PREVALENCE OF ULTRASOUND DIAGNOSED NON-ALCOHOLIC FATTY LIVER DISEASE AMONG RURAL INDIGENOUS COMMUNITY OF SARAWAK AND ITS ASSOCIATION WITH BIOCHEMICAL AND ANTHROPOMETRIC MEASURES

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Abstract. Although the association between non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome has been previously firmly established, the prevalence of NAFLD and its risk factors in rural communities remains incompletely defined. This study aimed to determine the prevalence and factors associated with ultrasound-diagnosed NAFLD amongst a rural community in Sarawak. An indigenous village was randomly selected where all adults aged 21 years and above underwent an abdominal ultrasound, biochemical tests and an anthropometric assessment. Respondents with a score ≥ 8 on an alcohol-use disorders-identification test (AUDIT) indicating harmful or hazardous drinking were excluded. Seventy-seven respondents (46.8% male, mean age 48.4 SD 16.64), met inclusion criteria. The prevalence of ultrasound diagnosed NAFLD was 44.2% (n=34), among them 52.9% had moderate NAFLD. There were no significant age or gender differences between respondents with and without NAFLD, although those with NAFLD were older. Respondents with NAFLD had a significantly higher BMI than those without NAFLD (p<0.001). Both male and female respondents with NAFLD had a significantly higher waist circumference than those without NAFLD (p<0.001). Prevalence of diabetes, hypertension, hyperglycemia and hypertriglyceridemia were significantly higher among those with NAFLD. However, there were no significant differences in terms of percentage of unhealthy body fat and muscle, and serum HDL levels. Risk factors independently associated with NAFLD included male gender (odd ratio 0.06; 95% CI 0.008-0.523) and waist circumference (odd ratio 1.2; 95% CI 1.036-1.421). There was a high prevalence of NAFLD and the presence of more severe stages of disease in this indigenous population. Life-style related diseases, such as fatty liver disease, can occur in rural as well as urban populations.

Keywords: ultrasound, NAFLD, rural communities

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most common causes of chronic liver disease in both Western countries and countries of in the Asia Pacific region (Amarapurkar *et al*, 2007; Cave *et al*, 2007). It poses a serious health problem; it can contribute to a spectrum of liver diseases, including necroinflammation, cirrhosis and hepatocellular carcinoma (Zafrani, 2004).

The diagnosis of fatty liver can be made using non-invasive imaging methods, such as ultrasonography, with an 80% sensitivity for diagnosing steatosis (Yajima *et al*, 1983; Fusamoto *et al*, 1991; Gore, 1994). However, necroinflammation and fibrosis can only be diagnosed with liver biopsy, an invasive procedure. Ultrasound can be used to determine the grade of steatosis. Ultrasound has sensitivity of 80%, a specificity of 99% and a negative predictive value of 96% for diagnosing NAFLD (Riley *et al*, 2006).

The relationship between NAFLD and obesity, impaired glucose tolerance, hypertriglyceridemia, elevated systolic blood pressure and cardiovascular disease has been confirmed by previous studies (Lee *et al*, 2006). However, of these factors, obesity is the only non-dependant factor associated with ultrasound-diagnosed NAFLD. Patients with NAFLD have been reported to have higher body fat levels, BMI and waist and hip circumferences than controls (Lee *et al*, 2006).

The prevalence of NAFLD varies by region. In Western countries, the prevalence is estimated to be between 15% and 30% (Cave *et al*, 2007). In the Asia Pacific region, the prevalence of NAFLD has been reported to be 9-10% in Japan (Nomura *et al*, 1988), 5-24% in China (Shen *et al*, 2003; Fan *et al*, 2005b) 18% in Korea (Park *et al*, 2006) 5-28% in India (Agarwal *et al*, 2001; Duseja *et al*, 2004) 30% in Indonesia (Hasan *et al*, 2002). In Malaysia, in an unpublished study by Goh *et al* the prevalence was estimated to be 15-17% with a slight male preponderance (Amarapurkar *et al*, 2007).

The prevalence of NAFLD is higher in Western countries (Amarapurkar *et al* 2007; Cave *et al*, 2007). This is probably related to obesity from unhealthy diet and lack of physical activity. A study done in rural Taiwan found a prevalence of NAFLD of 11.5% (Chen *et al*, 2006). An earlier study showed the rural population of Sarawak has a lower prevalence of obesity (Ulijaszek and Strickland, 1996), but a more recent, large scale (n=16,127) study showed the prevalence of obesity was only slightly lower in rural than urban dwellers in Malaysia (Rampal *et al*, 2007). This may indicate an increase in obesity prevalence in rural areas. An increase in obesity prevalence may also be associated with an increase in the prevalence of NAFLD.

There is little data about the prevalence of NAFLD in rural indigenous communities in Malaysia; therefore, we aimed to determine the prevalence of ultrasound-diagnosed NAFLD and associated factors among a rural population, particularly Iban communities in Sarawak, Malaysia.

MATERIALS AND METHODS

Simunjan is a small district located in the Samarhan Division of Sarawak. It lies 51.4 km Southeast of Kuching, the capital city of Sarawak. Simunjan consists mainly of Iban and Malay populations. Kampung Gayam was randomly selected among of Simunjan District. All adults aged 21 years and above were selected to participate in this study. Ethical approval was obtained from the Ethics Committee of the Universiti Sains Malaysia. Informed consent was obtained from each respondent prior to participation. Respondents were asked to fast for at least 8 hours, then come to the community hall early in the morning. An interview were conducted using a structured questionnaire which consisted of socio-demographic information, alcohol use disorder identification test (AUDIT) items and a history of chronic illnesses. Participants who scored ≥ 8 on the AUDIT, indicating harmful levels of drinking, were excluded. Body weight was taken using a SECA weighing scale (SECA 813, Germany) and height was taken using a SECA body meter (SECA 213, Hamburg, Germany) to calculate body mass index (kg/m^2). Classification of BMI was based on the World Health Organization (WHO)/ International Association for the Study of Obesity (IASO)/International Obesity Task Force (IOTF) guidelines (WHO/IASO/ IOTF, 2000), where a BMI of 23 kg/m^2 and above was classified as overweight and a BMI of more than 25 kg/m^2 is classified as obese.

Waist circumference was measured using a non-elastic tape measure at the midpoint between the lower costal margin and the iliac crest and hip circumference was measured as the maximum circumference of the buttocks. Abdominal obesity was defined as a waist measurement >90 cm in men and ≥80 cm in women (IDF, Task Force, 2006). Total body fat percentage and total muscle percentage were determined using a bioelectric impedance analyser (BodyStat 1500, Warwickshire, United Kingdom), and a frequency of 50 kHz. Measurement was taken with the respondents lying supine with electrodes on the right third metacarpal bone, the wrist, the second metatarsal bone and the dorsum of the ankle. Classification of a healthy range for body fat and muscles was based on the amount of body fat/ muscles as a proportion of the total body weight. The BodyStat 1500 analyser provides a standard range for comparison for each measurement.

Sonography was conducted by a qualified radiologist and 2 clinicians trained in basic sonography using a Sonosite 180 or General Electric (GE) Logic E portable ultrasound scanner with a convex abdominal transducer. The liver was imaged in conventional planes and the presence of increased reflectivity of the hepatic parenchyma was recorded and graded. A mild increase in hepatic echogenicity with preservation of the echogenicity of the portal vein wall and the diaphragm were graded as mild steatosis. A moderate increase in hepatic echogenicity with impaired visualization of the echogenic portal wall and diaphragm were graded as moderate steatosis. A marked increase in hepatic echogenicity with obscuration of the portal vein walls and diaphragm with posterior attenuation of the ultrasound beam were graded as severe steatosis (Karcaaltincaba and Akhan, 2007; Koda *et al*, 2007). The radiologist examined and decided on the final grade for each participant, to reduce inter-observer variation.

Laboratory examinations included measurement of fasting plasma glucose (FPG), triglycerides and high-density lipoprotein (HDL) cholesterol. Classification of the fasting triglycerides, HDL and glucose levels was based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (National Institute of Health, 2001) and the Malaysian Diabetes Mellitus Guidelines, 2009 (Ministry of Health Malaysia, 2009). Based on these guidelines, an HDL cholesterol <0.9 mmol/l and a triglyceride level >2.26 mmol/l were indicative of high risk for cardiovascular disease. For the blood glucose, a level >5.6 mmol/l was classified as high risk for hyperglycemia.

Data collected were analyzed using SPSS, version 17.0 (SPSS, Chicago, IL) to generate descriptive data and to determine factors associated with NAFLD. Significance was set at $p<0.05$ is used. Data were cleaned of outliers and checked for normality.

Table 1
Socio-demographic characteristics of respondents (N=77).

	n (%)	Mean (SD)
Age (years)		48.4 (16.64)
Gender		
Male	36 (46.8)	
Female	41 (53.2)	
Education level		
No education	29 (37.7)	
Primary	23 (29.9)	
Secondary	25 (32.5)	
Occupation		
Farmer	41 (53.2)	
Housewife	36 (46.8)	

RESULTS

Seventy-seven respondents (46.8% male, mean age 48.4 ± 16.6), who met both inclusion and exclusion criteria, participated in this study. More than 60% of respondents had an education level up to secondary level; 53.2% were farmers. Details regarding the socio-demographic characteristics of respondents are presented in Table 1.

Health profile of 77 respondents is presented in Table 2. The mean BMI of respondents indicates a tendency for overweight (26.88 ± 4.59 kg/m^2). The mean serum triglyceride level was in the normal range but both the mean glucose and HDL levels were slightly above normal (triglyceride ≤ 2.26 mmol/l, glucose ≤ 5.6 mmol/l and HDL ≥ 0.9 mmol/l). The mean waist circumferences for both males and females were above normal (male ≤ 90 cm, female ≤ 80 cm). The mean percent body fat was 30.8 ± 8.2% and the body muscle was 69.2 ± 8.2%. Based on the healthy range given by the body composition analyser, only 13 (16.9%) of the respondents had a percent body fat and muscle mass within the healthy range.

Table 2
Health profile of respondents (N=77).

Parameter (normal range)	Value ± SD
BMI (kg/m^2) (20-23)	26.88 ± 4.59
Waist circumference in males (cm)	93.25 ± 13.3
Waist circumference in females (cm)	82.50 ± 9.35
Percent body fat (%)	30.75 ± 8.19
Percent body muscle (%)	69.24 ± 8.18
Known diabetic-n(%)	9 (11.7)
Known hypertensive-n(%)	21 (27.3)
Glucose level (mmol/l)	5.98 ± 2.13
Triglyceride level (mmol/l)	1.90 ± 1.13
HDL level (mmol/l)	1.13 ± 0.28
NAFLD-n(%)	
No	43 (55.8)
Mild	15 (19.5)
Moderate	18 (23.4)
Severe	1 (1.3)

SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein

On sonography, 44.2% of the respondents (n=34) had NAFLD. Of those with NAFLD, more than half (52.9%) had a moderate grade NAFLD. There were no significant age or gender differences by respondents with and without NAFLD, although those with NAFLD tended to be older. In terms of BMI, respondents with NAFLD had a significantly higher BMI than those without NAFLD (p<0.001). Similarly for waist circumference, both male and female respondents with NAFLD had a significantly higher waist circumference than those without NAFLD (p<0.001). Percentages of those with diabetes, hypertension, higher serum glucose and triglycerides levels were significantly higher in the NAFLD group. However, there was no significant differences in terms of percents of body fat and muscles, and serum HDL levels between respondents with and without NAFLD.

Table 3
Comparison of various factors by presence or absence of NAFLD (mean ± SD).

Parameter	NAFLD (n=34)	Normal liver (n=43)	p-value
Age (in years)	50.09 ± 21.30	47.07 ± 1.81	0.433
Gender (% male)	50.0%	44.2%	0.651
BMI (normal ragne 20-23)	29.49 ± 3.74	24.81 ± 4.16	<0.001
Waist circumference in males (cm)	103.26 ± 9.48	84.28 ± 9.11	<0.001
Waist circumference in females (cm)	88.91 ± 5.98	77.95 ± 8.67	<0.001
Percent with excessive body fat (%)	91.3%	76.7%	0.083
Percent with normal body fat (%)	8.7%	23.3%	0.083
Known diabetic (%)	23.5%	2.3%	0.009
Known hypertensive (%)	41.2%	16.3%	0.018
Glucose level (mmol/l)	6.6 ± 2.86	5.48 ± 1.1	0.021
Triglyceride level (mmol/l)	2.42 ± 1.38	1.49 ± 0.65	<0.001
HDL level (mmol/l)	1.08 ± 0.26	1.17 ± 0.28	0.167

SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein

Table 4
Binary logistics regression analysis for NAFLD.

	B	SE	Wald	df	Sig	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Age	-0.037	0.036	1.004	1	0.316	0.964	0.898	1.036
Sex (male)	-2.589	1.088	5.666	1	0.017	0.075	0.009	0.633
Waist circumference	0.195	0.087	5.009	1	0.025	1.215	1.025	1.442
Percent body fat (healthy)	-0.833	1.436	0.337	1	0.562	0.435	0.026	7.258
Known diabetic	21.845	100,036	0.000	1	0.998	3.07E9	0.000	
Known hypertensive	1.23	0.963	1.633	1	0.201	3.422	0.519	22.577
BMI	0.004	0.185	0.001	1	0.981	1.004	0.698	1.445
Glucose	0.072	0.333	0.047	1	0.829	1.071	0.560	2.062
Triglyceride	0.962	0.558	2.967	1	0.085	2.616	0.876	7.815
HDL	-1.655	1.863	0.789	1	0.374	0.191	0.005	7.357
Constant	-13.941	4.954	7.919	1	0.005	0.000		

SE, standard errors; df, degree of freedom; Sig, significant p; Exp(B), odd ratio; 95% CI, 95%, confidence interval; BMI, body mass index; HDL, high-density lipoprotein

Logistic regression was used to examine the impact of age, sex, waist circumference, percent body fat, percent muscle mass, diabetes, hypertension, BMI, glucose, triglycerides, and HDL levels on NAFLD. Table 4 shows the results of this analysis. The full model containing all predictors was statistically significant, χ^2 (8, 77) = 55.68, p<0.001, indicating that the model was able to distinguish between respondents with and without NAFLD. This model containing the 8 independent variables explained between 0.5% (Cox and Snell R square) and 0.69% (Nagelkerke R squared) of the variance in NALFD. It was also able to classify 83.1% of the cases.

Table 4 shows sex and waist circumference had a significant association with NAFLD. The odds ratio or Exp (B) value for sex was 0.075, indicating male respondents were 0.075 times more likely to have NAFLD than female respondents. As for waist circumference, the odds ratio or Exp (B) value was 1.2, indicating respondents with a large waist circumference were 1.2 times more likely to have NALFD.

The Wald values for the independent variables indicate only sex and waist circumference were significant predictors of NALFD. Age, percent body fat, percent of muscle mass, diabetes, hypertension, elevated glucose triglycerides and HDL levels did not contribute significantly to NAFLD.

DISCUSSION

The prevalence of NAFLD (44.2%) in this rural indigenous population is alarmingly high. This was much higher than the prevalence (15-17%) observed in other ethnic groups in the same country and other Asia Pacific countries (Amarapurkar *et al*, 2007). Most countries in the Asia Pacific region have reported prevalences 5-30% for NAFLD (Amarapurkar *et al*, 2007). The prevalence of NAFLD in the US and some western countries ranges from 15% to 30% (Cave *et al*, 2007). The finding of more than half the respondents in our study with moderate NAFLD is in contrast with studies among other ethnic groups in Malaysia which reported a lower percent of moderate NAFLD but a higher percentage of mild NAFLD (Malik *et al*, 2007; Ministry of Health Malaysia, 2009). The mean BMI, waist circumference and fasting triglyceride levels among respondent in this study were above the normal limits. These could have contributed to the higher prevalence and more severe stages of NAFLD in this study population. Another possibility is genetic differences in this indigenous population could also be a contributing factor. Further studies are needed to explore this.

Most studies report obesity especially central obesity, is an important risk factor for NAFLD (Hsieh *et al*, 2000; Angulo, 2002; Fan *et al*, 2005a; Lee *et al*, 2006; Cave *et al*, 2007). Similarly, our study also found a higher BMI and waist circumference were associated with NAFLD. An increased waist circumference was associated with a 1.2 times greater chance of having NAFLD. Central obesity is correlated with visceral adiposity which is linked to insulin resistance, the central factor in developing nonalcoholic steatohepatitis (a more severe form of NAFLD), than is generalized obesity (Omagari *et al*, 2002). Thus, the direct association between abdominal fat and hepatic lipid content is probably accounted for by visceral adiposity (Fan *et al*, 2007). The overall mean BMI and waist circumference of the rural indigenous community in this study were above normal. A recent study in Malaysia found an increasing prevalence of obesity in rural areas (Rampal *et al*, 2007). This may be related to changing lifestyle in rural communities or genetically related pathogenesis of obesity. Ethnic differences in proclivity to central adiposity are well recognized (Fall, 2001; Deurenberg *et al*, 2002; Petersen *et al*, 2006).

The presence of type 2 diabetes mellitus (T2DM) significantly increases the risk and severity of NAFLD (Harrison, 2006). T2DM is present in 21% to 45% of people with NAFLD (Angulo, 2002; Chitturi *et al*, 2002; Harrison, 2006; Malik *et al*, 2007). The prevalence of diabetes and elevated serum fasting glucose were found to be significantly higher among respondents with NAFLD in our study. Seventy-six percent of respondents with NAFLD had a mean fasting glucose of 6.6 mmol/l, which is at the level of impaired fasting glucose (Ministry of Health Malaysia, 2009). Under-diagnosis of T2DM in this population may occur due to poor access to health care facilities. Most of the respondents were farmers living in a rural area. The increasing trend of the prevalence of T2DM in the Asia Pacific region (King *et al*, 1998) has begun to affect rural indigenous Borneo too. Traditional hunter-gatherer populations (Australian Aborigines, Nauruan fishermen, Maoris) have experienced a profound upsurge in the prevalence of T2DM (King *et al*, 1998; Harrison, 2006).

Dyslipidemia is known to be a risk factor for NAFLD in most Asia Pacific countries (Amarapurkar *et al*, 2007). Hypertriglyceridemia, which has a greater association with metabolic syndrome than hypercholesterolemia, may increase the risk of NAFLD (Marchesini *et al*, 1999; Angulo, 2002). In our study, triglycerides levels were significantly higher among those with NAFLD. Metabolic syndrome is an important risk factor for NAFLD (Hamaguchi *et al*, 2005). A study in China reported the risk of hepatic steatosis increased exponentially with the addition of each component of metabolic syndrome (Fan *et al*, 2005b). The presence of metabolic syndrome is related to more severe forms of NAFLD (Marchesini *et al*, 1999, 2001). Our study found a higher prevalence of central obesity, T2DM, hypertension, elevated mean fasting blood glucose and elevated triglycerides among respondents with NAFLD. Severe forms of NAFLD were found in this indigenous population. This may signify increasing prevalence of metabolic syndrome in this rural population.

Studies in the Asia Pacific region have reported a higher prevalence of NAFLD in men (Fan *et al*, 2007). However, our study found a lower odds ratio among men with NAFLD. The mean age of respondents with NAFLD in our study was 50 years. This may be explained by a bimodal age distribution of NAFLD by sex as reported by study from China (Fan *et al*, 2007) where the peak prevalence of NAFLD among men was age 40-49 years and among women was greater than 50 years. In women, the prevalence of NAFLD peaks after age 50 years (Fan *et al*, 2005a). Estrogens may be partially protective against steatosis (Farell, 2003; Shen *et al*, 2003; Fan *et al*, 2005a; Hamaguchi *et al*, 2005; Park *et al*, 2006).

Due to funding constraints this only a preliminary study looking into the prevalence of NAFLD and its associated risk factors in an indigenous population on Borneo. Further comprehensive studies are needed to explore the etiology and other risk factors of NAFLD, including genetics, traditional medicine use, physical inactivity, high fat intake, overeating, family history of obesity and diabetes. This is important for planning preventive strategies.

Future studies incorporating physical activity and diet may be useful in identifying lifestyle factors associated with central adiposity and NAFLY among the Iban community.

In conclusion, this preliminary study found a high prevalence of NAFLD and the presence of severe stages of this disease in this indigenous population. The presence of central obesity, T2DM, hypertension, elevated mean fasting blood glucose and triglycerides were associated with NAFLD. Central obesity and gender were significant risk factors of NAFLD. Life-style related diseases such as NAFLD, are not just confined to urban populations or higher socio-economic population.

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