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*Basic Study*

Body mass index and its effects on liver fat content in overweight and obese young adults by proton magnetic resonance spectroscopy technique

Pasanta D *et al.* Liver fat content

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**Abstract**

***AIM***

To assess the association between liver fat content (LFC) and weight status in young adults using proton magnetic resonance spectroscopy (1H MRS) technique.

***Methods***

Seventy eight healthy young adults, between 19-30 years of age participated in this study. This group was then separated into a control of 39 subjects and an overweight/obese group (OW/OB group) consisting of 39 subjects. Blood biochemical quantity and 1H MRS was performed for LFC assessment.

***Results***

LFC was found to be almost 3 times higher in OW/OB group when compared to the control group. A 48.7% incidence of non-alcoholic fatty liver disease in OW/OB group was found. Blood biochemical measurements showed statistically higher low density lipoproteins and triglyceride, lower high density lipoproteins with elevated glycosylated haemoglobin and fasting glucose in the OW/OB group. Body mass index was a significant independent predictor for LFC after adjusting for age and sex (multiple linear regression; β *=* 0.459, *P <* 0.001).

***Conclusion***

Due to the prevalence of high LFC in the OW/OB group, it can be proposed that weight gain and obesity are sensitive indicators of high hepatic fat content.

**Key words**: Young adults; Overweight; Obesity; Non-alcoholic fatty liver disease; Body mass index; Proton magnetic resonance spectroscopy; Cholesterol

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**Core tip:** Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. The prevalence of NAFLD in young adults has led to growing concerns about it. Interestingly, the liver fat content (LFC) of an overweight/obese group was approximately 3 times higher than the control group. This result suggests that obesity can increase LFC, and is a risk factor for higher NAFLD in overweight and obese young adults. This current study also demonstrated the importance of Body Mass Index as a tool for risk prevention and control of NAFLD and metabolic syndromes.

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# Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases and is increasing at an alarming rate. Previous studies have reported positive correlation of BMI and lipid accumulation in the liver, a higher risk of NAFLD, cirrhosis[1,2], and dyslipidaemia[3].

Due to modern lifestyles and diet, there has been a persistent increase in the number of NAFLD patients. This increase occurred at the same time that there were also increases in the number of people considered to be obese all over the world[4,5]. NAFLD in young adults is a topic that has received slight recognition, yet this age group is the most likely to gain weight and develop obesity from diet and lifestyle as they are transitioning into adulthood[6]. The prevalence of NAFLD in young adult has increased almost 2.5 times over 30 years with half of morbidly obese young adults having NAFLD[7]. However, despite the growing public health concern about obesity and NAFLD in young adults, necessary information addressing the effects of obesity and NAFLD pathogenesis in this age group is deficient in number, and there is an urgent need for better considerate of its effects and mechanisms[8,9]. Proton magnetic resonance spectroscopy (1H MRS) is a well-established non-invasive technique for liver metabolite assessment and is known for its high accuracy for determining liver fat quantification when compared to biopsy[10,11]. As far as we know, there’s no study to date that has investigated the effects of obesity on liver fat content (LFC) by 1H MRS in healthy young adults.

The aim of this present study is to assess the association between LFC by 1H MRS technique, blood serum biochemical measures of total cholesterol (Cho), low density lipoproteins (LDL), high density lipoproteins (HDL), fasting plasma glucose (FG), glycosylated haemoglobin (HbA1c), and being overweight/obese (OW/OB) as a young adult.

# Materials and methods

## Study population

The population of this current study is 78 healthy young adults between 19-30 years of age. Subjects were randomly chosen from a young adult population residing in Chiang Mai, Thailand through recruitment efforts using posters, or were personally invited to join the study. The control group was comprised of 39 subjects who had engaged in moderate physical activity, and who had a body mass index (BMI) in the normal range according to World Health Organization (15.8-24.9 kg/m2)[12]. OW/OB group was comprised of 39 subjects who had a BMI that was in the overweight and obese range > 25 kg/m2[12]. Exclusion criteria for both group was diagnoses with a chronic disease or liver injury in any form, alcohol consumption of more than 150 g/wk, hyperglycaemia (FBS > 140 mg/dL), hypertriglyceridemia (TG > 300 mg/dL), have received hepatotoxic medications, were athletes, had any contraindication for magnetic resonance imaging (MRI) and poor 1H MRS resolution. Subjects were given a questionnaire about health and lifestyle in order to include or exclude subjects for the study. Eating and exercise habits, occupation, personal and family medical history was also provided. All procedures were approved by the Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand (AMSEC-61EX-016).

## LFC assessment by 1H MRS

Liver metabolite spectra were obtained by 1H MRS technique on MRI 1.5 T (Achieva, Philips Medical Systems, Best, The Netherlands) using sense cardiac coil. T2-weighted turbo spin echo (TSE) transverse (TR/TE *=* 871/80 ms) and coronal T2-weighted (TR/TE *=* 829/80 ms) images were applied for localization. PRESS sequence with TR *=* 2000 ms, TE *=* 43 ms, nonenyl succinic acid *=* 96. Voxel size of 10 mm3 × 10 mm3 × 10 mm3 was carefully placed in right lobe of the liver (Couinaud lobe segment V-VIII), carefully avoiding any large vessels and bile duct. The liver metabolite signals without water suppression were obtained and analysed for metabolized quantification by AMARES algorithm available on jMRUI software[13-15]. Spectrum fitting and quantification was done for water peak (4.72 ppm), and major lipid spectrum peaks (CH3 *=* 0.9 ppm, CH2 *=* 1.3 ppm, 2.1 ppm) with prior knowledge and Gaussian line shape was then applied[16]. Signal intensity correction was done for T2 relaxation using linear least-square equation with previous determination for T2 of water and fat. LFC was calculated by a validated method described elsewhere[17,18]. NAFLD was determined as LFC > 5.56%[18].

## Blood examination

Blood collection of subjects was done by The Associated Medical Science Clinical Service Center, Chiang Mai University. 10 mL of intravenous blood was drawn from antecubital veins and was biochemically analysed using a fully automated analyser (Architect ci8200, Abbott Diagnostic). The test focused on Cho, HDL, VLDL, TG, FG, and HbA1c. Subjects were told to fast for 10-12 h prior to blood examination. Later, LDL concentration was calculated from novel adjustable LDL estimation equations[19,20].

Dyslipidemia was described as an abnormality of Cho levels in plasma including increased Tri, LDL, and low HDL. The National Cholesterol Education Project (NCEP) Adult Treatment Panel (ATP) III has defined dyslipidemia as Cho ≥ 200 mg/dL, Tri ≥ 150 mg/dL, LDL ≥ 130 mg/dL, HDL ≤ 40 mg/dL[21]. Normal FG ranges should be between 70-100 mg/dL, and FG between 100-125 mg/dL is considered as prediabetes. Normal HbA1c levels should be less than 6%[22].

## Anthropometry

Every subject was measured by the same examiner. Subjects wore only an examination cloth. Height and bodyweight were measured to the nearest 0.5 cm and 0.1 kg respectively. Hip circumference (HC) and waist circumference (WC) was acquired while instructed to breathe out mildly. Both measurements were done using non-elastic tape. WC was measured at the midpoint of the lower margin of rib and top of iliac crest. HC was measured at the widest section of buttocks. Waist to hip ratio (W/H ratio) was calculated from WC divided by HC.

## Statistical analysis

Statistical analysis was performed on SPSS using statistical software version 17.0. Normal distribution results are expressed as means ± SD. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were performed to determine data normality. Comparison of LFC and blood biochemical examination between groups was then further compared with an unpaired samples *t*-test. Relationship between groups was done with Pearson correlation. Multiple stepwise linear regression analysis was used to verify the relationships between LFC and independent of significant corelate variables. Results with *P*-value < 0.05 were considered statistically significant.

# Results

A total of 78 healthy subjects in the young adult age group (19-30 years old) participated in this study. Control group of 39 subjects and OW/OB of 39 subjects had BMI of 20.9 ± 0.3 and 31.3 ± 0.5 kg/m2 respectively. The characteristics of LFC, anthropometric and biochemical data of all subjects were shown in Table 1.

Seventy-eight spectra were obtained and were analysed for LFC. The corrected value of liver fat by weight was calculated by a method validated by Longo *et al*[17] and Szczepaniak *et al*[18]. Representative spectrum from the right lobe of liver is shown in Figure 1.

As expected, LFC, anthropometric, and biochemical results were significantly different between the two groups except for age and Cho. The OW/OB group reported statistically higher BMI, LFC, WC, HC, FG, Tri, LDL, HbA1c, and statistically lower HDL. Cho also was found to be increased in OW/OB group, but this tendency was not statistically significant. The prevalence of dyslipidaemia in OW/OB group (69.2%) was higher than in the control group (48.7%). There were no subjects in the control group who exceeded the normal FG and HbA1c ranges.

Interestingly, the LFC of OW/OB group was approximately 3 times higher than the control group. Additionally, 19 subjects (48.7 %) in OW/OB group had LFC > 5.56% which is considered to be a cut off point for NAFLD according to a previous large cohort 1H MRS LFC study[18]. Furthermore, dyslipidaemia was present in 47.4% of OW/OB groups, and abnormal HbA1c was found in 10.5% of OW/OB subjects, as well.

The data in this study was normally distributed. Pearson correlation analysis was conducted as preliminary analysis for possible predictor variable for LFC and is presented in Table 1. Various statistically significant correlations of LFC and variables were found, with moderate correlation occurring with BMI and mild correlation with W/H ratio, HbA1c, and Waist circumference. Among the blood biochemical results, HbA1c showed the highest correlation with LFC followed by Tri. The Pearson correlations and data distribution by sex in both groups is shown in Figure 2. This indicates that the overall data between male and woman in each group is distributed in the same way.

The correlation was then compared between HbA1c and FG to determine the indicator for diabetes. Even if a low positive correlation was found in FG, it is not statistically significant, while the HbA1c showed statistically significant positive correlation with LFC. The correlation of diabetes (HbA1c and FG) markers was compared in Figure 3.

A multiple linear regression was used to predict the LFC from significantly correlated blood biochemical marker (HbA1c, Tri) and anthropography marker (BMI, W/H ratio), standardized coefficient and correlations are presented in Table 2. BMI and HbA1c were found to be significant positive independent predictor for LFC after adjusting for age and sex. However, only BMI remained statistically significant as an independent predictor for LFC after adjusting for age, sex, and BMI.

# Discussion

In recent years, the prevalence of NAFLD in young adults has been increasing at an alarming rate that parallels with a global epidemic of weight gain and obesity. The prevalence of obesity in young adult is double that of younger ages[8]. Various studies have stated the close relationships of obesity, dyslipidaemia, insulin resistance, and NAFLD[23,24]. MRI has proven to be powerful imaging tools for liver cirrhosis diagnosis[25], and is known for its ability to non-invasively and accurately quantify liver fat in the liver using the 1H MRS technique which is suitable for longitudinal follow-ups when compared to liver biopsy. Liver biopsies are the gold-standard, but are an invasive method.

The results of this study confirmed once again the association between BMI and LFC, the higher risk of dyslipidaemia, the probability of insulin resistance, and the prospect of metabolic disease in young adults.

The highlight of this study is that LFC in OW/OB group is almost higher when compared to the control group, even if both groups were revealed to be healthy. This prevalent rate is consistent with earlier findings where 57.4% of NAFLD subjects in young adults also had high BMI[7,26]. This tendency also should also be considered with higher prevalence of dyslipidemia, prediabetes and hyperglycemia among subject with LFC > 5.56%. In accordance with the present results, previous studies have demonstrated that the risk for dyslipidaemia starts to increase progressively with the BMI at 21 kg/m2, as LDL and Tri levels are used to evaluate the risk for coronary artery disease[27].

A new important finding is that the biochemical and anthropographic markers associated with LFC are significantly different between OW/OB and control group. Among the blood lipid markers, Tri and LDL were found to be statistically higher, and HDL was found to be statistically lower when compared to control group. However, no significant differences were found for Cho, even if the Cho in OW/OB had increased slightly, with almost half of control group having dyslipidaemia. This could explained by the fact that the two characteristics of subjects in this age group were that they were exposed to high caloric, low fiber “ready-to-eat” foods, consumed sugary beverages, and had low physical activity. It can be expected that these effects can change the Cho levels in blood[6,28].

The Pearson correlation analysis showed moderate correlation of BMI and LFC (r *=* 0.531, *P* < 0.001) and mild correlation with W/H ratio (r *=* 0.388, *P <* 0.001) and WC (r *=* 0.259, *P =* 0.022). The association of BMI and LFC was additionally confirmed by multilinearity regression analysis as a significant independent variable after being adjusted for age, sex, and other anthropometric variables. This outcome is dissimilar with previous studies that proposed that W/H ratio can be used as a tool to predict the risks of liver cirrhosis and NAFLD in place of BMI[29,30]. A possible explanation is the difference in fat accumulation mechanisms and that weight gaining is the main pathogenic mechanism of liver fat accumulation in this age group as was previously proposed by Van Wagner *et al*[31].

HbA1c and FG are also found to be statistically different when compared to control, with a feeble positive correlation taking place with LFC. However, only HbA1c is the statistically significant independent variable for LFC after adjusting for age and sex. This result may suggest that HbA1c is a better tool for reflecting the NAFLD effects on insulin resistance than the FG. This assumption is reflected in other research done on the association between HbA1c and NALFD in non-diabetic subjects[32] and on the association of prediabetes characteristics independent of total body fat in obese adolescents with high liver fat assessment by MRI[23]. Elevated HbA1c further confirms the high risk of cardio vascular disease and insulin resistance in overweight and obese young adult.

This study has a few limitations such as the high prevalence of dyslipidemia in the control group that maybe caused by the sample characteristics. This group being mostly comprised of with young adults engaged in academic studies and whose exercise levels were determined by questionnaire. There may have been a potential for over reporting by the subjects. A second limitation is that LDL was calculated by an adjustable ratio equation and was not measured directly by biochemical assessment.

However, to best of our records, this is the first study on the topic of non-invasive assessment of LFC by 1H MRS technique in healthy young adults without any complications or earlier diagnosis of chronic disease. The high prevalence of NAFLD (LFC > 5.56%) contributed to the impact of silent chronic disease in young adults that had become obese. Although the current study is based on a small sample of subjects, the findings have drawn together various interesting subjects on the effects of BMI and how it contributes to LFC and how it is a high risk factor of metabolic syndrome in young adults. Previous studies on young adults after 39 years as a follow-up has shown that obesity obtained in the young adult age groups is sustained into adult life and increases the risk of developing severe liver disease[26]. This study suggests a role of BMI in increasing LFC and as a factor in higher NAFLD risks for overweight and obese young adults. The importance of weight control as the primary risk prevention and control of NAFLD and many metabolic syndromes has been proposed. However, this study may reveal the importance in raising awareness for early prevention before NAFLD transitions into chronic liver disease later in adulthood. Future studies on this topic are therefore recommended as young adults are at a high risk for developing severe liver disease. Further, implications of these findings may be forthcoming in future research using longitudinal studies with larger groups of subjects.

In conclusion, it is proposed that the prevalence of high LFC in OW/OB group can be the result of weight gain and obesity, and maybe a leading pathogenic mechanism of liver fat accumulation in young adults. This current study demonstrated the importance of BMI as a tool for the prevention and control of NAFLD and metabolic syndrome in young adults.

**ARTICLE HIGHLIGHTS**

***Research background***

In recent years, the prevalence of non-alcoholic fatty liver disease (NAFLD) in young adults has been increasing at an alarming rate that parallels with a global epidemic of weight gain and obesity. NAFLD in young adults is a topic that has received little recognition, yet this age group is the most likely to gain weight and develop obesity from diet and lifestyles, as they are transitioning into adulthood. However, despite the growing public health concern about obesity and NAFLD in young adults, necessary information addressing the effects of obesity and NAFLD pathogenesis in this age group is in short supply.

***Research motivation***

NAFLD is a chronic liver disease which is one of the most common health problem among young adults. We aim to identify the effects of obesity on of liver fat content (LFC) and health in this age group. This information is crucial for primary prevention and better understanding of NAFLD pathogenesis in young adults.

***Research objectives***

The aim of this present study is to assess the association between LFC by proton magnetic resonance spectroscopy (1H MRS) technique. Using biochemical measures of blood serum, the total cholesterol (Cho), low density lipoproteins (LDL), high density lipoproteins (HDL), fasting plasma glucose (FG), glycosylated haemoglobin (HbA1c), and being overweight/obese (OW/OB) will be determined for these young adult subjects.

***Research methods***

A total of 78 healthy subjects in the young adult age group (19-30 years old) participated in this study. A control group was made up of 39 healthy subjects, and 39 overweight or obese (OW/OB) young adult subjects made up the experimental group. We performed the liver fat assessment by 1H MRS technique on MRI 1.5 T that was calculated into LFC. Intravenous blood was drawn for biochemical analysis. The test focused on Cho, HDL, VLDL, TG, FG, and HbA1c. Every subject was measured for hip circumference (HC), waist circumference (WC), and waist to hip ratio (W/H ratio).

***Research results***

LFC from OW/OB group (8.07% ± 1.02%) was found to be statistically higher when compared to control group (2.74% ± 0.20%) with *P <* 0.001. Additionally, 48.7% of subjects in OW/OB group had LFC > 5.56% which is considered to be a cut off point for NAFLD. The OW/OB group reported statistically higher BMI, LFC, WC, HC, FG, Tri, LDL, HbA1c, and statistically lower HDL. Cho also was found to be increasing in OW/OB group, but this tendency was not statistically significant. The association of BMI and LFC was additionally confirmed by multilinearity regression analysis as a significant independent variable after being adjusted for age, sex, and other anthropometric variables with *P <* 0.001. These findings indicated that BMI is a sensitive marker for LFC in young adults.

***Research conclusions***

It is proposed that the prevalence of high LFC in OW/OB group can be the result of weight gain and obesity, and may be a leading pathogenic mechanism of liver fat accumulation in young adults. Moreover, high BMI is associated with being a high risk factor for metabolic syndrome in young adults. This current study demonstrated the importance of weight control as a tool for the prevention and control of NAFLD and metabolic syndrome in young adults.

***Research perspectives***

Further study on this topic may require larger groups of subjects, or should also investigate the alteration of LFC and BMI throughout the adult years as a longitudinal study.

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**Figure 1 Proton magnetic resonance spectroscopy technique was used for liver fat assessment,** **water peak was shown occurring at 4.72 ppm, peaks in fat for CH3 occurred at 0.9 ppm, and CH2 peaked at 1.3 ppm and 2.1 ppm.** A: Magnetic resonance imaging axial image of abdomen show voxel localization in right lobe liver for liver fat content quantification; B: Representative fitted proton magnetic resonance spectroscopy spectrum of right lobe liver.

**Figure 2 Pearson correlation coefficient (r) and data distribution by sex in each group between body mass index, Waist to hip ratio, glycosylated haemoglobin and liver fat content as measured by** **proton magnetic resonance spectroscopy.** BMI: Body mass index; HbA1c: Glycosylated haemoglobin; LFC: Liver fat content; W/H ratio: Waist to hip ratio.



**Figure 3 Pearson correlation between glycosylated haemoglobin (circle in red, lower x axis), fasting plasma glucose (star in blue, upper X axis), and proton magnetic resonance spectroscopy as measured liver fat content.** BMI: Body mass index; FG: Fasting plasma glucose; HbA1c: Glycosylated haemoglobin; LFC: Liver fat content.

**Table 1 Characteristic and biochemical analysis of 78 subjects of control and overweight/obese group**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control group** | **OW/OB group** | ***P*-value** | **Correlation with LFC** |
| **r** | ***P* value** |
| *n* | 39 | 39 | - | - | - |
| Gender (male/female) | 12/27 | 24/15 | - | - | - |
| LFC (%) | 2.74 ± 0.20 | 8.07 ± 1.02 | < 0.001b  | - | - |
| Age | 22.3 ± 1.6 | 22.1 ± 0.3 | 0.662 | -0.058 | 0.611 |
| BMI (kg/m2) | 20.9 ± 0.3 | 31.3 ± 0.5 | < 0.001b  | 0.531 | < 0.001b  |
| WC (cm) | 74.6 ± 1.4 | 112.6 ± 7.4 | < 0.001b  | 0.259 | 0.022a  |
| HC (cm) | 90.7 ± 1.3 | 122.5 ± 7.5 | < 0.001b | 0.212 | 0.062 |
| W/H ratio | 0.82 ± 0.01 | 0.91 ± 0.01 | < 0.001b  | 0.388 | < 0.001b  |
| FG (mg/dL) | 83.1 ± 1.1 | 89.9 ± 1.1 | < 0.001b  | 0.144 | 0.210 |
| Cho (mg/dL) | 187.3 ± 6.8 | 200.7 ± 6.1 | 0.147 | 0.093 | 0.419 |
| Tri (mg/dL) | 77.8 ± 5.2 | 117.1 ± 8.8 | < 0.001b  | 0.223 | 0.050  |
| HDL (mg/dL) | 59.3 ± 2.5 | 47.7 ± 1.4 | < 0.001b | -0.185 | 0.105 |
| LDL (mg/dL) | 111.1 ± 5.6 | 130.1 ± 5.1 | 0.014a  | 0.133 | 0.246 |
| HbA1c (%) | 5.06 ± 0.07 | 5.46 ± 0.07 | < 0.001b  | 0.345 | 0.002a  |

Data expressed as mean ± SD. *aP* < 0.05; b*P* < 0.001. OW/OB: Overweight/obese; LFC: Liver fat content; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; W/H ratio: Waist to hip ratio; FG: Fasting plasma glucose; Cho: Cholesterol; Tri: Triglyceride; HDL: High density lipoproteins; LDL: Low density lipoproteins; HbA1c: Glycosylated haemoglobin.

**Table 2 Multiple linear regression analysis showing relationship of blood biochemical marker and anthropometry marker with liver fat content as the dependent variable**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **R2** | **β(SE)** | ***P*** | **R2** | **β(SE)** | ***P*** | **R2** | **β(SE)** | ***P*** |
| HbA1c | 0.135 | 0.306(1.273) | 0.002 | 0.174 | 0.339 (1.283) | 0.004 | 0.298 | 0.120(1.379) | 0.327 |
| Tri | 0.131(0.012) | 0.247 |  | 0.065 (0.013) | 0.590 | -0.029(0.012) | 0.590 |
|  | Model 1 | Model 2 |
| R2 | β(SE) | *P* | R2 | β(SE) | *P* |
| BMI | 0.295 | 0.463(0.109) | < 0.001a | 0.299 | 0.459(0.111) | < 0.001a |
| WC | -0.026(0.016) | 0.824 | -0.034(0.017) | 0.774 |
| W/H ratio | 0.145(8.768) | 0.247 | 0.136(9.018) | 0.288 |

Model 1 is unadjusted model; Model 2 is model 1 adjusted for sex, age; Model 3 is Model 2 adjust for body mass index. Statistical significant: *aP* < 0.001. β: Standardized coefficient; SE: Estimated error; R2: Correction coefficient; LFC: Liver fat content; HbA1c: Glycosylated haemoglobin; Tri: Triglyceride; BMI: Body mass index; WC: Waist circumference; W/H ratio: Waist to hip ratio.