus core protein binds to apolipoprotein AII and its secretion is modulated by fibrates. *Hepatology* 1999; **30**: 1064-1076
10 **Czaja AJ,** Carpenter HA, Santrach PJ, Moore SB. Host and disease-specific factors affecting steatosis in chronic hepatitis C. *J Hepatol* 1998; **29**: 198-206
11 **Adinolfi LE,** Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; **33**: 1358-1364
12 **Ong JP,** Younossi ZM, Speer C, Olano A, Gramlich T, Boparai N. Chronic hepatitis C and superimposed nonalcoholic fatty liver disease. *Liver* 2001; **21**: 266-271
13 **Hourigan LF,** Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, Powell EE. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999; **29**: 1215-1219
14 **Potter JJ,** Womack L, Mezey E, Anania FA. Transdifferentiation of rat hepatic stellate cells results in leptin expression. *Biochem Biophys Res Commun* 1998; **244**: 178-182
15 **Romero-Gomez M,** Castellano-Megias VM, Grande L, Irles JA, Cruz M, Nogales MC, Alcon JC, Robles A. Serum leptin levels correlate with hepatic steatosis in chronic hepatitis C. *Am J Gastroenterol* 2003; **98**: 1135-1141
16 **Piche T,** Vandenbos F, Abakar-Mahamat A, Vanbiervliet G, Barjoan EM, Calle G, Giudicelli J, Ferrua B, Laffont C, Benzaken S, Tran A. The severity of liver fibrosis is associated with high leptin levels in chronic hepatitis C. *J Viral Hepat* 2004; **11**: 91-96
17 **Piche T,** Gelsi E, Schneider SM, Hebuterne X, Giudicelli J, Ferrua B, Laffont C, Benzaken S, Hastier P, Montoya ML, Longo F, Rampal P, Tran A. Fatigue is associated with high circulating leptin levels in chronic hepatitis C. *Gut* 2002; **51**: 434-439
18 **Kaser S,** Kaser A, Vogel W, Patsch JR, Tilg H. Interferon-alpha suppresses leptin levels: studies in interferon-alpha treated patients with hepatitis C virus infection and murine adipocytes. *Eur Cytokine Netw* 2002; **13**: 225-229
19 **Widjaja A,** Wedemeyer H, Tillmann HL, Horn R, Ockenga J, Jaeckel E, von zur Muhlen A, Manns MP, Brabant G. Hepatitis C and the leptin system: bound leptin levels are elevated in patients with hepatitis C and decrease during antiviral therapy. *Scand J Gastroenterol* 2001; **36**: 426-431
20 **Crespo J,** Rivero M, Fabrega E, Cayon A, Amado JA, Garcia-Unzeta MT, Pons-Romero F. Plasma leptin and TNF-alpha levels in chronic hepatitis C patients and their relationship to hepatic fibrosis. *Dig Dis Sci* 2002; **47**: 1604-1610
21 **Giannini E,** Ceppa P, Botta F, Mastracci L, Romagnoli P, Comino I, Pasini A, Risso D, Lantieri PB, Icardi G, Barreca T, Testa R. Leptin has no role in determining severity of steatosis and fibrosis in patients with chronic hepatitis C. *Am J Gastroenterol* 2000; **95**: 3211-3217

22 **Gurrici S,** Hartriyanti Y, Hautvast JG, Deurenberg P. Differences in the relationship between body fat and body mass index between two different Indonesian ethnic groups: the effect of body build. *Eur J Clin Nutr* 1999; **53**: 468-472

23 **Wang J,** Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr* 1994; **60**: 23-28

24 **Nagy TR,** Gower BA, Trowbridge CA, Dezenberg C, Shewchuk RM, Goran MI. Effects of gender, ethnicity, body composition, and fat distribution on serum leptin concentrations in children. *J Clin Endocrinol Metab* 1997; **82**: 2148-2152

25 **Perez-Bravo F,** Albala C, Santos JL, Yanez M, Carrasco E. Leptin levels distribution and ethnic background in two populations from Chile: Caucasian and Mapuche groups. *Int J Obes Relat Metab Disord* 1998; **22**: 943-948

26 **Ellis KJ,** Nicolson M. Leptin levels and body fatness in children: effects of gender, ethnicity, and sexual development. *Pediatr Res* 1997; **42**: 484-488

27 **He Q,** Horlick M, Thornton J, Wang J, Pierson RN, Heshka S, Gallagher D. Sex and race differences in fat distribution among Asian, African-American, and Caucasian prepubertal children. *J Clin Endocrinol Metab* 2002; **87**: 2164-2170

28 **Moriya K,** Yotsuyanagi H, Shintani Y, Fujie H, Ishibashi K, Matsuura Y, Miyamura T, Koike K. Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. *J Gen Virol* 1997; **78**(Pt 7): 1527-1531

29 **Yin CH,** Wang BE, Ma H, Jia JD, Shen FJ. Leptin and liver fibrosis. *Zhonghua Ganzangbing Zazhi* 2003; **11**: 60-61

30 **Uygun A,** Kadayifci A, Yesilova Z, Erdil A, Yaman H, Saka M, Deveci MS, Bagci S, Gulsen M, Karaeren N, Dagalp K. Serum leptin levels in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2000; **95**: 3584-3589

31 **Rosenbaum M,** Nicolson M, Hirsch J, Heymsfield SB, Gallagher D, Chu F, Leibel RL. Effects of gender, body composition, and menopause on plasma concentrations of leptin. *J Clin Endocrinol Metab* 1996; **81**: 3424-3427

32 **Nagy TR,** Gower BA, Trowbridge CA, Dezenberg C, Shewchuk RM, Goran MI. Effects of gender, ethnicity, body composition, and fat distribution on serum leptin concentrations in children. *J Clin Endocrinol Metab* 1997; **82**: 2148-2152

33 **Ostlund RE,** Yang JW, Klein S, Gingerich R. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab* 1996; **81**: 3909-3913

34 **Havel PJ,** Kasim-Karakas S, Dubuc GR, Mueller W, Phinney SD. Gender differences in plasma leptin concentrations. *Nat Med* 1996; **2**: 949-950

35 **Saad MF,** Damani S, Gingerich RL, Riad-Gabriel MG, Khan A, Boyadjian R, Jinagouda SD, el-Tawil K, Rude RK, Kamdar V. Sexual dimorphism in plasma leptin concentration. *J Clin Endocrinol Metab* 1997; **82**: 579-584

36 **Testa R,** Franceschini R, Giannini E, Cataldi A, Botta F, Fasoli A, Tenerelli P, Rolandi E, Barreca T. Serum leptin levels in patients with viral chronic hepatitis or liver cirrhosis. *J Hepatol* 2000; **33**: 33-37

37 **Wang YJ,** Wu JC, Lee SD, Tsai YT, Lo KJ. Gonadal dysfunction and changes in sex hormones in postnecrotic cirrhotic men: a matched study with alcoholic cirrhotic men. *Hepatogastroenterology* 1991; **38**: 531-534

38 **Giannini E,** Botta F, Cataldi A, Tenconi GL, Ceppa P, Barreca T, Testa R. Leptin levels in nonalcoholic steatohepatitis and chronic hepatitis C. *Hepatogastroenterology* 1999; **46**: 2422-2425

39 **Kalaivanisailaja J,** Manju V, Nalini N. Lipid profile in mice fed a high-fat diet after exogenous leptin administration. *Pol J Pharmacol* 2003; **55**: 763-769

40 **Schettler V,** Monazahian M, Wieland E, Ramadori G, Grunewald RW, Thomssen R, Muller GA. Reduction of hepatitis C virus load by H.E.L.P.-LDL apheresis. *Eur J Clin Invest* 2001; **31**: 154-155

41 **Enjoji M,** Nakamuta M, Kinukawa N, Sugimoto R, Noguchi K, Tsuruta S, Iwao M, Kotoh K, Iwamoto H, Nawata H. Beta-lipoproteins influence the serum level of hepatitis C virus. *Med Sci Monit* 2000; **6**: 841-844

42 **Greco AV,** Mingrone G, Favuzzi A, Capristo E, Gniuli D, Addolorato G, Brunani A, Cavagnin F, Gasbarrini G. Serum leptin levels in post-hepatitis liver cirrhosis. *J Hepatol* 2000; **33**: 38-42

43 **Faggioni R,** Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. *FASEB J* 2001; **15**: 2565-2571

44 **Lord GM,** Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998; **394**: 897-901

45 **Faggioni R,** Jones-Carson J, Reed DA, Dinarello CA, Feingold KR, Grunfeld C, Fantuzzi G. Leptin-deficient (ob/ob) mice are protected from T cell-mediated hepatotoxicity: role of tumor necrosis factor alpha and IL-18. *Proc Natl Acad Sci USA* 2000; **97**: 2367-2372

46 **Martin-Romero C,** Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin enhances activation and proliferation of human circulating T lymphocytes. *Cell Immunol* 2000; **199**: 15-24

47 **Farooqi IS,** Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S, Lechler RI, DePaoli AM, O'Rahilly S. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 2002; **110**: 1093-1103

48 **Motivala SJ,** Dang J, Obradovic T, Meadows GG, Butch AW, Irwin MR. Leptin and cellular and innate immunity in abstinent alcoholics and controls. *Alcohol Clin Exp Res* 2003; **27**: 1819-1824

49 **Siegmund B,** Lehr HA, Fantuzzi G. Leptin: a pivotal mediator of intestinal inflammation in mice. *Gastroenterology* 2002; **122**: 2011-2025

50 **Jacobson Brown PM,** Neuman MG. Immunopathogenesis of hepatitis C viral infection: Th1/Th2 responses and the role of cytokines. *Clin Biochem* 2001; **34**: 167-171

51 **Fan X,** Liu W, Li C. Determination of serum cytokines in individuals with HCV infection. *Zhonghua Shiyan He Linchuang Bingduxue Zazhi* 2000; **14**: 145-147

52 **Tsai SL,** Huang SN. T cell mechanisms in the immunopathogenesis of viral hepatitis B and C. *J Gastroenterol Hepatol* 1997; **12**: S227-S235

53 **Negro F,** Krawczynski K, Quadri R, Rubbia-Brandt L, Mondelli M, Zarski JP, Hadengue A. Detection of genomic and minus-strand of hepatitis C virus RNA in the liver of chronic hepatitis C patients by strand-specific semiquantitative reverse-transcriptase polymerase chain reaction. *Hepatology* 1999; **29**: 536-542

54 **Umemura T,** Yoshizawa K, Ota M, Katsuyama Y, Inada H, Tanaka E, Kiyosawa K. Analysis of T cell repertoire in the liver of patients with chronic hepatitis C. *Clin Exp Immunol* 2000; **121**: 120-126

55 **Gorden P,** Gavrilova O. The clinical uses of leptin. *Curr Opin Pharmacol* 2003; **3**: 655-659

56 **Matarese G,** Sanna V, Fontana S, Zappacosta S. Leptin as a novel therapeutic target for immune intervention. *Curr Drug Targets Inflamm Allergy* 2002; **1**: 13-22

57 **Huang L,** Li C. Leptin: a multifunctional hormone. *Cell Res* 2000; **10**: 81-92

Science Editor Wang XL and Guo SY **Language Editor** Elsevier HK