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RAPID COMMUNICATION

Visceral fat and insulin resistance as predictors of non-alcoholic steatohepatitis

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Abstract

AIM: To examine whether visceral fat is associated with non-alcoholic steatohepatitis (NASH), to assess for parameters associated with visceral adiposity and to investigate for factors associated with fibrotic severity in NASH.

METHODS: Thirty NASH and 30 control subjects underwent biochemical tests, anthropometric assessment, bioelectrical impedance, dual energy X-ray absorptiometry and abdominal fat study by CT scan. Liver biopsies were graded according to the Brunt criteria.

RESULTS: NASH subjects had elevated blood pressure, body mass index, waist circumference and waist-to-hip ratio. A greater number of diabetes mellitus, impaired glucose tolerance test and HOMA-IR > 3.5 were found in NASH patients. HOMA-IR > 2.8 (OR 20.98, 95% CI 3.22-136.62; $P < 0.001$) and visceral fat area > 158 cm^2 (OR 18.55, 95% CI 1.60-214.67; $P = 0.019$) were independent predictors for NASH. Advanced stage of NASH was found in 15 (50%) patients. HOMA-IR > 3.5 (OR 23.12, 95% CI 2.00-266.23; $P = 0.012$) and grading of portal inflammation (OR 7.15, 95% CI 1.63-31.20; $P = 0.009$) were determined as independent risk factors for advanced stage of NASH.

CONCLUSION: Obesity (especially central obesity) and metabolic syndrome are common in Thai NASH. Insulin resistance and elevated visceral fat are risk factors for the presence of NASH. The advanced stage of the disease is related to insulin resistance.

Key words: Non-alcoholic steatohepatitis; Visceral fat; Insulin resistance; Metabolic syndrome; Obesity

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INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is characterized by morphologic features indistinguishable from alcoholic liver diseases in patients who do not consume significant amount of alcohol[1,2]. Up to 20% of NASH progresses to cirrhosis over approximately 5-7 years[3]. The incidence of NASH and non-alcoholic fatty liver disease (NAFLD) are on the rise because of the global epidemic of obesity and type 2 diabetes mellitus[4]. From available data, the prevalence rates of NAFLD and NASH in western populations are in the range of 17%-33% and 5.7%-17%[5]. NASH and NAFLD are no longer considered strictly western diseases since they have been identified in urban areas around the world. Epidemiological studies in Asian countries found that 9.3%-36.9% of patients had fatty liver on ultrasound examination[6-8]. Metabolic syndrome, which is defined by the guideline of the Adult Treatment Panel Ⅲ (ATPⅢ) is prevalent in NAFLD and even more so in NASH[9]. From cross-sectional studies of NAFLD patients, obesity is found in 40%-100%, diabetes mellitus in 21%-75% and hyperlipidemia in 21%-83%[3,10-12]. Few studies have reported the association between features of metabolic syndrome and NASH in Asian patients[7,13]. In general, obesity is associated with NASH, nevertheless some Asian patients with metabolic syndrome do not have a high body mass index (BMI)[2]. Central (or visceral) obesity seems to be more important than total body obesity[14]. Visceral fat is a precursor to the increased lipolysis and free fatty acid characteristic of metabolic syndrome[14]. Furthermore, visceral fat is a potent modulator of insulin action[14]. We therefore prospectively conducted a study to

examine whether visceral fat is associated with NASH, to assess for parameters associated with visceral adiposity and to investigate for factors associated with fibrotic severity in NASH.

MATERIALS AND METHODS

Patients

From 1 January 2004 to 31 December 2004, patients who had chronic elevation of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) more than 1.5 x upper normal limit for at least 3 mo, but were negative for hepatitis B or C viral markers, had no evidence of autoimmune liver diseases, hemochromatosis or Wilson's disease, as well as no history of herbal or potential hepatotoxic drug use, alcohol drinking more than 20 g/d in male and 10 g/d in female underwent percutaneous liver biopsy. The patients who had liver histology consistent with NASH based on the Brunt criteria[15] were invited for study participation within 6 mo after liver biopsy. Controls subjects that were age- and sex-matched with cases and had negative history for liver diseases, diabetes mellitus, hyperlipidemia, hypertension, and also had normal levels of serum transaminase and normal liver as seen by abdominal ultrasound, were recruited from the hospital personals. The study protocol was approved by the Hospital Ethical Committee and was carried out according to the Helsinki Declaration guideline. Written informed consent was obtained from study participants prior to the study.

Biochemical tests

After fasting for 12 h, venous blood was taken for glucose, insulin, total cholesterol, high-density cholesterol (HDL-C), low-density cholesterol (LDL-C), triglyceride and uric acid. Patients without diabetes mellitus and control subjects underwent a 75-g oral glucose tolerance test (OGTT). Diabetes mellitus and impaired glucose tolerance test (IGT) were defined according to American Diabetes Association guidelines[16]. The index of insulin resistance was calculated on the basis of fasting glucose and insulin, according to the homeostasis model assessment (HOMA-IR), which was equal to fasting insulin (mIU/L) x fasting glucose (mmol/L)/22.5[17].

Anthropometric and body fat assessment

The following anthropometric measurements were obtained: height, weight, BMI, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and triceps skin fold. WC was measured at the midpoint between the lower border of the rib cage and the iliac crest, whereas HC was measured at the widest point between hip and buttock. BMI was calculated by the Quetlet index: weight in kilograms/height in meters squared (kg/m^2)[18]. According to modified criteria from the Asia-Pacific guideline, obesity and overweight were defined as follows: obese, BMI $\geqslant$ 25 kg/m^2; overweight, BMI 23 to 24.9 kg/m^2, increased WC was defined as $\geqslant$ 90 cm in men and $\geqslant$ 80 cm in women, and increased WHR was defined as $\geqslant$ 0.90 in men and $\geqslant$ 0.85 in women[4,19]. Subjects were labeled as having metabolic syndrome by the presence of 3 or more of the following modified criteria of the ATPIII[9]: (1) fasting glucose $\geqslant$ 6.11 mmol/L; (2) central obesity (or increased WC) (3) blood pressure $\geqslant$ 130/85 mmHg or on treatment; (4) triglyceride level $\geqslant$ 1.70 mmol/L or on treatment; and (5) HDL-cholesterol < 1.04 mmol/L (men) and < 1.30 mmol/L (women). Body composition was studied by bioelectrical impedance (BIA) (Biodynamics Corp., Seattle, WA) based on the conductance of a small alternating electrical current in body water[20]. Total body fat, regional (abdominal and thigh) fat and body composition were directly measured by dual energy X-ray absorptiometry (DEXA) (GE Medical Systems, Madison, WI) with 2 peak kilovoltages of 0 and 38 keV, filtration method and 150 μA[20]. Abdominal fat distribution was assessed with a single-slice CT image at the level of the umbilicus (or at the L4 spine) by a helical CT scanner (GE Medical Systems, Milwaukee, WI) during suspended respirations with 120 kv, 200 mA and 10 mm slice thickness. The area of subcutaneous fat and visceral fat were clearly defined with CT density in the range of -150 to -50 Hounsfield units. The percentage of visceral fat was derived from the formula of visceral fat/total fat x 100[21].

Histology assessment

Liver biopsy was prepared with hematoxylin and eosin stain, and Masson trichrome stain. It was scored according to the Brunt criteria[15]. Steatosis was graded from 0 to 3, necroinflammation was graded from 0 to 3, ballooning degeneration was graded as mild or marked, and fibrosis was graded from 0 to 4[15]. According to modified criteria[22], NASH patients were categorized as having early stage if bridging fibrosis and/or cirrhosis were absent (stages 0-2) or as advanced stage if either of these features were present (stages 3-4).

Statistical analysis

The study was designed to have a statistical power of 0.80 to detect an absolute difference of visceral fat area of 30 cm^2 between the NASH group and the control group with a two-sided significance level of $P < 0.05$. Given the specified statistical power and a 1:1 ratio, enrollment of at least 29 cases into each group was required. Continuous variables were summarized as mean ± SD and categorical variables as frequencies and percentages. Statistical analysis of continuous variables was performed by Student's *t*-test or non-parametric test as appropriate. χ^2 or Fisher exact test was used for analysis of categorical variables. The odds ratio (ORs) and 95% confidence interval (CI) for the risk factors of NASH were calculated using a logistic regression model. Receiver operating characteristic curves (ROC) analysis was used to explore appropriate cutoffs for the continuous variables that do not have accepted cutoffs for clinical importance, (e.g., visceral fat, insulin, HOMA-IR levels for predictive factors of NASH; WHR, AST to ALT ratio, HOMA-IR levels for risk factors associated with the advanced stage of the disease). Variables with *P*-value < 0.05 and having the highest likelihood ratio among the same group were selected to enter stepwise

Table1 Demographic data (means ± SD)

	NASH (n = 30)	Control (n = 30)	P-value
Mean age (yr)	53.7 (7.0)	51.0 (6.7)	
Female (n, %)	25 (83.3)	26 (86.7)	
Systolic blood pressure (mmHg)	137.8 (15.6)	123.4 (16.5)	0.001
Diastolic blood pressure (mmHg)	81.6 (7.5)	77.1 (9.7)	0.048
Body mass index (BMI) (kg/m^2)	27.7 (3.9)	23.9 (3.3)	< 0.001
BMI classification[1] (n, %)			
Normal	2 (6.7)	12 (40)	< 0.001
Pre-obesity	2 (6.7)	8 (26.7)	
Obesity class Ⅰ	18 (60)	9 (30)	
Obesity class Ⅱ	8 (26.7)	1 (3.3)	
Triceps skin fold (mm)	28.9 (6.0)	25.0 (6.5)	0.02
Waist circumference (cm)	89.1 (8.9)	76.4 (8.0)	< 0.001
Waist to hip ratio	0.87 (0.1)	0.81 (0.1)	< 0.001
Fat mass (kg)	21.2 (5.1)	15.8 (4.5)	< 0.001
Abdominal fat (x 10^3, g)	6.0 (1.4)	3.8 (1.5)	< 0.001
Visceral fat area (cm^2)	147.8 (38.7)	92.9 (29.9)	< 0.001
Subcutaneous fat area (cm^2)	272.2 (85.1)	189.7 (64.9)	< 0.001
Visceral to total fat ratio	0.36 (0.09)	0.34 (0.10)	
Visceral to subcutaneous fat ratio	0.60 (0.23)	0.55 (0.33)	

NASH: non-alcoholic steatohepatitis. [1]By the definition of Asia BMI.

Table 2 Biochemical tests (means ± SD)

	NASH	Control	P-value
AST (IU/L)	70.9 (40.4)	19.9 (5.6)	< 0.001
ALT (IU/L)	116.1 (45.2)	35.2 (9.7)	< 0.001
AST/ALT	0.6 (0.2)	0.6 (0.2)	
Glucose (mmol/L)	6.8 (2.8)	5.0 (0.4)	0.02
Insulin (pmol/L)	108.6 (55.0)	38.6 (20.7)	< 0.001
HOMA-IR	4.8 (3.7)	1.2 (0.7)	< 0.001
Cholesterol (mmol/L)	5.4 (0.9)	5.1 (0.5)	
LDL-C (mmol/L)	3.4 (0.9)	3.6 (0.4)	
HDL-C (mmol/L)	1.2 (0.3)	1.2 (0.3)	
Triglyceride (mmol/L)	1.7 (0.7)	0.8 (0.5)	< 0.001
Uric acid (μmol/L)	317.4 (83.8)	263.5 (53.9)	0.01

NASH: non-alcoholic steatohepatitis.

multivariate logistic regression analysis. Data analysis was performed with Stata version 9.0. A P-value < 0.05 was taken as statistically significant.

RESULTS

During the study period, 47 patients who had chronic elevation of serum transaminase with negative result of investigations underwent percutaneous liver biopsy. The pathological diagnosis of NASH was confirmed in 31 patients. All of NASH patients except one case who refused to participate with the research were included in the study. Demographic data of 30 NASH patients and 30 control subjects are shown in Table 1.

Comparison between NASH and control subjects

NASH subjects had elevated systolic and diastolic blood pressure; hypertension was found in 15 (50%) NASH and 4 (13.3%) control participants. BMI, triceps skin fold, WC and WHR of NASH subjects were greater than those of control subjects (Table 1). Twenty-six (86.7%) of NASH had BMI consistent with the definition of obesity by the Asian-Pacific guideline compared with 10 (33.3%) from the control group (P < 0.001). Mean fat mass and percentage of fat mass of NASH were greater than those of the controls. The amount of thigh fat mass was not different between the two groups. The elevated fat mass was contributed primarily by abdominal fat mass which was greater in NASH patients than control subjects (6.0 ± 1.4 *vs* 3.8 ± 1.5 kg, P < 0.001). Although NASH patients had more visceral and subcutaneous abdominal fat than controls, the percentages of visceral fat of the NASH group were not elevated. Mean AST, ALT, fasting glucose, insulin, HOMA-IR, triglyceride and uric acid levels were all higher among the NASH group than the control group (Table 2). Fifteen (50%) members of NASH had HOMA-IR > 3.5 but none of controls had elevated HOMA-IR. Impaired glucose tolerance test and diabetes mellitus was more common in NASH (P < 0.001). Metabolic syndrome was found in 19 (63.3%) NASH and 2 (6.7%) control groups (P < 0.001). An elevated triglyceride level was found in 12 (40%) NASH and 1 (3.3%) control groups.

Table 3 Univariate analysis for predictive factors of NASH

Factor	Odds ratio	95% CI	P-value
Hypertension	6.50	1.82-23.21	0.004
Body mass index (kg/m^2)	1.38	1.14-1.67	0.001
Triceps skin fold (mm)	1.11	1.01-1.21	0.024
Waist circumference (cm)	1.18	1.09-1.29	< 0.001
Fat mass (kg)	1.28	1.11-1.47	0.001
Visceral fat area > 158 (cm^2)	19.33	2.31-161.55	< 0.001
Subcutaneous fat area (cm^2)	1.01	1.01-1.02	0.001
Glucose (mmol/L)	2.88	1.29-6.43	0.01
Insulin > 11.9 (pmol/L)	58.00	6.87-489.58	< 0.001
HOMA-IR > 2.8	38.50	7.41-199.87	< 0.001
Triglyceride > 1.70 (mmol/L)	19.33	2.31-161.55	0.006
Uric acid (μmol/L)	1.97	1.12-3.47	0.019

ROC analysis was applied and found that the cutoff values for the 3 continuous variables based on ROC were > 158 cm^2 for visceral fat area, > 11.9 pmol/L for insulin level, > 2.8 for HOMA-IR and > 1.7 mmol/L for triglyceride level based on the ATPIII guideline[9]. Visceral fat area > 158 cm^2 yielded a sensitivity of 40%, a specificity of 96.7% and a positive likelihood ratio (LR+) of 12. Insulin level > 11.9 pmol/L yielded a sensitivity of 66.7%, a specificity of 93.3% and a LR+ of 10. HOMA-IR > 2.8 yielded a sensitivity of 73.3%, a specificity of 93.3% and a LR+ of 11. The risk of the development of NASH is shown in Table 3. Twelve variables; hypertension, BMI, triceps skin fold, waist circumference, fat mass, visceral fat area, subcutaneous fat area, glucose, insulin, HOMA-IR, triglyceride, and uric acid were significantly associated with NASH by univariate analysis. To avoid multi-colinearity, only seven variables (i.e. hypertension, BMI, visceral fat area > 158 cm^2, insulin level > 11.9 pmol/L, HOMA-IR > 2.8, triglyceride > 1.7 mmol/L and uric acid level) were included in stepwise multivariate logistic model. Among them, HOMA-IR > 2.8 and visceral fat area > 158 cm^2 were independently associated with NASH with ORs of 20.98 (95% CI, 3.22-136.62; P < 0.001) and 18.55 (95% CI, 1.60-214.67; P = 0.019), respectively.

Table 4 Correlation of visceral fat with anthropometric and metabolic parameters

Parameter	Correlation coefficient (*r*)	*P*-value
Systolic blood pressure	0.31	0.02
Diastolic blood pressure	0.35	0.006
Body mass index	0.66	< 0.001
Abdominal fat	0.74	< 0.001
Glucose	0.39	0.002
Insulin	0.47	< 0.001
HOMA-IR	0.47	< 0.001
Triglyceride	0.38	0.003

Table 5 Univariate analysis for risk factors of advanced stage of NASH

Factor	Odds ratio	95% CI	*P*-value
Waist-to-hip ratio > 0.88	4.57	0.90-23.14	
AST/ALT ratio > 0.65	12.25	1.27-118.36	0.03
HOMA-IR > 3.5	7.56	1.50-38.15	0.014
Grading of portal inflammation	4.3	1.31-14.08	0.016
Grading of NASH	4.0	1.18-13.51	0.026
Grading of steatosis	1.02	0.38-2.73	

Correlation of visceral fat by CT scan with anthropometric and metabolic parameters

The correlation between visceral fat and systolic blood pressure, diastolic blood pressure, BMI, abdominal fat, fasting glucose, insulin, triglyceride and HOMA-IR levels are shown in Table 4. BMI and abdominal fat distribution were the two most powerful factors relating to visceral fat area.

Histological distribution of NASH and risk factors associated with advanced stage of NASH

According to the Brunt criteria for grading and staging of NASH[15], 9 (30%) had steatosis < 33%, 12 (40%) had steatosis 33%-66% and 9 (30%) had steatosis > 66%; 19 (63.3%) had mild ballooning degeneration and 11 (36.7%) had marked ballooning degeneration. Nineteen (63.3%) had grade 1 NASH, 5 (16.7%) had grade 2 and 6 (20%) had grade 3. One (3.3%) had stage 0, 7 (23.3%) had stage 1, 7 (23.3%) had stage 2, 14 (46.8%) had stage 3 and 1 (3.3%) had stage 4. All in all, there were 15 (50%) in advanced stages of NASH.

The cutoff values for the 3 continuous variables based on ROC were > 0.88 for WHR, > 0.65 for AST to ALT ratio and > 3.5 for HOMA-IR. WHR > 0.88 yielded a sensitivity of 60%, a specificity of 80% and a LR+ of 3. AST to ALT ratio > 0.65 yielded a sensitivity of 53.3%, a specificity of 86.67% and a LR+ of 4. The risk of advanced stage NASH was estimated and is shown in Table 5. The variables for further stepwise multivariate logistic analysis were AST to ALT ratio > 0.65, HOMA-IR > 3.5, grading of portal inflammation and grading of NASH. The multivariate analysis revealed that HOMA-IR > 3.5 and grading of portal inflammation were independently associated with advanced stage NASH with ORs of 23.12 (95% CI, 2.00-266.23; $P = 0.012$) and 7.15 (95% CI, 1.63-31.20; $P = 0.009$), respectively.

DISCUSSION

The incidence of NASH is increasing worldwide due to the global epidemic of metabolic syndrome and insulin resistance-related diseases (e.g. obesity and type 2 diabetes mellitus)[2]. There have been a few reports of metabolic and anthropometric study of NASH among Asians[7,13]. In this study, obesity, diabetes mellitus, hypertension and an elevated triglyceride level were found in 26 (86.7%), 15 (50%), 15 (50%) and 12 (40%) NASH patients which agree well with the findings from previous studies[3,10-2]. Although 86.7% of NASH subjects were obese, the high BMI was not associated with the presence of NASH by adjusted multivariate analysis. Visceral or central obesity defined by elevated WC was detected in 24 (80%) NASH subjects. Visceral fat, a precursor of increased lipolysis and elevated free fatty acid flow and metabolism, is believed to be a more important factor in causing insulin resistance than overall obesity or subcutaneous fat[14,23]. It may be more favorable to pay attention to visceral adiposity in stead of overall obesity and encourage the combining use of BMI and WC in clinics[14]. This study reveals the relationships of visceral fat, obesity and metabolic syndrome. Visceral fat, as expected, has the highest correlation with abdominal fat and BMI. More than 50% of NASH patients fulfilled the criteria of metabolic syndrome. Features of metabolic syndrome, which is hyperinsulinemia or insulin resistance, are prevalent in NAFLD and NASH from previous reports[24,25]. Fasting insulin and glucose levels are used to construct the relatively crude but practically useful HOMA-IR which correlates closely with the euglycemic clamp technique[26,27]. The cutoff HOMA-IR at 3.5 is an accurate indicator of insulin resistance reported previously[28]. In this study, elevated HOMA-IR represented by HOMA-IR > 2.8 and visceral fat area defined by visceral fat > 158 cm^2 are independent predictors of the presence of NASH in Thai patients. The cutoff levels for HOMA-IR and visceral fat area in NASH patients, especially in Asians, have never been reported.

Of 30 NASH patients, 15 (50%) were diagnosed as having advanced stages of the disease. The study revealed that HOMA-IR > 3.5 and grading of portal inflammation were independent risk factors relating to the advanced fibrotic stage of the disease. From previous studies, risk factors identified as predictors for the development of progressive fibrosis and cirrhosis among NASH patients include obesity (or BMI), diabetes mellitus, old age, hypertension, AST to ALT ratio, triglyceride level and insulin resistance index by QUICKI[12,28]. The high number of advanced stage in this study may be due to the selection bias at the time of liver biopsy prior to the study.

One of the limitations of our study is that the number of NASH and control subjects is rather small. Further studies with larger number of study subjects are required to get the more accurate cutoff levels of visceral fat area and HOMA-IR. Moreover, we found it difficult to find BMI-matched control subjects who did not have any parameter of metabolic syndrome. There were 2 cases (6.7%) in the control group who were found to have the

criteria of metabolic syndrome after they were recruited into the study. From this study, though an inordinate number of female subjects predominate in this study, we cannot make a conclusion that the development of NASH has a sex preference since the study was carried out in a referral-based center.

In conclusion, obesity (especially central obesity) and metabolic syndrome features are common in Thai NASH. Insulin resistance and elevated visceral fat are risk factors for the development of NASH. The progression of the disease is related to insulin resistance.

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