# Value of Visceral Fat Area and Resting Energy Expenditure in Assessment of Metabolic Characteristics in Obese and Lean Nonalcoholic Fatty Liver Disease

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## ABSTRACT

**Background:** *The high prevalence and incidence of non-alcoholic fatty liver disease (NAFLD) have become a global medical concern. Compared with obesity, metabolic abnormalities may be more critical. Currently, there is lack of relevant data for nutritional status and energy metabolic characteristics in patients with obese and lean NAFLD.*

**Methods:** *All the enrolled NAFLD patients were divided into 2 groups: the obese group (205 patients with body mass index (BMI) ≥ 25 kg/m$^2$) and the lean group (73 patients with BMI < 25 kg/m$^2$). Using a body composition analyzer, we analyzed their nutritional status including skeletal muscle, body fat, protein content, and visceral fat area (VFA). Energy metabolic characteristics including resting energy expenditure (REE), respiratory quotient, and oxidation rate of 3 major nutrients (carbohydrate, CHO%, fat, FAT%, and protein, PRO%) were analyzed by metabolic cart.*

**Results:** *The lean NAFLD patients' LDL-c and UA even increased significantly than the obese patients (P = .001 and .006, respectively). Compared with the control group, VFA and REE were significantly higher in the lean NAFLD group (P = .008, P < .001 respectively). CHO%, FAT%, and PRO% in the lean NAFLD group were 29.31 ± 7.07%, 55.59 ± 12.09%, and 15.10 ± 4.07%, respectively, and there was no significant difference compared to the control. However, compared to the obese NAFLD group, their CHO% increased, whereas FAT% decreased (both P < .001).*

**Conclusion:** *NAFLD patients suffer from nutritional imbalances and energy metabolic abnormalities, regardless of whether they are associated with obesity. LDL, UA, VFA, and REE can be used as good evaluation indicators.*

**Keywords:** *Obese, lean, NAFLD, nutritional status, energy metabolism, REE*

## INTRODUCTION

The high prevalence of obesity, diabetes, and hyperlipidemia has resulted in a significant increase in the prevalence of nonalcoholic fatty liver disease (NAFLD) in recent years, which has become a global medical concern and social issue.[1] In fact, 25% of the world's population is currently thought to have NAFLD.[1] There are studies from Turkey that reported a prevalence of NAFLD reaching up to 60.1%.[2] In China, the prevalence of NAFLD in adults is about 30%.[3] It is, generally, believed that NAFLD is closely associated with obesity and metabolic syndrome.[4,5] Obesity is also a high-risk factor for disease progression.[6] However, there is increasing evidence that lean NAFLD is not uncommon, and it is attracting more and more attention. The latest research shows that 40.8% of NAFLD patients are non-obese,[7] and they may even have worse outcomes than obese persons with NAFLD.[7,8]

Obesity is the accumulation of body fat caused by overnutrition and long-term disturbance of energy metabolism.[9] Lean NAFLD is not uncommon, and previous reports found that the prevalence of lean NAFLD can reach 6.4-19%.[6,10] Metabolic status is more important than obesity in the process of developing NAFLD.[6] Currently, there is lack of relevant data for nutritional status and energy metabolic characteristics in patients with obese and lean NAFLD. This study aims to assess the characteristics of

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obese and lean NAFLD patients in terms of nutritional status and energy metabolism using a body composition analyzer and metabolic cart and provide targets for clinical evaluation and intervention.

## MATERIALS AND METHODS

### Study Subjects

We enrolled 278 NAFLD patients (143 male, 135 female; average age 57.4 years, age range 35-70 years) with moderate to severe fatty liver detected by B-mode ultrasound who were treated in the Hepatology Department between January 1, and December 31, 2017. According to the standard for adult obesity recommended by the WHO,[11,12] all NAFLD patients were divided into 2 groups: the obese group (205 cases with body mass index (BMI) ≥ 25) and lean group (73 cases with BMI <25). The control group was 50 healthy subjects who underwent physical examination in the medical examination center of the same hospital during the same period.

All the enrolled NAFLD patients satisfied the standard "Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease" revised by the NAFLD Group of the Chinese Society of Hepatology, Chinese Medical Association in 2010.[13] The diagnostic criteria for NAFLD were as follows: (1) near-field echo of the liver region was diffusely enhanced (stronger than the echo of the kidney and spleen), while far-field echo gradually attenuated; (2) structure of the intrahepatic ducts was unclear; (3) liver showed mild to moderate swelling, and the edge angle was round and blunt; (4) color Doppler flow imaging indicated that the blood flow signal in the liver was reduced or was not easily displayed, while the intrahepatic blood vessels were normal; and (5) echo display of the right hepatic lobe capsule and the diaphragm was unclear or incomplete. Patients who met criterion 1 and 1 of the criteria 2-4 had mild fatty liver disease (FLD); patients who met criterion 1 and 2 of the criteria 2-4 had moderate FLD; and patients who met criterion 1, 2 of the criteria 2-4 and criterion 5 had severe FLD.

The exclusion criteria were: (1) mild FLD by ultrasound B-mode scanning; (2) long-term history of alcohol consumption (alcohol content >30 g/day for men and >20 g/day for women) for >5 years; (3) coexistent viral hepatitis; (4) cirrhosis and liver malignancy diagnosed by ultrasound B-mode, computed tomography (CT), or magnetic resonance imaging (MRI) scanning or imaging; (5) pregnant and lactating women; (6) coexistent autoimmune and hereditary liver diseases as well as thyroid disease; (7) coexistent infection, anemia, and vital organ diseases; (8) consumption of any drugs in the past 1 month that affects glucose and fat metabolism; and (9) unwilling to participate in this study.

### Measurement of Biochemical Indicators

Peripheral venous blood was collected from all the patients and controls in the morning after 12 h of fasting. Clinical indicators were detected, including liver and kidney function, total cholesterol (TC), glycerol triglyceride (TG), fasting blood sugar (FBS), hepatitis, and tumor markers, as well as thyroid function.

### Measurement of Anthropometric Indicators

After 12 h of fasting, all the patients and controls were asked to wear a single cloth and barefoot to take measurements after passing urine and stools in the morning. Height and weight were simultaneously measured by 2 trained physicians, and BMI was calculated.

### Body Composition Analysis

All the patients and controls were measured in the fasting state in the morning using a body composition analyzer (InBody 720; Biospace Co. Ltd., Korea). After emptying of urine and stool, intracellular water (ICW), extracellular water (ECW), protein, fat, skeletal muscle content, and visceral fat area (VFA) of the patients were recorded.

Patients were not allowed to carry electronic components and metal objects when taking measurements. The body composition analyzer used a whole-body 4-electrode contact method. A multi-frequency impedance analyzer was used to generate 100 mA alternating current at 1 kHz. The operating frequencies were 5, 50, and 100 kHz when 800 mA alternating current was applied.

### Metabolic Measurement

Measurements were performed using a $V_{max}$ 229 metabolism cart (SensorMedics, Yorba Linda, CA, USA). The subjects were required to fast for >8 h before examination. The subjects lay flat in bed after resting for 30 min quietly. The ambient temperature was 24-26°C, and the humidity was 45-60%. The examination laboratory was kept quiet during the measurement and monitoring that continued for 20 min. All subjects were required to remain awake throughout the examination as well as be as quiet

as possible. Before measurement, the metabolic cart was warmed up for 30 min, and then calibrated for gas flow. Face masks were placed on the heads of the subjects and sealed. Concentrations of $O_2$ and $CO_2$ in the inhaled and exhaled gases were analyzed using gas analyzers. Oxygen consumption ($VO_2$) and carbon dioxide production ($VCO_2$) during this time period were calculated. Meanwhile, the volume of inhaled and exhaled gases, and concentrations of $O_2$ and $CO_2$ were precisely calculated, and thus the respiratory quotient (RQ), which was the ratio of the average $CO_2$ production to the $O_2$ consumption, was calculated. Resting energy expenditure (REE) (kcal/day) = $[(3.9 \times VO_2) + (1.1 \times VCO_2)] \times 1440$ was calculated based on the Weir formula,[14] and then the REE and 3 major nutrient oxidation rates, including the rates of carbohydrate oxidation (CHO%), fat oxidation (FAT%), and protein oxidation (PRO%) were measured. The testers were unaware of the clinical indicators of the patients and controls.

### *Statistical Analysis*

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). The normality and variance homogeneity of indicators in each group were examined. Continuous data that met a normal distribution were represented by mean ± standard deviation. One-way analysis of variance was used for comparison between groups. If variances were homogeneous, multiple comparisons were performed using the least significant difference method. Otherwise, Dunnett's test was used for making multiple comparisons. The $\chi^2$ test was used to compare the percentages, and $P < .05$ was considered significant.

## *RESULTS*

### *Serological and Anthropometric Indicators in Obese NAFLD, Lean NAFLD, and Control Groups*

Anthropometric and biochemical indicators such as BMI, alanine aminotransferase (ALT), TG, TC, low-density lipoprotein (LDL), high-density lipoprotein (HDL), FBS, and uric acid (UA) in the obese and lean NAFLD groups are shown in Table 1. There was no significant difference in age, sex, and TC among the obese NAFLD, lean NAFLD, and control groups ($P = .895$, .306, and .379, respectively). Compared with the control group, the levels of ALT, TG, LDL, FBS, and UA significantly increased in the lean NAFLD group ($P = .007$, .032, .001, <.001, and <.001, respectively); no difference in BMI was observed ($P = .104$), and the HDL level was significantly lower ($P = .007$). Compared with the obese NAFLD group, BMI significantly decreased in the lean NAFLD group ($P < .001$), while the levels of LDL and UA significantly increased ($P = .001$ and 0.006, respectively).

### *Body Composition Analysis in the Obese NAFLD, Lean NAFLD, and Control Groups*

ICW, ECW, protein, body fat, skeletal muscle, and VFA were measured using a body composition analyzer to evaluate changes in body composition in patients (Table 2). Skeletal muscle content was not significantly different among the 3 groups ($P = .067$). ICW, ECW, protein, and body fat in the lean NAFLD group were not significantly different compared to the control group ($P = .373$, .133, .489, and .033, respectively), whereas VFA increased significantly ($P = .008$). ICW, ECW, protein, body fat, and VFA in the lean NAFLD group were all lower than that in the obese NAFLD group (all $P < .001$).

**Table 1.** Measurement and Biochemical Indicators of NAFLD Patients and Controls

| Indicator | Obese NAFLD Group, $n = 205$ | Lean NAFLD Group, $n = 73$ | Control Group, $n = 50$ | Test Value | *P* |
|---|---|---|---|---|---|
| Gender (Male/Female) | 105/100 | 38/35 | 29/21 | 6.0 | .306 |
| Age | 57.35 ± 12.06 | 57.59 ± 10.10 | 56.43 ± 5.23 | 0.111 | .895 |
| BMI | 31.91 ± 3.43 | 23.97 ± 1.67* | 24.12 ± 1.94* | 107.77 | <.001 |
| ALT | 28.11 ± 13.79 | 29.95 ± 19.16 | 18.82 ± 9.72*& | 5.573 | .021 |
| TG | 2.09 ± 0.97 | 2.88 ± 1.56 | 1.21 ± 0.76*& | 3.676 | .028 |
| TC | 4.76 ± 1.22 | 4.83 ± 0.75 | 4.49 ± 0.72 | 0.973 | .379 |
| HDL | 1.22 ± 0.31 | 1.13 ± 0.33 | 1.48 ± 0.35*& | 9.847 | <.001 |
| LDL | 2.53 ± 0.97 | 2.89 ± 0.94* | 2.21 ± 0.37*& | 6.991 | .003 |
| FBS | 6.17 ± 2.64 | 5.96 ± 2.31 | 5.20 ± 1.45*& | 19.74 | <.001 |
| UA | 327.31 ± 87.31 | 355.81 ± 82.31* | 273.16 ± 81.41*& | 67.91 | <.001 |

*Means that compared with obese NAFLD group, $P < .01$. &Compared with lean NAFLD group, $P < .01$.

**Table 2.** Body Compositions and Metabolism Indicators Between NAFLD Patients and Controls

| Indicator | Obese NAFLD Group, $n = 205$ | Lean NAFLD Group, $n = 73$ | Control Group, $n = 50$ | $F$ | $P$ |
|---|---|---|---|---|---|
| ICW | 22.18 ± 5.06 | 20.58 ± 3.63* | 19.66 ± 4.14* | 5.722 | .003 |
| ECW | 14.17 ± 2.75 | 13.15 ± 2.18* | 12.21 ± 2.25* | 8.974 | <.001 |
| Protein | 9.65 ± 2.06 | 8.90 ± 1.51* | 8.67 ± 1.84* | 6.432 | .002 |
| Fat | 27.84 ± 7.80 | 20.13 ± 9.23* | 20.75 ± 7.64* | 75.93 | <.001 |
| Skeletal muscle | 26.98 ± 6.16 | 24.85 ± 6.29 | 25.69 ± 5.36 | 1.076 | .067 |
| VFA | 111.21 ± 20.31 | 90.84 ± 21.18* | 85 ± 16.37*& | 23.72 | <.001 |
| RQ | 0.76 ± 0.06 | 0.78 ± 0.08 | 0.80 ± 0.02* | 1.64 | .024 |
| REE | 1866.21 ± 317.12 | 1707.87 ± 374.40 | 1407.31 ± 314.29*& | 28.02 | <.001 |
| REE/Weight | 24.3 ± 3.98 | 27.47 ± 5.3* | 24.81 ± 4.95& | 20.57 | <.001 |

*Compared with obese NAFLD group, $P < .01$; &Compared with lean NAFLD group, $P < .01$.
ICW, intracellular water; ECW, extracellular water; VFA, visceral fat area; RQ, respiratory quotient; REE, resting energy expenditure.

**Table 3.** The Oxidation Rates of the 3 Major Nutrients Between NAFLD Patients and Controls

| Indicator | Obese NAFLD Group, $n = 205$ | Lean NAFLD Group, $n = 73$ | Control Group, $n = 50$ | $F$ | $P$ |
|---|---|---|---|---|---|
| CHO% | 16.23 ± 7.41 | 29.31 ± 7.07* | 31.46 ± 9.26* | 6.681 | .003 |
| FAT% | 67.40 ± 11.31 | 55.59 ± 12.09* | 54.22 ± 18.47* | 4.586 | .014 |
| PRO% | 16.37 ± 4.12 | 15.10 ± 4.07 | 14.32 ± 5.55 | .394 | .676 |

*Compared with obese NAFLD group, $P < .01$; &Compared with lean NAFLD group, $P < .05$.
CHO%, carbohydrate oxidation rate; FAT%, fat oxidation rate; PRO%, protein oxidation rate.

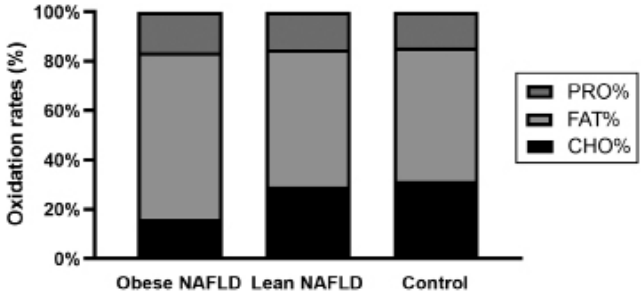


**Figure 1.** Oxidation rates of the 3 major nutrients.

### *Comparison of Metabolic Status Among the Obese NAFLD, Lean NAFLD, and Control Groups*

In this study, RQ and REE of the 3 groups were detected by metabolic cart. The 24 h urine nitrogen value was inputted to obtain the oxidation rates of the 3 major nutrients, including the percentages of CHO%, FAT%, and PRO% (Tables 2, 3 and Figure 1). The results showed that REE of the lean NAFLD group was not significantly different compared to that of the obese NAFLD group ($P = .309$); however, it was significantly higher than that of the control group ($P < .001$). REE/Weight of the lean NAFLD group was higher than that of the obese NAFLD and control ($P < .001$). CHO%, FAT%, and PRO% in the lean NAFLD group were 29.31 ± 7.07%, 55.59 ± 12.09%, and 15.10 ± 4.07%, respectively, and there was no significant difference compared to the control group. However, when compared to the obese NAFLD group, the lean NAFLD patients' CHO% increased, whereas FAT% decreased (both $P < .001$).

## *DISCUSSION*

In this study, the nutritional status of NAFLD patients was comprehensively evaluated by analyzing changes in body composition using serological indicators and bioelectrical impedance analysis (BIA). Glucose and fat metabolism of lean NAFLD patients was disordered, which was similar to the obese NAFLD patients. Moreover, ALT, TG, LDL, FBS, and UA were significantly higher than in the control group, while HDL was significantly lower. The above-mentioned results suggested that NAFLD was closely associated with a disorder in glucose and fat metabolism, which is a typical manifestation of metabolic syndrome. Our findings were consistent with reports from China and other countries.[4,5] Recently, scholars have proposed the concept of MAFLD, which highlighted the importance of metabolic dysfunction in NAFLD patients.[15]

LDL and UA in patients with lean NAFLD were even higher than in patients with obese NAFLD. It has been

reported that elevated LDL is an independent risk factor for lean NAFLD.[16] In addition, UA is the final product of purine metabolism, while imbalance of UA excretion and secretion can lead to hyperuricemia. Hyperuricemia is the pathological basis of gout and is closely associated with hypertension, obesity, insulin resistance, and atherosclerosis.[17] Studieshave demonstrated that UA is involved in the development of NAFLD, and the 2 interact with each other.[18,19] Liver fat content is positively correlated with blood UA level. A cross-sectional study has shown that the incidence rate of lean NAFLD is higher compared to that of obese NAFLD with increased levels of blood UA.[20] Thus, it is speculated that monitoring of LDL and level of blood UA in lean individuals, and earlier intervention may be useful methods to control the occurrence and development of NAFLD.

Body composition analysis includes measurement of muscle, protein and fat, along with ICW and ECW. Clinically, a composition analyzer is used most frequently for measurement and analysis, with the advantages of BIA. Electrical characteristics of the human body are used in BIA for measurement of the composition and percentages of different components, such as muscle, protein, and body fat. After years of development and clinical practice, BIA has been widely applied in different fields (e.g., nutrition and rehabilitation). The accuracy and practicability of BIA in measuring body composition have been recognized in China and other countries.[21-23] Therefore, BIA was used in the current study to further assess the nutritional status of obese and lean NAFLD patients.

Our study clearly revealed the changes in body composition in patients with obese NAFLD, which were similar to those in patients with lean NAFLD and the controls. ICW, ECW, protein, and body fat of patients with lean NAFLD were lower compared to patients with obese NAFLD, while skeletal muscle content did not differ significantly among the 3 groups. However, VFA was different among the 3 groups, suggesting that although the BMI of patients with lean NAFLD was similar to that in the control group, the level of VFA significantly increased. Previous studies have demonstrated that people with visceral obesity (or named as abdominal obesity) are susceptible to FLD, which is because fat cells around the abdomen are more sensitive to irritation, resulting in increased fatty acid transportation from the abdominal fat cells to the liver. The results indicated that VFA may be a more sensitive indicator to evaluate lean NAFLD. Therefore, evaluation of the nutritional status of NAFLD patients does not solely depend on BMI, and an indicator of visceral obesity should also be included as well.[24]

It is well known that REE is the main indicator for assessing energy metabolism in the body. REE refers to energy consumption after fasting for >2 h, in addition to resting in the supine position for 30 min at an appropriate temperature, which is mainly used to maintain the normal function of cells and organs in the human body, as well as in the waking state. Indirect calorimetry is a method for accurately estimating energy consumption in humans and is considered to be the gold standard. At present, the metabolic cart is a widely used and accurate method for evaluating patients' energy consumption and is used as a gold standard for evaluating energy metabolism as well.[25] REE accounts for 60-75% of the total energy consumption of the human body, and thus it is an important monitoring indicator for determining energy consumption as well as preventing and treating obesity.[26] The classical theory demonstrates that the metabolism of obese people is slow[27]; however, in recent years, opposing opinions have considered that REE of obese individuals or NAFLD patients is higher.[28-31]

Our study showed that REE of the obese and lean NAFLD groups was significantly higher than that of the control group. REE is affected by several factors. Previous studies have shown that REE is significantly associated with fat content,[32] which may be because the VFA of NAFLD patients is significantly increased.[33] Higher REE is caused by imbalance of body compositions.[34] Our study demonstrated that increased REE in lean NAFLD patients was consistent with the increase in VFA.

After balancing REE with body weight, we found that the REE/weight of lean NAFLD patients was higher than that of obese NAFLD patients and control. Previous studies report that the REE per body weight may be more useful in the evaluation of energy consumption status and indirectly on the inflammatory status of NAFLD patients by minimizing the effects of body weight.[35] People with non-obese NAFLD are metabolically unhealthy and many have NASH (40%) and fibrosis (≥stage 2; 30%).[7] We speculate that lean NAFLD patients may have worse metabolic performance.

RQ refers to the ratio of the $CO_2$ volume released by an organism to the absorbed $O_2$ volume at the same time, that is, the ratio of the number of molecules of $CO_2$ released to the number of molecules of $O_2$ absorbed by respiration. During oxidation, the respiratory quotients of fat, protein, and carbohydrate were about 0.7,

0.8, and 0.95-1.0, respectively. Our study showed that the RQ of obese NAFLD patients significantly decreased, while that of lean NAFLD patients did not differ significantly from that of the control group. A previous study has demonstrated that sympathetic activity in the muscles of obese patients is low, which may affect RQ.[36] Another study has shown that RQ is negatively correlated with body weight; the lower the body weight, the higher the RQ,[37] which is consistent with our results. BMI of lean NAFLD patients was not significantly different compared to that in the control group, and thus, the RQ level did not change.

It can be concluded from the oxidation rates of the 3 major nutrients that CHO%, FAT%, and PRO% of the lean NAFLD group were not significantly different compared to those in the control group. CHO% of the lean NAFLD patients decreased compared to the controls, although not significantly. Although CHO% decreased and FAT% increased, there was no significant change in PRO% in the obese NAFLD group compared to the control and lean NAFLD groups. The oxidation rate of carbohydrates was significantly reduced, suggesting that there was a disorder in glucose utilization, which may have been related to insulin resistance.[38] The results demonstrated that controlling visceral fat content and reducing insulin resistance were important for improving prognosis in obese or lean NAFLD patients. For the obese and lean NAFLD patients, they all had higher REE, but their CHO% was relatively low than the control. Diet and physical exercise are very important for improving metabolic status.[31] They are the first-line treatment modalities. Diet and exercise that result in a sustained body weight reduction of 7-10% can improve liver fat content, NASH, and fibrosis.[39,40] We believe that changing REE and body composition by physical exercise and proper diet intake could improve the NAFLD patients' metabolic abnormality.

However, there were still some limitations in our study. First, this study was a single-center study and was conducted with patients of Asian ethnicity. Therefore, whether these results are suitable for other races needs further demonstration. And the results should be further supplemented by more data in order to reduce bias. Second, we did not record the diet and exercise habits in this observational cross-sectional study. Although the REE, RQ, and oxidation rate of 3 major nutrients (carbohydrate, CHO%, fat, FAT%, and protein, PRO%) can indirectly reflect the status of diet and exercise habits, direct data may be more illustrative. And in future studies, these data and in-depth investigations on the intervention and mechanism of the disease are needed. Third, metabolic dysregulation is accepted to be the driving force in the pathogenesis of NAFLD. Therefore, recently a change in acronym from NAFLD to MAFLD (metabolic associated fatty liver disease) was recommended.[15,41] But when we selected the cases 3 years ago, we still followed NAFLD standards, and so in this paper, the term NAFLD is used. We will further improve this in future research.

In summary, this study demonstrated that patients with obese/lean NAFLD had nutritional imbalance and disorder of energy metabolism. The body composition analyzer and metabolic cart can comprehensively evaluate the nutritional status and energy metabolism of patients with NAFLD, which can provide a reliable basis for clinical intervention and monitoring of the disease.

***Ethics Committee Approval:*** This research was approved by the Institutional Review Board (IRB).

***Informed Consent:*** All the NAFLD patients and controls signed informed consent.

***Peer-review:*** Externally peer-reviewed.

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***Conflicts of Interest:*** The authors have no conflict of interest to declare.

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