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Metabolic Syndrome Is Related to Nonalcoholic Steatohepatitis in Severely Obese Subjects

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Background: Metabolic syndrome (MetS) and nonalcoholic fatty liver disease (NAFLD), ranging from simple steatosis to steatohepatitis (NASH), have become important health issues in obese subjects. In this study, we investigated the relationship between MetS and NASH in severely obese subjects.

Methods: A total of 111 non-alcoholic obese patients who underwent laparoscopic bariatric surgery (BMI 45.4±5.7 kg/m^2) were enrolled from February to September 2004 in a referral center in North Taiwan. MetS and its individual components were defined using the American Heart Association/National Heart, Lung, and Blood Institute criteria. Based on liver biopsy during surgery, subjects were classified into either having NASH or not. The relationship among NASH, adiponectin, insulin resistance, MetS and its individual components was examined using a multivariate logistic regression analysis.

Results: The prevalence of NASH and MetS in these subjects was 79.3% and 68.5%, respectively. Using a multivariate logistic regression analysis with NASH as the outcome variable, odds ratio (OR) of NASH for subjects with MetS versus without MetS was 2.96 (95% CI= 1.14-7.68) adjusted for age, gender, and BMI. Also, high blood pressure (OR= 2.97, 1.31-6.73) and high fasting glucose (OR= 2.94, 1.13-7.67) were independently associated with NASH after adjustment for age, gender, and BMI. Insulin resistance measured as HOMA-IR and serum adiponectin level were not significantly different between the NASH and non-NASH group.

Conclusion: MetS and NASH were common in severely obese Taiwanese adults. Presence of MetS, high blood pressure, and high fasting glucose was independently related to increased risk of NASH. The underlying mechanism deserves to be explored in the future.

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Introduction

Obesity and metabolic syndrome (MetS) have become worldwide health problems in recent decades. In addition to increasing mortality, obesity has been known to be associated with hypertension, type 2 diabetes, dyslipidemia, and cardiovascular diseases (CVD).[1-3] MetS, a constellation of central obesity, impaired glucose metabolism, dyslipidemia, and hypertension, is associated with subsequent development of type 2 diabetes and CVD.[4,5] Furthermore, nonalcoholic fatty liver disease (NAFLD) is also related to obesity and MetS.[6-9] Thus, the presence of NAFLD is being recognized as a common liver disorder in subjects with obesity and MetS.

Recently, NAFLD has become the most common liver disease in western countries. Depending on different methodologies and study populations, however, the prevalence of NAFLD varies. Moreover, NAFLD is characterized by a wide spectrum of liver damage ranging from simple steatosis, steatohepatitis (NASH) to cirrhosis.[10] In addition, NAFLD usually increases with increments of body mass index (BMI),[11,12] as steatosis was observed in 86% of severely obese patients.[13] Interestingly, the prevalence of NASH also varies from 9.8-60.3% in severely obese patients.[13-17] Moreover, predictors of NASH are inconsistent in these studies. Therefore, it

suggests that risk factors for NAFLD progression in obese subjects may be different among various populations. In addition, liver biopsy is the gold standard to differentiate innocent steatosis from progressive steatohepatitis. In the present study, we set out to investigate the relationship between MetS and NASH by liver biopsy in severely obese Taiwanese adults.

Materials and Methods

Subjects and Measurements

A total of 158 severely obese subjects (BMI >40 kg/m^2 or >35 kg/m^2 with co-morbidities) received laparoscopic bariatric surgery in a referral hospital in North Taiwan from February to September 2004. After excluding 28 subjects with hepatitis B infection, 3 subjects with hepatitis C, and 16 subjects with habitual drinking (estimated daily alcohol intake >30 g in men or >20 g in women by questionnaire), 111 subjects were recruited into this study. Anthropometric measurement and blood pressure were taken as standard procedure. The study protocol was approved by the Human Ethics Committees of En Chu Kong Hospital, and informed consent was obtained from each study subject.

A venous blood sample was taken after an 8-hr fast. Plasma alanine aminotransferase (ALT), glucose, insulin, and lipids were measured using HITACHI 7150 (Tokyo, Japan). ALT levels <41 U/L in men and <31 U/L in women were defined as normal. Plasma insulin levels were determined by a microparticle enzyme immunoassay using AxSYM system from Abbott Diagnostics (Abbott Laboratories, Dainabot Co. Ltd., Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was applied to estimate the degree of insulin resistance [HOMA-IR = fasting insulin x fasting plasma glucose/22.5, where insulin in μU/mL and glucose in mmol/L].[18] Plasma adiponectin was assayed in duplicates using radioimmunoassay kits (Linco Research Inc., St. Louis, MO, USA). The average of the duplicates was used in subsequent statistical analyses. The intra-assay and inter-assay coefficients of variation were 6.8% and 9.6% for plasma adiponectin levels.

MetS was defined clinically, based on the presence of three or more of the American Heart Association and National Heart Lung Blood Institute (AHA/NHLBI) criteria:[19] 1) central obesity (waist circumference (WC) >90 cm in men and >80 cm in women for Asians); 2) high triglycerides (>1.69 mmol/L) or on drug treatment for high triglycerides; 3) low HDL (high-density lipoprotein) -cholesterol level (<1.03 mmol/L for men and <1.29 mmol/L for women) or on drug treatment for low HDL-cholesterol; 4) high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or on antihypertensive drug treatment in a patient with a history of hypertension; 5) high fasting glucose (≥5.55 mmol/L) or on drug treatment for type 2 diabetes.

Liver biopsy with at least 1.0 cm length through left lobe of liver was obtained during surgery, and all the specimens were considered adequate for diagnosis of NASH by the same pathologist.[20,21] Specimen was embedded in paraffin and stained with hematoxylin and eosin for histological examination. Silver reticulin and Masson trichome stain were used for evaluation of fibrosis and architectural change. Immunohistochemical staining for unbiquitin was used to help identify Mallory bodies.[22] One pathologist unaware of the clinical information and laboratory data examined all specimens (Dr. Phui-Ly Liew). Histological classification was based on the classification proposed by Brunt[23] with minor modification. Six histological features of NASH were scored semi-quantitatively from 0 to 4, including steatosis, acinar zone 3 hepatocellular injury with ballooning degeneration, parenchymal inflammation, portal inflammation, perisinusoidal fibrosis, and Mallory bodies. NASH was defined by the presence of fibrosis (grade 1 or higher) or acinar zone hepatocellular injury with ballooning degeneration (grade 2 or higher).

Statistical Analyses

Data were expressed as the mean ±SD or medians with interquartile ranges. Student's *t*-test for unpaired data was used for the comparison of mean values between NASH and non-NASH groups. Log transformation was performed for variables with significant deviation from normal distribution assessed by Kolmogorov-Smirnov test before further analyses. Proportions and categorical variables

were tested by the χ^2 test. Using a multivariate logistic regression analysis with NASH as the outcome variable, odds ratios (ORs) of NASH for subjects *with* versus *without* MetS and its individual components were calculated with the adjustment for age, gender, and BMI. These statistical analyses were performed using the PC version of SPSS statistical software (13th version; SPSS, Chicago, IL).

Results

On the basis of liver biopsy, 88 subjects (79.3%) were classified as having NASH. In Table 1, there was no significant difference among their mean age, BMI, WC, HOMA-IR, adiponectin, and ALT levels between NASH and non-NASH groups. In contrast, the prevalence of MetS, high fasting glucose, high blood pressure, four and five components was higher in the NASH group than non-NASH group ($P<0.05$). The prevalence of MetS was 68.5% in these subjects (73.9% in NASH group and 47.8% in non-NASH group, respectively).

The crude and adjusted ORs of NASH in subjects *with* versus *without* MetS and its individual components are shown in Table 2. The mean crude ORs of NASH among subjects with high blood pressure, high fasting glucose, and MetS were 3.33, 3.96, and 3.08, respectively ($P< 0.05$). Furthermore, using a multivariate logistic regression analysis adjusted for age, gender, and BMI, we found that high blood pressure, high fasting glucose, and MetS were still independently associated ($P<0.05$) with NASH. The adjusted ORs of NASH among subjects with high blood pressure, high fasting glucose, and MetS were 3.43 (95% CI= 1.29-9.16), 3.82 (1.15-12.68), and 2.96 (1.14-7.68), respectively. In addition, we also found only the metabolic syndrome was independently associated with fibrosis in these subjects (OR=2.79, 1.20-6.45).

The diagnostic utility of MetS and its individual components for predicting NASH are shown in Table 3. We found that the high fasting glucose seemed to have the best positive predictive value (90.5%) and highest specificity (82.6%). Moreover, the high blood pressure tended to have the highest sensitivity (78.4%) and best negative predictive value (36.7%).

Prevalence of NASH in different categories of MetS components is shown in Figure 1. The highest prevalence of NASH was 93.5% in subjects with high blood pressure and high fasting glucose. In contrast, only 47.1% of subjects without the two components had NASH.

Discussion

In the present study, we found that MetS and NASH were common disorders (prevalence 68.5% and 79.3%, respectively) in severely obese subjects undergoing bariatric surgery. Compared to the Americans and French with similar BMI levels, the prevalence of NASH was much higher[14-16,24] but that of MetS was lower[15,24] in our study. Besides, we showed that subjects with NASH were at higher risk for metabolic syndrome (OR=2.96) than those without NASH. Furthermore, we also demonstrated that high blood pressure, high fasting glucose, and AHA/NHLBI criteria-defined MetS were independently associated with higher risk of NASH.

The high prevalence of NASH in the present study, similar to our previous report,[21] may be due to several reasons. Firstly, increased risk for obesity-related co-morbidities has been found at lower BMI and WC levels in Taiwanese adults.[2,25] It has been also shown in other Asian populations.[26] Secondly, similar to other Asians, Taiwanese subjects have a higher body fat percentage in any given BMI than Caucasians.[26-28] Finally, the criteria for grading and staging the histological lesions of liver may be inconsistent.[23,29] Taken together, it suggests that bariatric surgery may be considered at a lower BMI, as we proposed previously for the Asia-Pacific countries.[30] It has been shown that gender differences exist in the spectrum of NAFLD. For instance, Arun et al[15] have shown that severely obese men have twice the prevalence of NASH relative to severely obese women. In contrast, Palekar et al[17] have reported that severely obese women have higher prevalence of NASH than severely obese men. In our present study, however, we found no statistical significance in the prevalence of NASH between men (75.8%) and women (80.8%) (Table 1).

Up to 60% of our subjects had abnormal ALT levels in the present study. Although ALT, a liver-spe-

Table 1. Demographic data, ALT, metabolic syndrome (MetS), and its individual components categorized by presence of NASH (N=111)

	NASH (n=88)	non–NASH (n=23)	Total	*P* value
Age (years)	29.6 ± 8.6	28.2 ± 8.8	29.3 ± 8.6	0.511
Gender (%)				0.556
Male	25 (28.4)	8 (34.8)	-	
Female	63 (71.6)	15 (65.2)	-	
Height (cm)	165.4 ± 7.8	166.8 ± 7.9	165.7 ± 7.8	0.450
Weight (kg)	124.7 ± 20.6	125.4 ± 19.9	124.9 ± 20.3	0.896
BMI (kg/m^2)	45.5 ± 5.9	44.9 ± 4.7	45.4 ± 5.7	0.648
WC (cm)	125.3 ± 13.8	124.9 ± 14.7	125.2 ± 13.9	0.911
Fasting glucose (mmol/L)†	5.86 ± 1.97	5.37 ± 1.69	5.76 ± 1.92	0.146
Insulin (pmol/L)†	163.1 ± 128.3	128.6 ± 76.7	151.9 ± 114.8	0.242
HOMA-IR†	4.51 ± 3.91	4.27 ± 2.35	4.43 ± 3.47	0.526
Triglycerides (mmol/L)†	17.73 ± 9.22	15.36 ± 7.46	17.24 ± 8.90	0.344
HDL-C (mmol/L)†	1.23 ± 0.32	1.18 ± 0.27	1.22 ± 0.31	0.565
Adiponectin (μg/mL)	4.88 ± 1.65	5.19 ± 1.78	5.01 ± 1.69	0.533
ALT (U/L)†	50.7 ± 38.7	49.1 ± 45.6	50.4 ± 40.4	0.246
Abnormal ALT (%)	62.5	55.2	60.4	0.367
Central obesity (%)	100	100	100	-
High BP (%)*	78.4	52.2	73.0	0.012
High fasting glucose (%)*	45.5	17.4	39.6	0.014
High triglycerides (%)	46.6	30.4	43.2	0.164
Low HDL-cholesterol (%)	58.0	47.8	55.9	0.384
MetS (%)*	73.9	47.8	68.5	0.017
4 components of MetS (%)*	44.3	13	37.8	0.006
5 components of MetS (%)	10.2	0	8.1	0.11
Type 2 diabetes	21.6	8.7	18.9	0.16

Data are means ± SD. BMI, body mass index; WC, waist circumference; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; ALT, alanine aminotransferase; BP, blood pressure.
*P <0.05 using Student's t-test for mean values (±SD) or χ^2 test for proportions and categorical variables between NASH and non-NASH.
† Statistics were tested using the log-transformed values.

cific enzyme, is a sensitive marker of liver injury and elevated ALT levels are associated with obesity and metabolic syndrome,[9 31,32] We found no significant difference between the NASH and non-NASH groups (Table 1). This is similar to other studies, which showed aspartate aminotransferase (AST) as a predictive marker of NASH rather than ALT.[17,33] Recently, Dixon et al[14] have also demonstrated that decreasing AST levels, not ALT levels, are predictive of improved lobular inflammation and fibrosis in obese patients with NASH. Taken together, the ALT level may not be a good indicator for denoting the progression of NASH in the severely obese subjects.

It is well known that there is close association between obesity, MetS, and NAFLD. Previously, we have demonstrated that NAFLD based on the brightness picture of liver ultrasonography is independently associated with MetS.[9] Several possible mechanisms for this relationship had been postulated such as insulin resistance, oxidative stress, or many adipokines. It has been recognized that the underlying pathophysiology of metabolic syndrome is related to insulin resistance,[19,34,35] and insulin resistance plays a central role in the accumulation of triglycerides within the hepatocytes and in the initiation of the inflammatory cascade.[10] On the other hand, MetS is associated with elevated oxidative stress,[36] which is one of the causal factors in the development of NASH. Therefore, this implies that metabolic syndrome is related to the initiation and progression of NASH. Moreover, several adipokines are believed to be involved in the development of insulin resistance, and adiponectin is one of those being substantially studied.[37] The association of low

Table 2. Crude and adjusted odds ratios† (ORcru and ORadj) of NASH in subjects *with* versus *without* metabolic syndrome and its individual components except central obesity

	ORcru (95%CI)	ORadj (95%CI)
High blood pressure	3.33 (1.27-8.72)*	3.43 (1.29-9.16)*
High fasting glucose	3.96 (1.25-12.59)*	3.82 (1.15-12.68)*
High triglycerides	1.99 (0.75-5.32)	2.12 (0.77-5.82)
Low HDL-cholesterol	1.50 (0.60-3.78)	1.47 (0.57-3.81)
Metabolic syndrome	3.08 (1.20-7.94)*	2.96 (1.14-7.68)*

* P <0.05
† Adjusted ORs: ORs with adjustment for age, gender, and BMI (All P >0.05).

Table 3. Sensitivity(SEN), specificity(SPE), positive predictive value (PPV), and negative predictive value (NPV) of metabolic syndrome, its individual components except central obesity

	SEN (%)	SPE (%)	PPV (%)	NPV (%)
High blood pressure	78.4	47.8	85.2	36.7
High fasting glucose	45.5	82.6	90.9	28.4
High triglycerides	46.6	69.6	85.4	25.4
Low HDL-cholesterol	58	52.2	82.3	24.5
Metabolic syndrome	73.9	52.2	85.5	34.3

serum adiponectin and NAFLD has been found in several studies.[38-40] Similarly, we found that metabolic syndrome was independently associated with NASH when adjusted for other variables (Table 2). In the present study, however, there was neither significant association between BMI and MetS (data not shown), nor BMI and NASH (Table 2). Insulin resistance measured as HOMA-IR, and serum adiponectin level were not statistically different between the NASH and non-NASH group. These could be due to our study subjects being extremely obese, relatively few subjects, or other underlying mechanisms not yet discovered.

Among the various components of MetS, high fasting glucose and high blood pressure were significantly associated with NASH in our present study (Table 2 and Figure 1). In addition to insulin resistance and MetS described above, type 2 diabetes also has been found to be a risk factor for NASH.[15,33] Similarly in our results, type 2 diabetes was also related to NASH without statistical significance (Table 1). In addition, Dixon et al[41] have shown that hypertension is a strong predictor of NASH in the severely obese patients. Interestingly, angiotensin-II receptor antagonist can improve necroinflammation and fibrosis in hypertensive NASH patients, with concurrent blood pressure lowering.[42] Recently, Uno et al[43] have demonstrated that a neuronal pathway consisting of the vagus nerve from the liver and the sympathetic nerve to adipose tissue was involved in energy expenditure and insulin sensitivity in a mouse model. Taken together, these findings suggest that

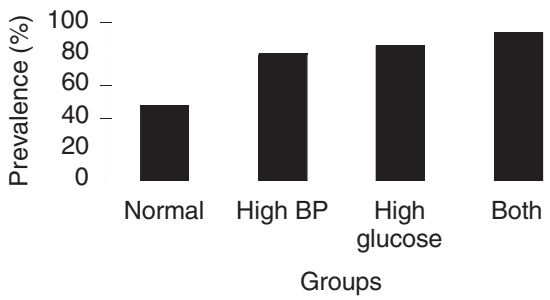

Figure 1. Prevalence of NASH in severely obese subjects *with* high blood pressure (High BP, 80.0%), high fasting glucose (High glucose, 84.6%), and Both (93.5%) versus *without* high BP and fasting glucose (normal, 47.1%)

NASH is not only a liver disease but also a systemic disease involved in the development of CVD.

In summary, we found that MetS and NASH were common disorders in severely obese subjects. The prevalence of NASH was much higher in our study than others. Furthermore, high blood pressure, high fasting glucose, and AHA/NHLBI criteria-defined metabolic syndrome were independently associated with increased risk of NASH. Although our study was limited by the cross-sectional design and there was potential bias for the participation by the subjects, our results suggest that MetS and its individual components may play important roles in the development of NASH in severely obese subjects, and vice versa. The underlying mechanism deserves to be explored in the future.

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