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Contents

ABOUT COVER

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AIMS AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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ORIGINAL ARTICLE

Basic Study

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

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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 (^{1}H 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 ^{1}H MRS was performed for LFC assessment.

RESULTS
LFC was found to be almost three times higher in OW/OB group when compared to the control group. A 48.7% incidence of non-alcoholic fatty liver disease in the OW/OB group was found. Blood biochemical measurements showed statistically higher low-density lipoproteins and triglyceride, lower high-density lipoproteins, and increased glycosylated hemoglobin 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.

Core tip: Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. The prevalence of NAFLD in young adults is a growing public health concern. Interestingly, the liver fat content (LFC) of an overweight/obese group was approximately three 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.

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 a positive correlation between BMI and lipid accumulation in the liver, which leads to a higher risk of NAFLD, cirrhosis[1,2], and dyslipidemia[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 adults 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 lacking, and there is an urgent need for better consideration of its effects and mechanisms[8,9]. Proton magnetic resonance spectroscopy (^{1}H 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 ^{1}H MRS in healthy young adults.

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

MATERIALS AND METHODS

Study population

The subjects of this current study were 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 the World Health Organization (15.8-24.9 kg/m²)[12]. The 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 groups was diagnoses with a chronic disease or liver injury in any form, alcohol consumption of

more than 150 g/wk, hyperglycemia (FBS > 140 mg/dL), hypertriglyceridemia (TG > 300 mg/dL), hepatotoxic medication usage, athletes, contraindication for magnetic resonance imaging (MRI), and poor ^{1}H 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, and personal and family medical history were also provided. The Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand (AMSEC-61EX-016) approved all procedures.

LFC assessment by ^{1}H MRS

Liver metabolite spectra were obtained by ^{1}H 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, number of signal averages = 96. Voxel size of $10 \times 10 \times 10$ mm^3 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 analyzed 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 (CH_3= 0.9 ppm, CH_2= 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. Ten milliliters of intravenous blood was drawn from antecubital veins and was biochemically analyzed using a fully automated analyzer (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 and LDL, and decreased 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, and HDL ≤ 40 mg/dL[21]. Normal FG ranges should be between 70-100 mg/dL, and FG between 100-125 mg/dL is considered prediabetes. Normal HbA1c levels should be less than 6%[22].

Anthropometry

The same examiner measured every subject. Subjects wore only an examination cloth. Height and bodyweight were measured to the nearest 0.5 cm and 0.1 kg respectively. Waist circumference (WC) and hip circumference (HC) 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 the rib and the top of the iliac crest. HC was measured at the widest section of the buttocks. Waist-to-hip ratio (W/H ratio) was calculated from WC divided by HC.

Statistical analysis

Statistical analysis was performed using SPSS statistical software version 17.0. Normal distribution results are expressed as mean ± 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. The control group of 39 subjects and the OW/OB group of 39 subjects had an average BMI of 20.9 ± 0.3 and 31.3 ± 0.5 kg/m^2, respectively. The characteristics of LFC, anthropometric, and biochemical data of all subjects are shown in Table 1.

Table 1 Characteristic and biochemical analysis of 78 subjects in the control and overweight/obese groups

	Control group	OW/OB group	*P*-value	Correlation with LFC	
				r	*P* value
n	39	39	-	-	-
Gender (male/female)	12/27	24/15	-	-	-
LFC (%)	2.7 ± 0.2	8.1 ± 1.0	< 0.001[b]	-	-
Age	22.3 ± 1.6	22.1 ± 0.3	0.662	-0.058	0.611
BMI (kg/m^2)	20.9 ± 0.3	31.3 ± 0.5	< 0.001[b]	0.531	< 0.001[b]
WC (cm)	74.6 ± 1.4	112.6 ± 7.4	< 0.001[b]	0.259	0.022[a]
HC (cm)	90.7 ± 1.3	122.5 ± 7.5	< 0.001[b]	0.212	0.062
W/H ratio	0.8 ± 0.0	0.9 ± 0.0	< 0.001[b]	0.388	< 0.001[b]
FG (mg/dL)	83.1 ± 1.1	89.9 ± 1.1	< 0.001[b]	0.144	0.21
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	< 0.001[b]	0.223	0.05
HDL (mg/dL)	59.3 ± 2.5	47.7 ± 1.4	< 0.001[b]	-0.185	0.105
LDL (mg/dL)	111.1 ± 5.6	130.1 ± 5.1	0.014[a]	0.133	0.246
HbA1c (%)	5.1 ± 0.1	5.5 ± 0.1	< 0.001[b]	0.345	0.002[a]

Data expressed as mean ± SD.
[a]P < 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 hemoglobin.

Seventy-eight spectra were obtained and were analyzed 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 the liver was shown in Figure 1.

As expected, LFC, anthropometric, and biochemical results were significantly different between the two groups with the exception of 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 the OW/OB group, but this tendency was not statistically significant. The prevalence of dyslipidemia in the 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 the OW/OB group was approximately three times higher than the control group. Additionally, 19 subjects (48.7%) in the OW/OB group had LFC > 5.56%, which is considered to be a cut off point for NAFLD according to a previous large cohort ^{1}H MRS LFC study[18]. Furthermore, dyslipidemia was present in 47.4% of participants in the OW/OB group, and abnormal HbA1c was found in 10.5% of OW/OB subjects.

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 a statistically significant positive correlation with LFC. The correlation of diabetes (HbA1c and FG) markers is 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
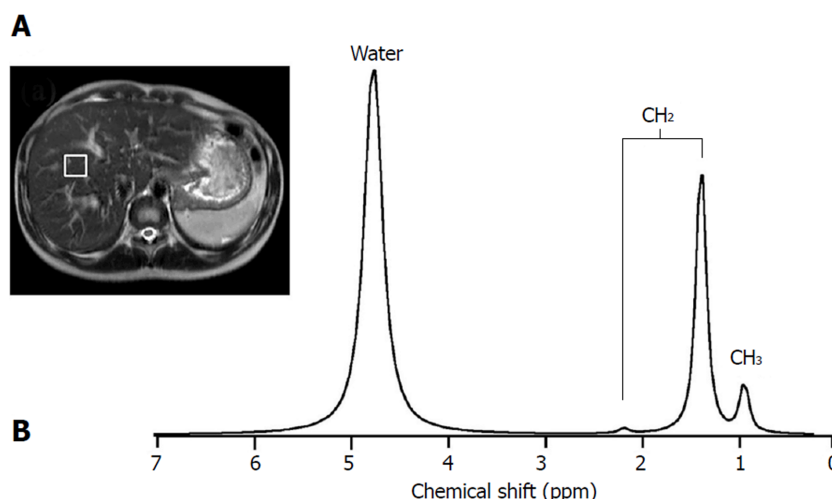
Figure 1 Proton magnetic resonance spectroscopy technique was used for liver fat assessment. Water peak was shown occurring at 4.72 ppm, peaks in fat for CH_3 occurred at 0.9 ppm, and CH_2 peaked at 1.3 ppm and 2.1 ppm. A: Magnetic resonance imaging axial image of abdomen show voxel localization in right lobe liver for liver fat content quantification. B: Representative fitted proton magnetic resonance spectroscopy spectrum of right lobe liver.

adjusting for age and sex. However, only BMI remained statistically significant as an independent predictor for LFC after HbA1C 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 the 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 between obesity, dyslipidemia, insulin resistance, and NAFLD[23,24]. MRI has proven to be a powerful imaging tool for liver cirrhosis diagnosis[25], and is known for its ability to non-invasively and accurately quantify liver fat using the ^{1}H 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 dyslipidemia, the probability of insulin resistance, and the prospect of metabolic disease in young adults.

The highlight of this study is that LFC in the OW/OB group is 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 should also be considered with a higher prevalence of dyslipidemia, prediabetes, and hyperglycemia among subjects with LFC > 5.56%. In accordance with the present results, previous studies have demonstrated that the risk for dyslipidemia starts to increase progressively with a BMI over 21 kg/m^2 and 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 the OW/OB group and the 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 the control group. However, no significant differences were found for Cho, even though the Cho in the OW/OB subjects had increased slightly with almost half of the control group having dyslipidemia. This could be explained by the fact that the two characteristics of the 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 and mild correlation with W/H ratio and WC. 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
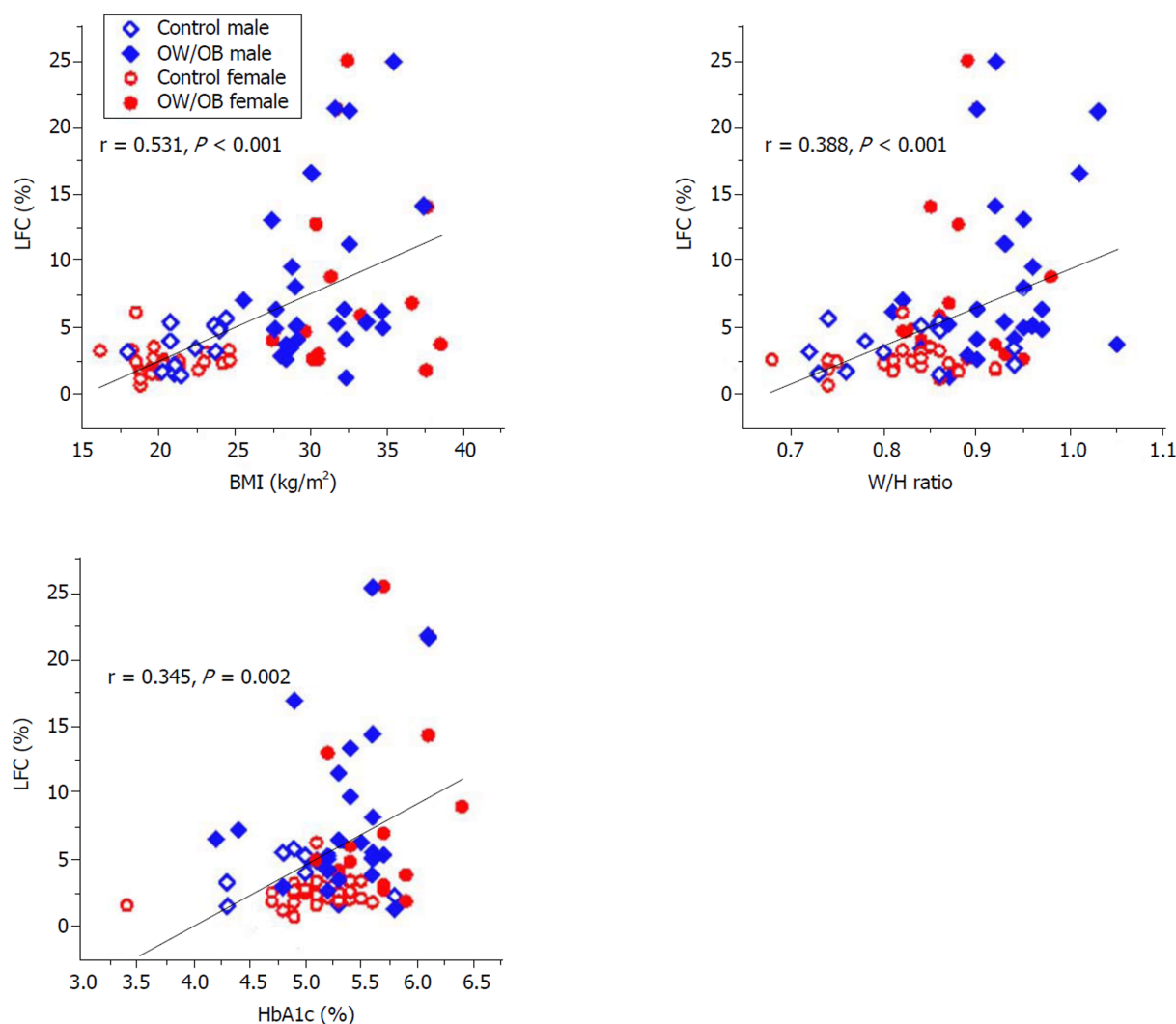
Figure 2 Pearson correlation coefficient (r) and data distribution by sex in each group between body mass index, waist-to-hip ratio, glycosylated hemoglobin, and liver fat content as measured by proton magnetic resonance spectroscopy. BMI: Body mass index; HbA1c: Glycosylated hemoglobin; LFC: Liver fat content; W/H ratio: Waist-to-hip ratio.

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 gain 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 between the two groups with a slightly positive correlation with LFC. However, only HbA1c is a 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 cardiovascular disease and insulin resistance in overweight and obese young adults.

This study has a few limitations such as the high prevalence of dyslipidemia in the control group that may be caused by the sample characteristics. This group being mostly comprised of young adults engaged in academic studies and whose exercise levels were determined by a 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.

To our knowledge, this is the first study on the topic of non-invasive assessment of LFC by ^{1}H MRS technique in healthy young adults without any complications or earlier diagnoses 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
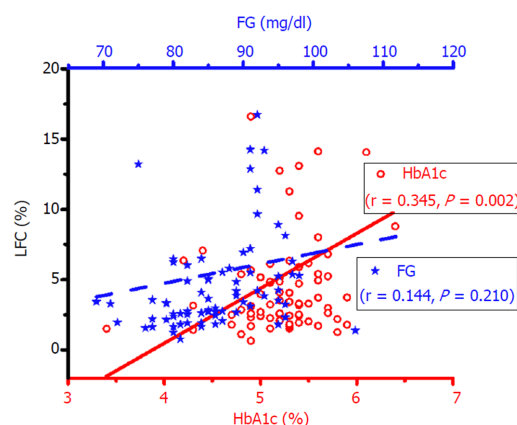
Figure 3 Pearson correlation between glycosylated hemoglobin (circle in red, lower x axis), fasting plasma glucose (star in blue, upper X axis), and liver fat content as measured by proton magnetic resonance spectroscopy. BMI: Body mass index; FG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; LFC: Liver fat content.

have drawn together various interesting subjects on the effects of BMI, 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 a 39 year follow-up has shown that an obese young adult who remained obese throughout their adult life increased their risk of developing severe liver disease[26]. This study suggested a role of BMI in increasing LFC and as a factor in higher NAFLD risk 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 the 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. This current study demonstrated the importance of BMI as a tool for the prevention and control of NAFLD and metabolic syndrome in young adults.

Table 2 Multiple linear regression analysis showing relationship of blood biochemical marker and anthropometry marker with LFC as the dependent variable

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

Model 1 is unadjusted model. Model 2 is Model 1 adjusted for sex and age. Model 3 is Model 2 adjust for body mass index. Statistical significance:
[a]$P < 0.001$. β: Standardized coefficient; SE: Estimated error; R^2: Correction coefficient; LFC: Liver fat content; HbA1c: Glycosylated hemoglobin; Tri: Triglyceride; BMI: Body mass index; WC: Waist circumference; W/H ratio: Waist-to-hip ratio.

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 the 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 their diet and lifestyle 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 lacking.

Research motivation

NAFLD is a chronic liver disease that is one of the most common health problems among young adults. We aim to identify the effects of obesity on liver fat content (LFC) and health in this age group. This information is crucial for primary prevention and a 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 (^{1}H MRS) technique. Using biochemical tests, the total cholesterol (Cho), low-density lipoproteins (LDL), high-density lipoproteins (HDL), fasting plasma glucose (FG), glycosylated hemoglobin (HbA1c), and being overweight/obese (OW/OB) will be determined.

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 the experimental group was made up of 39 overweight or obese (OW/OB) subjects. We performed the liver fat assessment by ^{1}H 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. The waist circumference (WC) and hip circumference (HC) of each subject was measured, and the waist-to-hip ratio (W/H ratio) was calculated.

Research results

LFC from the OW/OB group (8.1% ± 1.0%) was found to be statistically higher when compared to the control group (2.7% ± 0.2%) ($P < 0.001$). Additionally, 48.7% of subjects in the 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 was increased in the OW/OB group compared to the control group, but 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 and sex ($P < 0.001$). 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 the 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 a 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, and should also investigate the alteration of LFC and BMI throughout the adult years as a longitudinal study.

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