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Fatty liver and chronic inflammation in Chinese adults

Pei-Wen Wang [a,*], Ching-Jung Hsieh [a], Leung-Chit Psang [b], Yu-Fan Cheng [b], Chia-Wei Liou [c], Shao-Wen Weng [a], Jung-Fu Chen [a], I-Ya Chen [a], Rong-Hwai Li [b], Hock-Liew Eng [d]

[a] Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, 123 Ta-Pei Road, Niao-Sung Hsiang, Kaohsiung Hsien 83305, Taiwan
[b] Department of Radiology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[c] Department of Neurology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[d] Department of Pathology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 1 November 2007
Accepted 7 April 2008
Published on line 5 June 2008

Keywords:
Fatty liver
Insulin resistance
Metabolic syndrome
C-reactive protein
Adiponectin

ABSTRACT

Objective: To investigate the significance of fatty liver as predictor of insulin resistance (IR) and chronic inflammation.

Research design and methods: This cross-sectional study included 450 adults of Han Chinese origin aged ≥35. Excluded were cases with hepatitis B or C, alcoholic liver disease, or currently using thiazolidinedione. The volunteers were screened for the presence of the components of metabolic syndrome (MtS). IR index was estimated by the homeostasis model assessment. The fatty liver index was evaluated by computed tomography, calculated as the liver/spleen (L/S) ratio arrived at by averaging Hounsfield values obtained for five 3-mm slices. Serum levels of adiponectin, C-reactive protein (CRP), leptin, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were checked in 100 subjects with low-L/S ratio and 100 age- and sex-matched controls.

Results: Fatty liver index correlated with all MtS traits and IR index. The values of L/S ratios in subjects with 0, 1, 2, 3 and ≥4 traits of MtS were 1.25 ± 0.13, 1.18 ± 0.16, 1.12 ± 0.21, 1.05 ± 0.25 and 0.92 ± 0.25, respectively ($p < 0.001$). In our stepwise regression analysis to compare the L/S ratios to the conventional traits of MtS for association with adipokine dysregulation, we found L/S ratio to be independently associated with most of them: adiponectin ($p < 0.001$), CRP ($p < 0.001$), IL-6 ($p = 0.005$) and TNF-α ($p = 0.014$).

Conclusion: In Chinese, fatty liver index correlated well with IR index and can be a better marker of chronic inflammation than the conventional components of MtS.

1. Introduction

All traits of metabolic syndrome (MtS) are risk factors for atherosclerosis [1–4]. Although the original conceptualization of this syndrome was based on insulin resistance (IR) in the metabolic action of insulin, the pathogenesis remained unclear [1]. Accumulating evidence suggests that deranged adipocyte metabolism and altered body fat distribution are

* *Corresponding author*. Tel.: +886 7 7317123x8302; fax: +886 7 7322402.
E-mail addresses: wangpw@adm.cgmh.org.tw, c2607c@ms56.hinet.net (P.-W. Wang).
0168-8227/$ – see front matter
doi:10.1016/j.diabres.2008.04.014

important determinants of IR [5–10]. Studies in lipoatrophic patients [11,12] and fatless mice [13] have demonstrated that fat accumulation in liver and skeletal muscle is associated with IR. Fat accumulation in an insulin-sensitive tissue is an important determinant of the latter's sensitivity to insulin [5,6,14]. Therefore, fatty liver, or hepatic steatosis, is no longer considered a benign manifestation [15–18].

Recent understanding of the molecular events linking excessive fat to IR has focused on oxidative stress and chronic inflammation in accumulated adipose tissue [19–25]. This study is designed to examine the relationship between fatty liver, MtS and the adipokine regulation in the Chinese population.

2. Research design and methods

2.1. Subjects

Four hundred and fifty volunteers (90 with type 2 diabetes (T2DM), 44 with impair fasting glucose (IFG), and 316 with normal plasma glucose) participated in the study. Glucose dysregulation status was determined according to the 1997 diagnostic criteria of American diabetic association, which was defined as IFG when subjects with fasting plasma glucose (FPG) between 110 and 125 mg/dL (6.1–6.9 mmol/L) and defined as diabetes when subjects with FPG at least 126 mg/dL (≥7 mmol/L). The study group included 89 patients from the Meta/Endo clinic and 361 subjects from our health screening center, as well as some medical center employees. All subjects were 35 years old or older and of Han Chinese origin. They were excluded if they had type 1 diabetes, were being treated with thiazolidinedione, had secondary diabetes or hypertension caused by endocrinopathy or drug use, were carriers of hepatitis B or C, and were chronic alcohol drinkers.

The participants were divided into two groups: those who had MtS ($N = 156$) and those who did not ($N = 294$). Diagnosis of MtS was based on the definition by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [26,27]. The waist circumference cut-off point in the ATP III criteria was revised as suggested by the 2000 World Health Organization (WHO) Asia-Pacific Guidelines because the absolute risk of diabetes and cardiovascular disease (CVD) is higher in Asians who are less obese [28–30]. Participants were defined as having MtS if they had three or more of the following five components of metabolic syndrome: (1) waist circumference ≥90 cm in men and ≥80 cm in women, (2) triglycerides ≥150 mg/dL, (3) high-density lipoprotein (HDL) <40 mg/dL in men and <50 mg/dL in women, (4) blood pressure ≥130/85 mmHg or if they were taking antihypertension medication and (5) fasting plasma glucose ≥110 mg/dL or if they were taking hypoglycemic medication.

2.2. Laboratory method

2.2.1. Measurement of clinical variables of cardiometabolic risks

We screened the fasting glucose, insulin, lipid profile and liver enzyme levels of all subjects. The blood pressure, body height, body weight, waist and hip circumferences were recorded. IR index in non-diabetic subjects was estimated by measuring their fasting plasma glucose and insulin levels, and evaluating them by homeostasis model assessment [31].

2.2.2. Assessment of liver fat

Liver fat was assessed in all subjects by computed tomography (CT) examination. The examination was performed with a GE Prospeed (GE Medical System, Yokogawa, Japan) using 80 Kvp, 60 mAs, and slice thickness of 3 mm with a scan time of 1 s. Five slices were acquired from each individual on the basis of a scout view from the dome of the liver. The average of the five Hounsfield values obtained for each slice was calculated and reported as the computed tomography density (CTD) of liver for each test subject [32]. The ratio of liver to spleen (L/S ratio) for CT attenuation, as modified from the report of Kelly et al. [46], was determined by calculating the mean Hounsfield units of the liver (2 times of right lobe value + 1 time of left lobe value)/3, and that of the spleen. A L/S ratio <1 was considered to be indicative of fatty liver.

2.2.3. Measurement of cytokines

One hundred subjects with the lowest L/S ratio and 100 age- and sex-matched controls were examined. None were taking statin, fibrate or thiazolidinedione. Adipokine level measurements were based on plasma that had been collected after overnight fasting and frozen. The specimens were frozen at −70 °C and measured in duplicate by immunoassay kits. The adiponectin kit (Quantikine, Human Adiponectin/Acrp30 Immunoassay), the interleukin-6 (IL-6) kit (Quantikine, Human IL-6 Immunoassay) and the tumor necrosis factor-α (TNF-α) kit (Quantikine, Human TNF-α/TNFSF1A Immunoassay), which were purchased from R&D Systems (Minneapolis, MN, USA) had a minimum detectable dosage of 0.246 ng/mL, 0.70 pg/mL and 1.6 pg/mL, respectively. The high-sensitive C-reactive protein (hs-CRP) was measured by an enzymatically amplified "two-step" sandwich-type immunoassay (US C-Reactive Protein ELISA, Diagnostic Systems Laboratories Inc., Texas, USA), which had a detection limit of 1.6 ng/mL. The leptin level was measured by a commercially available radioimmunoassay kit (Human Leptin RIA Kit, LINCO Research, Missouri, USA) with a detection limit of 0.5 ng/mL.

2.2.4. Statistical analysis

We performed logarithmic transformation of adipokine data because the original values were non-normally distributed. Continuous variables were expressed as means ± S.D. Comparison of continuous and categorical data was performed using general linear model and Chi-square test, respectively. The relationships between the variables were analyzed by Pearson correlation and stepwise multiple regression analyses. A $p < 0.05$ was considered significant. All statistical operations were performed using the Statistical Package for Social Science Program (SPSS for Windows, Version 11.5; SPSS, Chicago).

3. Results

3.1. Prevalence of fatty liver

A L/S ratio <1 was considered to indicate the presence of fatty liver. As such, the overall prevalence of fatty liver was 24.7%

Table 1 – Comparison of clinical characteristics of individuals with fatty liver (L/S < 1.0) and those without (L/S ≥ 1.0)

	L/S < 1.0	L/S ≥ 1.0	p
Age (year)	51.0 ± 9.8	50.4 ± 10.2	0.55
Sex (female/male)	62/49	210/129	0.25
Waist circumference (cm)	92.8 ± 9.9	87.6 ± 9.8	<0.001
BMI (kg/m^2)	27.1 ± 3.6	24.2 ± 3.3	<0.001
Hypertension (%)	55/111 (49.5%)	105/339 (30.9%)	0.001
Hyperglycemia (%)	57/111 (51.4%)	79/339 (23.3%)	<0.001
HDL-cholesterol (mg/dL)	42 ± 9	48 ± 11	<0.001
Triglyceride (mg/dL)	175 ± 108	114 ± 70	<0.001
LDL-cholesterol (mg/dL)	120 ± 33	117 ± 32	0.39
AST (U/L)	32 ± 24	23 ± 13	0.001
ALT (U/L)	42 ± 39	22 ± 17	<0.001

Hypertension subjects were taking antihypertension medication or their blood pressure was at least 130/85 mmHg. Hyperglycemic subjects were taking antidiabetic agents or their fasting plasma glucose was at least 110 mg/dL (7 mmol/L).

(111/450) in our series of individuals aged 35 or older. The clinical characteristics of individuals with or without fatty liver are listed in Table 1. The 156 subjects with MtS had a significantly greater percent (68/156; 43.6%) of fatty liver than the 294 subjects who did not have MtS (43/294; 14.6%) ($p < 0.001$). There was a significant difference in the prevalence of fatty liver in individuals with T2DM (44/90; 48.9%), IFG (12/44; 27.3%) and normal blood glucose (55/316; 17.4%) ($p < 0.001$). In all 450 volunteers, there was a good correlation between L/S ratios and serum levels of alanine transferase (ALT) ($r = -0.38$, $p < 0.001$).

3.2. Relation of fatty liver to the trait of metabolic syndrome

As can be seen in Table 2, the fatty liver index (L/S ratio) correlated with BMI ($r = -0.39$, $p < 0.001$), waist circumference ($r = -0.27$, $p < 0.001$), hypertension status ($r = -0.23$, $p < 0.001$), hyperglycemia status ($r = -0.27$, $p < 0.001$), high-density lipoprotein (HDL) ($r = 0.25$, $p < 0.001$) and triglyceride ($r = -0.31$, $p < 0.001$).

The values of L/S ratios in subjects with 0 ($N = 65$), 1 ($N = 111$), 2 ($N = 118$), 3 ($N = 85$) and ≥4 ($N = 71$) traits of MtS were 1.25 ± 0.13, 1.18 ± 0.16, 1.12 ± 0.21, 1.05 ± 0.25 and 0.92 ± 0.25, respectively. The difference was significant ($p < 0.001$).

The prevalence of fatty liver in subjects with 0, 1, 2, 3 and ≥4 traits of MtS were 6.2% (4/65), 9.9% (11/111), 23.7% (28/118), 32.9% (28/85) and 56.3% (40/71), also statistically significant ($p < 0.001$).

In non-diabetic subjects, IR index estimated by the homeostasis model assessment correlated with the L/S ratio very well ($r = -0.21$, $p < 0.001$).

3.3. Physiological significance of fatty liver in subjects with diabetes and metabolic syndrome

In the subgroup with T2DM, those with fatty liver were found to have increased body mass index (BMI) (27.4 ± 3.7 kg/m^2 vs. 25.3 ± 4.1 kg/m^2, $p = 0.015$) and elevated levels of plasma triglyceride (188.9 ± 130.6 mg/dL vs. 120.1 ± 61.2 mg/dL, $p = 0.002$) and ALT (46.5 ± 28.5 U/L vs. 27.1 ± 17.2 U/L, $p < 0.001$) compared with T2DM patients without fatty liver.

In the subgroup with MtS, more subjects with fatty liver had a fasting glucose level >110 mg/dL than MtS subjects without fatty liver (44/68 = 64.7% vs. 40/88 = 45.5%, $p = 0.02$).

3.4. The relationship of inflammatory cytokines to metabolic variables

The relationships between adipokines and metabolic variables are shown in Table 3. Leptin correlated with BMI ($r = 0.42$, $p < 0.001$) and waist circumference ($r = 0.20$, $p = 0.04$). Adiponectin correlated with HDL ($r = 0.38$, $p < 0.001$), L/S ratio ($r = 0.35$, $p < 0.001$), BMI ($r = -0.20$, $p = 0.005$) and triglyceride

Table 2 – Relationship of fatty liver to metabolic variables in the 450 cases

	BMI	Waist	Hypertension	Hyperglycemia	HDL	TG	L/S ratio	IR
BMI	1							
Waist	0.68**	1						
Hypertension	0.32**	0.25**	1					
Hyperglycemia	0.25**	0.20**	0.21**	1				
HDL	−0.38**	−0.33**	−0.16**	−0.16**	1			
TG	0.26**	0.23**	0.10*	0.16**	−0.42**	1		
L/S ratio	−0.39**	−0.27**	−0.23**	−0.27**	0.25**	−0.31**	1	
IR	0.36**	0.26**	0.18**	0.37**	−0.25**	0.31**	−0.21**	

Hypertension subjects were taking antihypertension medication or their blood pressure was at least 130/85 mmHg. Hyperglycemic subjects were taking antidiabetic agents or their fasting plasma glucose was at least 110 mg/dL (7 mmol/L). IR index by the homeostasis model assessment was estimated in non-diabetic subjects only.

* p value < 0.05.

** p value < 0.01.

Table 3 – Relationship of inflammatory cytokines to metabolic variables

	BMI	Waist	Hypertension	Hyperglycemia	HDL	TG	L/S ratio	IR
Adiponectin	−0.20**	−0.09	−0.13	−0.10	0.38**	−0.15*	0.35**	−0.21**
CRP	0.38**	0.24**	0.15*	0.14	−0.13	0.10	−0.29**	0.22**
Leptin	0.42**	0.20**	−0.09	−0.07	0.07	0.07	−0.12	0.28**
IL-6	0.30**	0.25**	0.17*	0.04	−0.18*	−0.02	−0.23**	0.15
TNF-α	0.13	0.03	0.03	0.07	−0.11	0.09	−0.17*	0.04

Hypertension subjects were taking antihypertension medication or their blood pressure was at least 130/85 mmHg. Hyperglycemic subjects were taking antidiabetic agents or their fasting plasma glucose was at least 110 mg/dL (7 mmol/L). IR index by the homeostasis model assessment was estimated in non-diabetic subjects only.

* p value < 0.05.

** p value < 0.01.

($r = -0.15$, $p = 0.03$). CRP correlated with BMI ($r = 0.38$, $p < 0.001$), L/S ratio ($r = -0.29$, $p < 0.001$), waist circumference ($r = 0.24$, $p = 0.001$) and hypertension ($r = 0.15$ $p = 0.04$). IL-6 correlated with BMI ($r = 0.30$, $p < 0.001$), waist circumference ($r = 0.25$, $p < 0.001$), L/S ratio ($r = -0.23$, $p = 0.001$), HDL ($r = -0.18$, $p = 0.01$) and hypertension ($r = 0.17$, $p = 0.02$). TNF-α correlated with L/S ratio ($r = -0.17$, $p = 0.02$).

3.5. *Independent predictor of adipokines*

We used stepwise regression analysis to compare the fatty liver index to the five known components of MtS by ATP III definition and clarify their association with adipokine dysregulation. HDL ($p < 0.001$) and L/S ratio ($p < 0.001$) were independently related to serum level of adiponectin (for the entire model, $R^2 = 0.21$). L/S ratio ($p < 0.001$) and waist circumference ($p = 0.018$) were independent predictors of serum level of hs-CRP (for the entire model, $R^2 = 0.11$). L/S ratio ($p = 0.005$) and waist circumference ($p = 0.007$) were independent predictors of serum level of IL-6 (for the entire model, $R^2 = 0.095$). Waist circumference ($R^2 = 0.042$, $p = 0.004$) was independent predictor of serum level of leptin. L/S ratio ($R^2 = 0.03$, $p = 0.014$) was independent predictor of serum level of TNF-α. Among the five cytokines assayed, four, three and one were independently predicted by L/S ratio, waist circumference and HDL, respectively. The L/S ratio could predict more number of adipokines as well as the most informative adipokines (adiponectin and hsCRP) in this study. It was a better predictor of adipokines dysregulation than the five known components of MtS defined by ATP III.

4. Discussion

Despite the ongoing debate regarding the clinical use of MtS [33–35], its constituent risk factors are well recognized as predictors of cardiovascular disease and T2DM [36–39]. As cardiometabolic risk factors tend to cluster, patients often have additional subclinical features that can be discovered through comprehensive evaluation. This study provides data regarding fatty liver in a Chinese population in Taiwan. Like a previous study of Chinese population in Shanghai [40], it found a strong association between fatty liver and the risk factors characteristic of MtS.

Based on our studies using CT imaging, there is a much higher prevalence of fatty liver in patients with type 2 diabetes (48.9%) and MtS (43.6%) than in those without these metabolic defects (14.6–17.4%) in the people of Han Chinese origin in Taiwan. The prevalence was similar to that observed by a study using ultrasonography in a Chinese population in Shanghai (type 2 diabetes, 41.2%; MtS, 48.2%) [40], though our results were more precisely quantitated using L/S ratio. We also found a significant association between fatty liver index and individual traits of MtS, including waist circumference, hypertension status, a fasting glucose level >110 mg/dL, plasma HDL and triglyceride levels. Furthermore, the more components of MtS present in an individual, the lower the fatty liver index, suggesting that the fatty liver index may be able to reflect the severity of this metabolic disorder quantitatively. This quantitative index can be well estimated by our routine liver function test of ALT. Our findings support the data of Vozarova et al. [41], in which elevated ALT levels in cases of nonalcoholic fatty liver disease (NAFLD) were associated with decreased hepatic insulin sensitivity and predictive of future development of diabetes. These observations are enforced by a recent publication of Lee et al. [42] who pointed out that serum gamma-glutamyl transferase (GGT) predicts CVD morbidity and mortality, suggesting that GGT can be used as a marker of metabolic and cardiovascular risk. Haffner further proposed that elevated liver enzymes, an indicator of non-alcoholic fatty liver disease (NAFLD), may comprise an additional component of the MtS [43].

The ATP III criteria have been evaluated by Cheal et al. for their ability to identify IR, and they found that the individual components varied in their relationship to IR, with the obesity and lipid criteria being most useful [44]. In our series, individuals with T2DM and fatty liver (L/S ratio <1.0) had a significantly greater increase in BMI and plasma triglyceride levels than such patients without fatty liver. We also found that a greater percentage of individuals with MtS and fatty liver had a fasting glucose >110 mg/dL than MtS individuals without it. These data suggest that fatty liver index may provide additional information about IR for those with diabetes or MtS when diagnosed using the ATP III criteria. Toledo et al. in a study using CT imaging has recently reported that hepatic steatosis influenced the severity and composition of dyslipidemia in T2DM patients by increasing triglycerides, reducing HDL levels and increasing small, dense LDL [45]. Using the more sophisticated euglycemic insulin infusion for insulin sensitivity measurement and ($^2H_2$) glucose infusion to assess endogenous glucose production, Kelly et al. [46] have also demonstrated that individuals with T2DM and fatty liver

were more insulin resistant and had more severe dyslipidemia than those who had diabetes but no fatty liver.

Taking an adipocentric point of view, we found that fatty liver index, waist circumference and serum HDL level were better predictors of the proinflammatory adipokines than hyperglycemia and hypertension. With regard to fatty liver index and waist circumference, fatty liver index could independently predict adiponectin (but not leptin), while waist circumference could independently predict leptin (but not adiponectin). The relationship between adiponectin and fatty liver in our study has been supported by several previous clinical studies [47–50]. The role of leptin in liver injury is less frequently mentioned [51], though it has been suggested that the adiponectin–leptin ratio is a more efficacious measure of IR [52].

Leptin is secreted from adipocytes in proportion to adipose tissue mass [53]. What is known about its relationship with IR comes from studies of rare leptin-deficiency patients with lipodystrophy [11,12]; most obese insulin resistant individuals are not in the same condition. Circulating adiponectin levels, on the contrary, correlate more with hyperinsulinemia and IR than obesity or body fat [54]. Although IR and obesity are both associated with lower plasma adiponectin concentrations, Abbasi et al. have demonstrated that adiponectin levels were more closely related to differences in insulin-mediated glucose disposal than BMI [55]. Furthermore, low-plasma adiponectin has been found to be an independent risk factor for future development of T2DM [56,57], not for obesity [58]. The beneficial effect of thiazolidinedione on insulin sensitivity and reversing the abnormality in hepatic fat mobilization is proved to be related to its ability to increase plasma adiponectin concentrations [59]. In addition to being able to predict adiponectin, we found the fatty liver index independently predict serum hs-CRP levels. It has been reported that mild chronic elevations of CRP concentrations are independently predictive of future CVD events both in women and men [60,61]. Recently, in the Framingham Offspring Study of 3037 subjects, CRP has also been proved to predict new CVD events over a 7-year follow-up [62]. Taken together, these findings support the notion that fatty liver plays an important role in the chronic inflammation triggering of CVD.

In conclusion, in the people of Han Chinese origin in Taiwan, the fatty liver index can be a quantitative index for MtS and may be a good marker of IR related to chronic inflammation than the currently recognized components of MtS.

Acknowledgements

This work was supported by research grant (CMRPG8065) from Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Taiwan.

Conflict of interest

There are no conflicts of interest.

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