Original Article

Associations between combinations of body mass index plus non-alcoholic fatty liver disease and diabetes mellitus among Korean adults

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The purpose of this study was to investigate associations between combinations of body mass index (BMI) categories plus non-alcoholic fatty liver disease (NAFLD) and diabetes mellitus (DM) among Korean adults. We prepared the data of 5665 subjects aged 20 years and over who had visited a health promotion center. We excluded 582 subjects as they had a viral or alcoholic liver disease. According to BMI-NAFLD status, the subjects were categorized as non-obese (BMI<25 kg/m^2) without NAFLD (n=2568), obese (BMI≥25 kg/m^2) without NAFLD (n=572), non-obese with NAFLD (n=748), or obese with NAFLD (n=1195). The prevalence of NAFLD was highest in the obese subjects with DM (87.9%). In non-obese and non-DM subjects, the prevalence of NAFLD was lowest (18.4%). After adjustment of age, gender, waist circumference, smoking status, alcohol drinking, regular exercise, the odd ratios for DM or DM plus impaired fasting glucose (IFG) of subjects with mild NAFLD regardless of obesity were almost 2-fold compared to non-obese subjects without NAFLD. Moreover, those of subjects with moderate or severe NAFLD regardless of obesity were about 4- fold. Clinicians and investigators need to pay attention to non-obese patients with fatty liver.

Key Words: fatty liver, glucose metabolism, diabetes, body mass index, obesity

INTRODUCTION

Diabetes mellitus (DM) is diagnosed and characterized by chronic hyperglycemia.[1] The effects of DM include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, heart, and blood vessels.[2] The incidence of DM is increasing rapidly worldwide, with the economic burden of diabetes caused by increased health resource use and lost productivity increase rapidly.[3]

Non-alcoholic steatohepatitis (NASH) was first described by Ludwig *et al.*[4] about 30 years ago and is now considered part of a spectrum of non-alcoholic fatty liver diseases (NAFLD). Epidemiological studies have documented that NAFLD is independently associated with obesity, hypertriglyceridemia, low HDL-cholesterol, insulin resistance.[5-8] Patients with NAFLD have an increased risk of developing not only liver but also cardiovascular morbidity.

Once the liver is fatty, the action of insulin to inhibit hepatic glucose production is impaired, which results in hyperglycemia and hyperinsulinemia.[9] Although the prevalence of DM increased in obesity,[10] not all obese subjects are going to be DM patients. Furthermore, insulin resistance can be found even in lean individuals.[11] NAFLD is considered to be an important predisposing step in obese individuals towards the development of diabetes.[12]

However, in the cases of non-obese patients with fatty liver or obese patients without fatty liver, the relationship between their health status and DM is quite unknown. The purpose of this study was to examine the prevalence of NAFLD in both non-obese and obese people according to DM classification and to investigate associations between combinations of body mass index categories plus NAFLD and DM among Korean adults.

MATERIALS AND METHODS

Subjects

We prepared the data of 5665 subjects aged 20 years and over who had visited a health promotion center from January 2006 and December 2007. Subjects were subsequently divided into groups of normal glucose (NG), impaired fasting glucose (IFG), and DM.[13] Subjects with normal fasting glucose had values below 100 mg/dL. According to the American Diabetes Association guidelines,[14] subjects with IFG were defined by fasting glucose values of 100 to 125 mg/dL. Subjects with DM were defined by fasting glucose above 126 mg/dL or by taking any hypoglycemic agents including insulin.

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We excluded subjects from the analysis if they had a daily alcohol consumption of more than 2 drinks (alcohol use ≥30 g/day) for men or more than 1.5 drinks (alcohol use ≥20 g/day) for women. We also excluded subjects who were positive for the hepatitis B surface antigen or hepatitis C virus antibody. Subjects who had a medical history of chronic liver disease or liver cirrhosis, as well as those taking current medications for liver disease were also excluded from the study. The final study population consisted of 5083 subjects (2552 men and 2531 women). The institutional review board of the Myongji Hospital approved this study.

Measurements

During subjects' health promotion center visits, medical history and life-style-related data (alcohol consumption, smoking, and exercise status) were collected via a questionnaire and history taking. Current medication use was verified by an examination of prescriptions. A smoking habit was defined as currently smoking cigarettes. Alcohol consumption was measured according to the amount of alcohol more than one bottle of soju (a kind of distilled spirits containing 56.8 g of pure alcohol) consumed per week. Regular exercise was defined as 30 min or more at a time, three times per week regularly.

Body weight was measured to the nearest 0.1 kg using an electronic scale. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Obesity was defined as BMI over 25 according to Western Pacific Region of

Table 1. Clinical and metabolic characteristics of subjects

Variables	NG† n=4072	IFG‡ n=675	DM§ n=336	*p*-value
Age (years)	45.8 ± 11.8	50.8 ± 10.5*	54.8 ± 9.4**,***	<0.001
Gender (male), n (%)	1925(47.3)	423(62.7)	204(60.7)	<0.001
BMI¶ (kg/m^2)	23.5 ± 3.1	25.1 ± 3.0*	25.1 ± 2.9**	<0.001
Waist circumference (cm)	80.4 ± 9.3	85.9 ± 8.3*	87.3 ± 7.5**,***	<0.001
Body fat (%)	25.8 ± 6.6	26.9 ± 6.5*	27.4 ± 6.8**	<0.001
Blood pressure (mmHg)				
Systolic	125.6 ± 16.4	134.8 ± 16.5*	135.0 ± 16.0**	<0.001
Diastolic	73.2 ± 10.7	78.9 ± 10.4*	78.3 ± 9.6**	<0.001
Current smoker, n (%)	841 (20.7)	149 (22.1)	77 (22.9)	0.470
Alcohol drinking, n (%)	892 (21.9)	244 (36.2)	83 (24.7)	<0.001
Regular exercise, n (%)	1962 (48.2)	249 (36.9)	138 (41.1)	<0.001
HTN†† medication, n (%)	382 (9.4)	117 (17.3)	104 (31.0)	<0.001
Grade of fatty liver				
No (N=3140), n (%)	2782(88.6)	259(8.3)	99(3.2)	
Mild (N=1087), n (%)	800(73.6)	204(18.8)	83(7.6)	
Moderate (N=767), n (%)	445(58.0)	186(24.3)	136(17.7)	
Severe (N=89), n (%)	45(50.6)	26(29.2)	18(20.2)	<0.001
Fibrosis score	-3.2±1.0	-2.0±1.0*	-1.8±1.1†	<0.001
Fasting glucose (mg/dl)	86.4 ± 7.0	107.0 ± 6.4*	150.0 ± 43.9**,***	<0.001
Fasting insulin†††\ (uIU/L)	5.9 ± 3.3	7.9 ± 4.4*	7.5 ± 5.1**,***	<0.001
HOMA-IR‡‡, †††\	1.3 ± 0.7	2.1 ± 1.2*	2.7 ± 2.0**,***	<0.001
HbA1c§§ (%)	5.2 ± 0.4	5.7 ± 0.5*	7.7 ± 1.6**,***	<0.001
Total cholesterol (mg/dl)	189.6 ± 33.9	203.5 ± 36.4*	201.2 ± 39.2**	<0.001
Triglyceride†††\ (mg/dl)	131.6 ± 84.5	174.0 ± 115.2*	200.1 ± 130.3**,***	<0.001
HDL-cholesterol (mg/dl)	57.1 ± 13.0	54.7 ± 12.3*	50.6 ± 11.5**,***	<0.001
LDL-cholesterol (mg/dl)	107.1 ± 29.2	118.2 ± 32.4*	115.3 ± 34.4**	<0.001
AST (IU/L)	26.0 ± 7.8*†	29.3 ± 10.0*	28.6 ± 12.0**	0.003
ALT (IU/L)	25.4 ± 12.9*†	31.8 ± 16.1*	33.1 ± 17.3**	0.039
r-GT (IU/L)	32.5 ± 64.8*†	52.0 ± 58.8*	53.4 ± 80.6**	0.265
WBC (x 10^3/ul)	6.5 ± 1.8	6.8 ± 1.8*	7.6 ± 2.2**,***	<0.001
hs-CRP¶¶, †††\ (mg/dl)	0.17 ± 0.45	0.21 ± 0.59*	0.30 ± 0.85**,***	<0.001

Data are shown as means ± the standard deviation.

†fasting blood sugar (FBS) <100 mg/dL, ‡100≤FBS<126 mg/dL, §FBS≥126 mg/dL or taken anti-diabetic agents, ¶body mass index, ††hypertension, ‡‡homeostasis model assessment of insulin resistance, §§hemoglobin A1c, ¶¶high sensitivity C-reactive protein, †††\values have been analyses after log-transformation

*NG versus IFG: p<0.05, **NG versus DM: p<0.05, ***IFG versus DM: p<0.05.

Fibrosis score=-1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet (x10^9/l) - 0.66 x albumin (g/dl).

WHO criteria.[15] Waist circumference was measured midway between the lowest rib and the iliac crest with subjects in the standing position. The percent body fat was determined using bioelectrical impedance analysis (InBody 720, Biospace Co., Seoul, Korea). An abdominal ultrasonography was conducted to assess the presence and severity of NAFLD. The same operator who was blinded to the medical histories and laboratory results of the participants performed all of the ultrasounds. Fatty liver was diagnosed on ultrasound when there is a diffuse increased echogenicity of the liver texture compared to the right kidney. The ultrasounds were performed with a high resolution B-mode scanner (EnVisor HD, version C.0.1, USA).

Blood samples collected after overnight fasting (>12 hours), and were analyzed for fasting glucose, lipid metabolites indices such as total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol (ADVIA 1650, Siemens, Tarrytown, NY, USA), and hemoglobin A1c (HbA1c) (HLC-723GHb, TOSOH, Siba, Minaoto-ku, Japan). We measured high-sensitive C-reactive protein as a marker of systemic low-grade inflammation, which was measured by turbidmetric immunoassay using a Hitachi 7170 S (Hitachi Hi-Tech, Tokyo, Japan). Additionally, insulin was measured by chemiluminescence using Advia Centaur XP (Siemens Healthcare Diagnostics, Los Angeles, CA, USA) and, as a marker of insulin resistance, homeostasis model assessment of insulin resistance (HOMA-IR) index [(Insulin (μIU/ml) × Fasting glucose (mg/dl)/18)/22.5]) was calculated.

Statistical analyses

Data are presented as mean±SD. Variables such as fasting insulin, HOMA-IR, triglyceride, and hs-CRP were logarithmically transformed prior to statistical analyses to approximate a normal distribution. Clinical characteristics were compared among the three groups using one-way analysis of variance. Prevalence of NAFLD in both non-obese and obese people according to DM categories was calculated with chi-square test. After adjusting for age, gender and waist circumference, an analysis of covariance was used to seek differences in adiposity indices, glucose metabolism-related parameters, liver functions, and fibrosis score among BMI-NAFLD categories. A logistic regression analysis for DM or DM plus IFG was performed to determine the associations with combinations of BMI categories plus NAFLD grades after adjustment of potential confounders. Significance was defined at the 0.05 level of confidence. All calculations were performed using the SPSS software, version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics of the subjects

Clinical and metabolic characteristics of the subjects are presented in Table 1. Statistic significances were found in age, gender, BMI, waist circumference, body fat, blood pressure, alcohol, exercise, hypertension, grade of fatty liver, fibrosis score, glucose indices, lipid profiles, AST, ALT, WBC and hs-CRP between normal glucose, IFG, and DM group. Current smoking and r-GT were not significantly different between 3 groups.

Prevalence of NAFLD in both non-obese and obese people according to DM categories

Overall prevalence of NAFLD in the present study was 38.2% and the prevalences of NAFLD in subjects with normal glucose, IFG, and DM were 31.7%, 61.6%, and 70.5%. In both obese and non-obese subjects, prevalence of NAFLD increased according to DM categories. Prevalence of NAFLD was lowest in the non-obese group with normal glucose (18.4%), highest in the obese group with diabetes (87.9%). (Figure 1)

Associations between BMI-NAFLD categories and glucose metabolism

Having either obesity or not, subjects with NAFLD have higher glucose indices, liver enzyme levels, and fibrosis scores than non-obese subjects without NAFLD. And non-obese subjects with moderate or severe NAFLD also have higher glucose indices than obese subjects without NAFLD. In each obesity or non-obesity group, all variables show an increasing tendency according to the severity of NAFLD (Table 2).

After adjustment of age, gender, waist circumference,

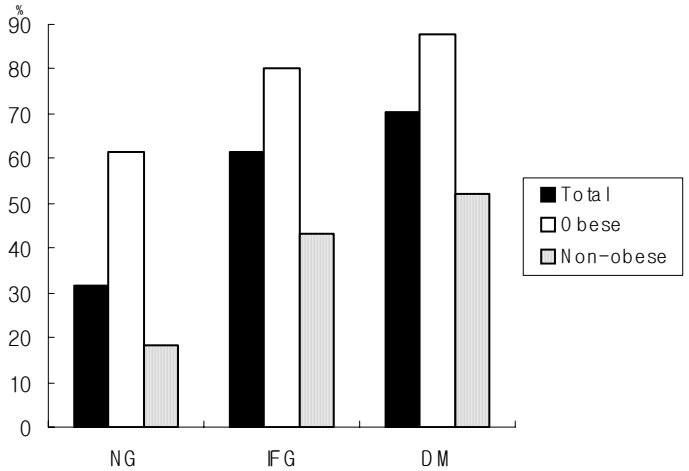

Figure 1. Prevalence of NAFLD in subjects with normal glucose (NG), impaired fasting glucose (IFG), and diabets mellitus (DM) according to obesity. NG: fasting blood sugar (FBS) <100 mg/dL, IFG: 100≤FBS<126 mg/dL, DM: FBS≥126 mg/dL or taken anti-diabetic agents.

Table 2. Adiposity indices and glucose metabolism related variables according to BMI-NAFLD categories

Variables	OB†(-),FL‡(-)	OB (-),mild FL	OB(-),>mod FL	OB(+), FL (-)	OB(+),mild FL	OB(+),>mod FL	*p*-value
	n=2568	n=509	n=239	n=572	n=578	n=617	
Adiposity indices							
BMI§ (kg/m^2)	21.69±1.96	23.18±1.41*	23.55±1.17*	26.64±1.56*,**,***	27.18±1.87*,**,***	27.84±2.20*,**,***,§	<0.001
Abdominal fat (%)	23.99±6.06	24.63±5.67*	24.40±4.96*	29.75±6.30*,**,***	29.62±6.56*,**,***	29.67±6.14*,**,***,§	<0.001
Glucose indices							
Fasting glucose (mg/dl)	88.72±16.67	95.21±18.66*	108.38±35.71*,**	90.86±13.99**,***	95.94±19.75*,***,§	104.83±29.65*,**,§,‖	<0.001
Fasting insulin‡‡(uIU/L)	4.89±2.54	5.85±2.82*	7.70±3.81*,**	6.60±3.30*,***	7.97±4.05*,**,***,§	9.72±4.81*,**,§,‖	<0.001
HOMA-IR¶, ‡‡	1.08±0.63	1.38±0.76*	2.04±1.20*,**	1.50±0.92*,**,***	1.91±1.11*,**,***,§	2.52±1.50*,**,§,‖	<0.001
HbA1c†† (%)	5.27±0.68	5.52±0.79*	6.01±1.49*,**	5.36±0.59**,***	5.56±0.75*,***,§	5.85±1.10*,†,‡,§,‖	<0.001
Liver function test							
AST	24.77±6.96	27.68±9.29*	30.15±10.73*,**	25.09±6.38**,***	27.49±8.03*,***,§	32.45±11.53*,**,***,§,‖	<0.001
ALT	21.58±9.88	28.10±12.43*	36.12±16.21*,**	25.30±10.79**,***	30.85±12.86*,***,§	41.06±18.59*,**,***,§,‖	<0.001
r-GT	25.27±68.36	46.22±66.87*	56.26±83.73*	2.03±32.23**,***	45.65±43.66*,***,§	63.00±73.79*,**,§,‖	<0.001
Fibrosis score	-3.19±1.07	-3.06±1.18*	-2.96±1.27*	-2.85±1.15*,**,***	-2.73±1.20*,**,***	-2.57±1.30*,**,***,§,‖	<0.001

P-values were calculated by the ANCOVA model, adjusted for age, gender and waist circumference. Data are shown as mean ± standard error.
†obesity, ‡non-alcoholic fatty liver disease, §body mass index, ¶homeostasis model assessment of insulin resistance, ††hemoglobin A1c, ‡‡values have been analyses after log-transformation
*p<0.05 vs. OB(-), FL(-),**p<0.05 vs. OB(-),mild FL, ***p<0.05 vs OB(-),>moderate FL, §p<0.05 vs OB(+), FL(-) , ‖p<0.05 vs OB(+), mild FL.

Table 3. Logistic regression analysis for DM or DM plus IFG

Dependant variable	DM†, OR (95% CI)			DM + IFG‡, OR (95% CI)		
	Prevalence	Crude	Adjusted	Prevalence	Crude	Adjusted
OB§(-), FL¶(-)	3.04	1	1	10.48	1	1
OB (-), mild	7.47	2.58 (1.73-3.84)	1.72 (1.13-2.62)	24.75	2.81 (2.22-3.57)	1.91 (1.47-2.46)
OB (-),>mod	19.67	7.82 (5.29-11.55)	5.53 (3.62-8.46)	43.10	6.47 (4.87-8.61)	4.39 (3.23-5.97)
OB (+), FL(-)	3.67	1.23 (0.75-1.99)	1.00 (0.59-1.73)	15.56	1.58 (1.22-2.04)	1.16 (0.85-1.57)
OB (+), mild	7.79	2.70 (1.85-3.94)	1.91 (1.18-3.07)	27.85	3.30 (2.64-4.12)	2.10 (1.57-2.81)
OB (+),>mod	17.34	6.70 (4.93-9.10)	4.45 (2.83-6.99)	42.63	6.35 (5.18-7.78)	3.80 (2.83-5.09)

Adjusted by age, gender, waist circumference, smoking status, alcohol drinking, regular exercise. Prevalence is shown as %.
†fasting blood sugar (FBS) ≥126 mg/dL or taking anti-diabetic agents, ‡100≤FBS<126 mg/dL, §obesity, ¶non-alcoholic fatty liver disease

smoking status, alcohol drinking, regular exercise, the odds ratios (95% confidence interval) for DM were 1.00 (0.59-1.73) in obese participants without NAFLD, 1.72 (1.13-2.62) in non-obese participants with mild NALFD, 5.53 (3.62-8.46) in non-obese participants with moderate or severe NALFD, 1.91 (1.18-3.07) in obese participants with mild NALFD and 4.45 (2.83-6.99) in obese participants with moderate or severe NALFD compared with non-obese individuals without NALFD. And odds ratios (95% confidence interval) for DM+IFG were 1.16 (0.85-1.57) in obese participants without NAFLD, 1.91 (1.47-2.46) in non-obese participants with mild NALFD, 4.39 (3.23-5.97) in non-obese participants with moderate or severe NALFD, 2.10 (1.57-2.81) in obese participants with mild NALFD and 3.80 (2.83-5.09) in obese participants with moderate or severe NALFD compared with non-obese individuals without NALFD (Table 3).

DISCUSSION

The number of patients with DM have increased worldwide.[10] In order to prevent the development of DM, medical interventions such as metformin or life style change have been studied.[16,17] WHO proposed two approaches for the prevention of DM. One is preventing obesity in general population, and the other is preventing and delaying the development of DM in high-risk groups.[18] Therefore, it is important to find patients at high-risk of DM and manage their changeable risk factors.

In a study among healthy Japanese adults, the prevalence of NAFLD was 27% in subjects with normal glucose and 43% in those with impaired fasting glucose and 62% in subjects with diabetes.[19] In our study, overall prevalence of NAFLD in the present study was 38.2% and prevalence of NAFLD in subjects with normal glucose, impaired fasting glucose, and DM were 31.7%, 61.6%, and 70.5%. Although the prevalence of NAFLD in obese subjects was higher than in non-obese subjects, prevalence of NAFLD in both obese and non-obese subjects increased according to DM categories.

There have been many studies about the relationship between obesity and DM.[20-22] and NAFLD is well known to be associated with DM and insulin resistance.[23-29] Most

studies mentioned obesity explaining relationship of NAFLD and DM and insulin resistance. But, DM is not always found in obese person.

In our study, subjects with NAFLD had higher in all glucose intolerance indexes (fasting glucose, fasting insulin, HOMA-IR, HbA1c) than non-obese subjects without NAFLD regardless of obesity. It is of interest that non-obese subjects with moderate or severe NAFLD also had higher in all glucose intolerance indexes than obese subjects without NAFLD. Similarly, fasting glucose and HbA1c of non-obese subjects with mild NAFLD were higher than those of obese subjects without NAFLD. In addition, odd ratios for DM or DM plus IFG of subjects with mild NAFLD regardless of obesity were almost 2-fold compared to non-obese subjects without NAFLD. Moreover, the odd ratios of subjects with moderate or severe NAFLD regardless of obesity were almost 4- fold compared to non-obese subjects without NAFLD. However, this relationship was not found in obese subjects without NAFLD.

Insulin, the most important hormone in diabetes, promotes glucose disposal in adipose tissue and muscle and prevents glucose production by inhibition of glycogenolysis and gluconeogenesis in the liver, one of the insulin-sensitive tissues in the human body.[30] A defect in insulin suppression of glucose production is found in fatty liver[9] and then glucose production increases as a consequence of increased hepatic gluconeogenesis.[31]

There were several limitations in this study. It was not possible to determine if NAFLD itself regardless of obesity plays a causal role in the development of DM because of the cross-sectional nature of this study. In this study, NAFLD was diagnosed through the abdominal ultrasonography. Although sensitivity is reduced when hepatic fat infiltration upon liver biopsy is less than 33%, ultrasonography has a sensitivity of 90% and a specificity of 95% in detecting moderate and severe steatosis.[32] There were several confounders affecting to NAFLD in this study, including liver disease and alcohol consumption. We excluded subjects who had liver disease such as viral and alcoholic origin and used statistical analysis after adjusting for lifestyle factors such as smoking, alcohol habit and exercise. This was done to lower the possibility of residual confounding effects.

Clinically, these fatty liver and obesity are all readily measured and are usually used as a part of routine health check-up programs in Korea. Our data may suggest that liver ultrasonography may be a better screening tool than the BMI for detecting high-risk group of DM in general population and is a non-invasive procedure. Nowadays attention is focused on the prevention, earlier diagnosis and more aggressive control of DM in high-risk groups. Therefore, clinicians and investigators need to pay attention to non-obese patients with fatty liver.

AUTHOR DISCLOSURES

No conflicts of interest.

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Original Article

Associations between combinations of body mass index plus non-alcoholic fatty liver disease and diabetes mellitus among Korean adults

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韓國成年人身體質量指數及非酒精性脂肪肝與糖尿病的相關性

本研究調查韓國成年人在不同身體質量指數下合併非酒精性脂肪肝 (NAFLD)與糖尿病之間的關係。研究對象為年齡 20 歲或以上，在健康促進中心有就診紀錄者，共 5665 位。進一步排除 582 位患有病毒性或酒精性肝臟疾病者。將研究對象分成四組，分別為未患 NAFLD 且非肥胖者(BMI<25 kg/m^2) (n=2568)、未患 NAFLD 但肥胖者(BMI≥25 kg/m^2) (n=572) 、患 NAFLD 但非肥胖者(n=748)、患 NAFLD 且肥胖者(n=1195)。結果發現在肥胖 並患有糖尿病者，其 NAFLD 盛行率最高 (87.9%)。而在非肥胖且未患糖尿病者，其 NAFLD 盛行率最低 (18.4%)。在校正年齡、性別、腰圍、抽菸、飲酒、運動後，患有輕微 NAFLD 者，不論是否肥胖，發生糖尿病或糖尿病及空腹血糖偏高情形的勝算比，為未患 NAFLD 且非肥胖者者的兩倍。再者，不論是否肥胖，患有中度或嚴重的 NAFLD 者，其發生糖尿病的勝算比為未患 NAFLD 且非肥胖者的四倍。因此，臨床醫師及研究者應更加注意正常體位但患有脂肪肝者。

關鍵字：脂肪肝、葡萄糖代謝、糖尿病、身體質量指數、肥胖