UNIVERSITI PUTRA MALAYSIA

ASSOCIATION BETWEEN RISK FACTORS OF NON-ALCOHOLIC FATTY LIVER WITH THE SONOGRAPHIC FINDINGS AMONG ADULTS AT GOLDEN HORSES HEALTH SANCTUARY, SELANGOR, MALAYSIA

ABDUL SATTAR ARIF KHAMMAS

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By

ABDUL SATTAR ARIF KHAMMAS

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Science

March 2017

DEDICATION

In the name of Allah, most gracious, most merciful

I dedicate this thesis to my family for nursing me with affections and love and their dedicated partnership for success in my life

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Master of Science

ASSOCIATION BETWEEN RISK FACTORS OF NON-ALCOHOLIC FATTY LIVER WITH THE SONOGRAPHIC FINDINGS AMONG ADULTS AT GOLDEN HORSES HEALTH SANCTUARY,SELANGOR,MALAYSIA

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Chairman : Professor Rozi Mahmud, PhD
Faculty : Medicine and Health Sciences

NAFLD is the most common type of hepatic steatosis, developing through three main stages, from simple hepatic steatosis to non alcoholic steatohepatitis (NASH), that leads to fibrosis and cirrhosis with the end-stage of HCC. It is strongly associated with metabolic syndrome, such as dyslipidemia, T2DM, hypertension and obesity. Therefore, NAFLD is considered an independent risk factor for the development of cardiovascular disease (CVD). The present study was proposed to determine the contributing factors to NAFLD amongst Malaysian adults in the Klang Valley as well as the association between these factors and grading of NAFLD. This study was also designed to assess the differences of hepatic echo-intensity attenuation rate and subcutaneous tissue thickness between NAFLD patients and non-NAFLD subjects.

An analytical cross-sectional study design was achieved prospectively amongst Malaysian adults who underwent the routine screening programme at the Golden Horses Health Sanctuary (GHHS) in the Klang Valley for the period from 15th August 2015 until 15th Juanuary 2016. A self-administered questionnaire was adopted as the instrument for data collection. Qualitative ultrasound for diagnosis of NAFLD was performed based on increasing echogenicity of hepatic parenchyma in comparison with echogenicity of the spleen and right renal cortex. In contrast, Quantitative ultrasound for detecting NAFLD was performed by quantifying the hepatic echo-intensity attenuation rate. Moreover, subcutaneous tissue thickness was measured from the skin surface into the liver capsule.

A total of 628 subjects were recruited to participate in the study. There were 235 (37.4%) subjects with NAFLD and 393 (62.6%) normal subjects. The mean age of the participants was 54.54 ±6.69 years and the mean BMI was 24.72 ±3.96 kg/m^2. The results showed that the peak prevalence of NAFLD involved subjects aged between 53-60 years old. Additionally, the results demonstrated that the prevalence of NAFLD was significantly higher in males, Indians and Malays compared to Chinese, with high BMI (≥ 23.0 kg/m^2), high WHR, hypertriglyceridemia, low HDL-C, physical inactivity, DM, and hypertension. Median daily caloric intake of protein, fat, and carbohydrate was also significantly higher in subjects with NAFLD than those without NAFLD. However, when further analysis for percentage of protein intake was done, no association between the daily percentage of protein intake and the prevalence of NAFLD was found. Amongst the NAFLD grades, there was a significant association of high BMI and high WHR with NAFLD grades. Similarly, the median triglyceride was significantly higher amongst NAFLD grade III (2.15 ±1.7 mmol/L) than in grade II (1.50 ±0.70 mmol/L) and grade I (1.40 ±0.80 mmol/L). In the same context, the mean HDL-C was significantly lower amongst NAFLD grade III (1.21 ±0.21 mmol/L) than grade II (1.31 ±0.30 mmol/L) and grade I (1.40 ±0.30 mmol/L). Otherwise, the differences of the mean total cholesterol, LDL-C, median protein, fat, and carbohydrate amongst the NAFLD grades were not reported to be significant. The multiple logistic regression analysis demonstrated that male gender, high BMI, physical inactivity, hypertriglyceridemia, DM, and thickened subcutaneous tissue were independent predictive risk factors for developing NAFLD. However, ages > 60 years old decreased the risk of NAFLD significantly. For the Malay and Indian races, high WHR, low HDL-C, and hypertension were not detected to be significant risk predictors for progression of NAFLD. Interestingly, daily caloric intake of protein, fat, and carbohydrate, were also not found to increase the risk of NAFLD. The differences of mean hepatic echo-intensity attenuation rate and subcutaneous tissue thickness between NAFLD patients and normal subjects were found to be statistically significant. Sonographically, a hepatic echo-intensity attenuation rate of 1.7 dB/cm.MHz and above made the diagnosis of NAFLD more probable. Similarly, subjects with a subcutaneous tissue thickness measuring 2.1 cm and above were more likely to have NAFLD.

In conclusion, NAFLD is common in the urban Malaysian population with a higher prevalence amongst Indians and Malays than Chinese. The quantitative ultrasound was valuable to assess NAFLD based on quantifying the hepatic echo-intensity attenuation rate. A large population-based study is recommended to determine prevalence of NAFLD amongst the entire Malaysian population as well as to determine further contributing risk factors of NAFLD.

Key words: Non alcoholic fatty liver disease, sonography, Malaysia, risk factors.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

HUBUNGAN DI ANTARA FAKTOR RISIKO BUKAN ALKOHOL LEMAK HATI DENGAN PENEMUAN SONOGRAFI KALANGAN ORANG DEWASA DI GOLDEN HORSES HEALTH SANCTUARY, SELANGOR

Oleh

ABDUL SATTAR ARIF KHAMMAS

Mac 2017

Pengerusi : Profesor Rozi Mahmud, PhD
Fakulti : Perubatan dan Sains Kesihatan

NAFLD adalah jenis steatosis hepatik yang paling biasa, membangun melalui tiga peringkat utama, dari steatosis hepatik mudah sehingga steatohepatitis bukan disebabkan alkohol (NASH), yang membawa kepada fibrosis dan sirosis dengan HCC peringkat-akhir. Ia berkait rapat dengan sindrom-sindrom metabolik, seperti dyslipidemia, T2DM, hipertensi dan obesiti. Oleh itu, NAFLD dianggap sebagai suatu faktor risiko bebas terhadap perkembangan penyakit kardiovaskular (CVD). Kajian ini telah dicadangkan untuk menentukan faktor-faktor yang menyumbang kepada NAFLD di kalangan orang dewasa di Malaysia di Lembah Klang dan juga hubungan antara faktor-faktor ini dengan penggredan NAFLD. Kajian ini juga direka bentuk untuk menilai perbezaan kadar pengecilan keamatan-gema hepatik dan ketebalan tisu subkutaneus antara pesakit NAFLD dan subjek bukan-NAFLD.

Suatu reka bentuk kajian keratan-rentas beranalisis dicapai secara prospektif di kalangan orang dewasa Malaysia yang menjalani program pemeriksaan rutin di Golden Horses Health Sanctuary (GHHS) di Lembah Kelang bagi tempoh dari 15hb Ogos 2015 sehingga 15hb Januari 2016. Soal selidik yang ditadbir sendiri telah diguna pakai sebagai alat untuk pengumpulan data. Ultrasound kualitatif untuk diagnosis NAFLD telah dijalankan berdasarkan peningkatan echogenisiti parenchyma hepatic berbanding dengan echogenisiti limpa dan korteks ginjal kanan. Sebaliknya, ultrasound kuantitatif untuk mengesan NAFLD telah dilakukan secara mengukur kadar pengecilan keamatan-gema hepatik. Selain itu, ketebalan tisu subkutaneus diukur dari permukaan kulit ke dalam kapsul hati.

Seramai 628 subjek telah dipilih untuk mengambil bahagian di dalam kajian ini. Terdapat 235 (37.4%) subjek mengidap NAFLD dan 393 (62.6%) subjek yang normal. Min umur peserta adalah 54.54 ± 6.69 tahun dan min BMI adalah 24.72 ± 3.96 kg/m^2. Hasil kajian menunjukkan bahawa puncak kewujudan NAFLD melibatkan subjek berusia antara 53-60 tahun. Tambahan lagi, keputusan menunjukkan bahawa kewujudan NAFLD adalah jauh lebih tinggi di kalangan lelaki, orang India dan orang Melayu berbanding dengan orang Cina, dengan BMI tinggi (≥ 23.0 kg/m^2), WHR tinggi, hypertriglyceridemia, HDL-C rendah, ketidakaktifan fizikal, DM, dan hipertensi. Median pengambilan kalori harian dari protein, lemak, dan karbohidrat juga jauh lebih tinggi di kalangan subject yang mengidap NAFLD berbanding dengan mereka yang bebas dari NAFLD. Walau bagaimanapun, apabila analisis lanjut untuk peratusan pengambilan protein dilakukan, tiada kaitan antara peratusan harian pengambilan protein dan kewujudan NAFLD ditemui. Di antara gred-gred NAFLD, terdapat hubungan yang ketara di antara BMI yang tinggi dan WHR tinggi dengan gred NAFLD. Begitu juga, trigliserida median adalah lebih tinggi di kalangan NAFLD gred III (2.15 ± 1.7 mmol/L) berbanding gred II (1.50 ± 0.70 mmol/L) dan gred I (1.40 ± 0.80 mmol/L). Dengan konteks yang sama, min HDL-C adalah ketara lebih rendah di kalangan NAFLD gred III (1.21 ± 0.21 mmol/L) berbanding gred II(1.31 ± 0.30 mmol/L) dan gred I (1.40 ± 0.30 mmol/L). Sebaliknya, perbezaan min jumlah kolesterol, median LDL-C, protein, lemak, dan karbohidrat di kalangan gred-gred NAFLD tidak dilaporkan sebagai penting. Analisis regresi logistik pelbagai menunjukkan bahawa jantina lelaki, ketinggian BMI, ketidakaktifan fizikal, hypertriglyceridemia, DM, dan tisu subkutaneus menebal adalah faktor-faktor bebas ramalan risiko bagi membangunnya NAFLD. Walau bagaimanapun, umur > 60 tahun mengurangkan risiko NAFLD dengan ketara. Bagi kaum Melayu dan India, WHR tinggi, HDL-C rendah, dan hipertensi tidak dikesan sebagai peramal risiko penting bagi perkembangan NAFLD. Menariknya, pengambilan harian kalori protein, lemak, dan karbohidrat, juga tidak didapati sebagai meningkatkan risiko NAFLD. Perbezaan kadar pengecilan keamatan-gema hepatik min dan ketebalan tisu subkutaneus antara pesakit NAFLD dan subjek normal didapati ketara secara statistik. Dari segi sonografi, kadar pengecilan keamatan-gema hepatik sebanyak 1.7 dB/cm.MHz ke atas menjadikan diagnosis NAFLD lebih mungkin. Begitu juga, subjek yang mempunyai ketebalan tisu subkutaneus berukuran 2.1 cm ke atas lebih mungkin mengidap NAFLD.

Sebagai kesimpulan, NAFLD adalah biasa didapati di kalangan penduduk Malaysia bandar dengan kewujudan yang lebih tinggi di kalangan orang India dan orang Melayu berbanding dengan orang Cina. Ultrasound kuantitatif sangat berguna untuk menilai NAFLD berdasarkan ukuran kadar pengecilan keamatan-gema hepatik. Satu kajian besar berasaskan-populasi adalah disyorkan untuk menentukan kewujudan NAFLD di kalangan keseluruhan penduduk Malaysia serta untuk menentukan dengan lebih lanjut lagi faktor-faktor penyumbang risiko NAFLD.

Kata kunci: Penyakit hati berlemak bukan disebabkan alkohol, sonografi, Malaysia, faktor-faktor risiko.

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I certify that a Thesis Examination Committee has met on 21 March 2017 to conduct the final examination of Abdul Sattar Arif Khammas on his thesis entitled "Association between Risk Factors of Non-Alcoholic Fatty Liver with The Sonographic Findings among Adults at Golden Horses Health Sanctuary, Selangor, Malaysia" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

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Date: 28 April 2017

The thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the supervisory Committee were as follows:

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Date:

Declaration by graduate student

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

Signature: _____
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Signature: _____
Name of Member of Supervisory Committee: Dr. Hasyma Abu Hassan

Signature: _____
Name of Member of Supervisory Committee: Dr. Hayati Kadir

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LIST OF ABBREVIATIONS

ALT	Alanine aminotranferase
Ang II	Angiotensin II
B	Beta Coefficient
BMI	Body Mass Index
BP	Blood Pressure
CAP	Controlled Atenuation Parameter
CBD	Common Bile Duct
CHD	Common Hepatic Duct
CI	Confidence Intervals
DBP	Diastolic Blood Pressure
df	degree of freedom
DM	Diabetes Mellitus
DNL	*De Novo* Lipogenesis
2D	Two-Dimensional
GGT	Gamma-Glutamyl Transferase
HDL-C	High Density Lipoprotein-Cholesterol
IDF	International Diabetes Federation
IVC	Inferior Vena Cava
LHD	Left Hepatic Duct
LDL-C	Low Density Lipoprotein -Cholesterol
LK	Left Kidney
MET	Metabolic Equivalent Task
MRS	Magnetic Resonance Spectroscopy
MUFA	monounsaturated fatty acid

NAFLD	Non Alcoholic Fatty Liver Disease
NASH	non alcoholic steatohepatitis
NCEP	National Cholesterol Education Program
OR	Odds Ratio
PUFA	Polyunsaturated fatty acid
RC	Renal Cortex
RHD	Right Hepatic Duct
RK	Right Kidney
SBP	Systolic Blood Pressure
S.E	Standard Error
SFFQ	Semi-Food Frequency Questionnaire
SMA	Superior Mesenteric Artery
TC	Total Cholesterol
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TE	Transient Elastography
TG	Triglyceride
VCTE	Vibration Control Transient Elastography
VLDL	Very Low-Density Lipoprotein
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 What is Non-alcoholic Fatty Liver Disease (NAFLD)?

Non-alcoholic fatty liver disease (NAFLD) is one of types of fatty liver in which fat is accumulated (steatosis) in the hepatocyte due to causes other than significant alcohol consumption (Shaker, Tabbaa, Albeldawi, & Alkhouri, 2014). It represents a wide spectrum of the liver disease ranging from simple hepatic steatosis to non alcoholic steatohepatitis (NASH) that lead to fibrosis and cirrhosis with end-stage of hepatocellar carcinoma (HCC) (Fon Tacer & Rozman, 2011; Ozturk & Kadayifci, 2014). First discripation of NAFLD was by Ludwig, Viggiano, McGill, & Oh, in 1980. The disease is the most common cause of chronic liver disease in Western countries with prevalence up to 40% of general population (Li et al., 2015). In United States, fatty liver changes have affected over 66% of obese subjects and around 19% of them with NASH (Sass, Chang, & Chopra, 2005). In Asia, NAFLD was initially uncommon but recently it has been affected 12-37% of general population (OSHIBUCHI, NISHI, SATO, OHTAKE, & OKUDA, 1991; Lai, Tan, & Ng, 2002; Omagari et al., 2002; Shen et al., 2003; Fan et al., 2005a; Jimba et al., 2005; PARK et al., 2006; Amarapurkar et al., 2007; Fan et al., 2007; Malik et al., 2007; Zhou et al., 2007).

To date, simple hepatic steatosis is considered as benign disease but it is susceptible to predictors that lead to inflammation and fibrosis (Mehta, Thomas, Bell, Johnston, & Taylor-Robinson, 2008). Likewise, a study by Neuschwander-Tetri & Caldwell, (2003) confirmed that hepatic steatosis alone is broadly benign with no advancing disease. However, when simple hepatic staetosis is accompanied with cell inflammation and injury (NASH), it can be serious and mostly progressed into fibrosis, cirrhosis and HCC. Hui et al., (2003) mentioned that around 33% of patients with NASH developed to fibrosis of which; 2-20% of them progressed to cirrhosis. In NAFLD, the liver produces many factors that are related with atheromas such as bad lipid and cytokines.

1.2 Appearance NAFLD on Ultrasound

Ultrasound is widely used to detect fatty liver disease as it is non-invasive tool, safety (no ionizing radiation is used) and availability, as well as its lower cost as compared to other diagnostic radiological modalities such as CT scan and MRI. Ultrasound is always the first diagnostic tool used in patients who are clinically diagnosed with diffuse liver diseases or who have repeatedly suffered from alternations in the liver enzymes levels (P. Allan, Baxter, & Weston, 2011).

Fatty liver disease is due to excess synthesis of fats in the liver cells that cause increased hepatic parenchymal reflectivity which in turn leads to markedly increase in echogenicity of liver parenchyma as compared to the right renal cortex and spleen (Figure 1.2) (Hamer et al., 2006). Furthermore, visibility of the diaphragm and intrahepatic vascular walls is decreased (X. Ma et al., 2009). Lose vasualization of intrahepatic vascular walls and diaphragm is attributed to reducing in acoustic penetration, as liver parenchyma echogenicity increases (Tchelepi et al., 2002). Similarly; due to high reflectivity of portal vein branches, the walls will appear bright. Therefor, excess liver parenchyma echogenicity results in impaired vasualization of portal vascular walls (P. Allan, Baxter, & Weston, 2011).

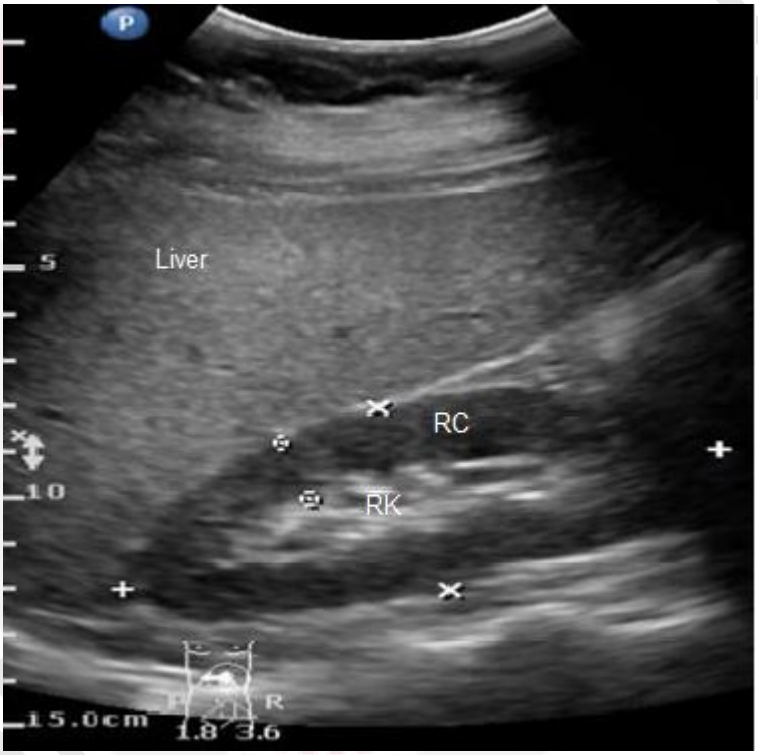

Figure 1.1 : Longitudinal section of the liver and right kidney (RK). Liver echogenicity is markedly higher than renal cortex (RC) (fatty liver changes) (taken from the study population).

In general, fatty liver infiltration is classified into four various grades from 0-III, which represented no fatty changes, mild, moderate and severe, respectively. When there is slightly increased in the liver parenchyma echogenicity, it is described as mild. In addition, when there is moderate increased in liver echogenicity with poor visualization of portal vascular walls, particularly peripheral branches, it is described as moderate. Moreover, when there is markedly increased of liver echogenicity with impaired or no visualization of the diaphragm and posterior portion of right liver lobe, it is described as severe fatty liver (S. Chen et al., 2008; Singh et al., 2013).

1.3 Statement of the Problem

NAFLD is a common cause of liver diseases worldwide. Most of the patients with NAFLD are asymptomatic but others may complain fatigue, malaise, and right upper quadrant abdominal discomfort and they may be accompanied with hepatomegaly on physical examination as well as mild jaundice and elevated liver enzymes levels (Table 1.1). It is known as one component of metabolic syndrome. NAFLD is a very common in Western countries but is rapidly growing in Asia-pacific region as well with affecting up to 30% of general population (Bedogni et al., 2005; Chan et al., 2013; Williamson et al., 2011). For many years, hepatic steatosis was presumed to be scarce among Asian particularly in those with low prevalence of obesity. However, to date, the reports on increased prevalence of T2DM and obesity in this region have confirmed that prevalence of hepatic steatosis has risen among Asians and reached those levels in Western countries. In Malaysia, where DM and obesity have been an increase, it is presumed that the prevalence of NAFLD would be alarmingly amongst Malaysians as well (Rampal et al., 2007).

NAFLD represents a spectrum of liver diseases that histologically ranges from hepatic fat accumulation without inflammation or fibrosis (simple hepatic steatosis) to hepatic steatosis with necroinflammatory components (steatohepatitis) that lead to fibrosis, cirrhosis (scar replace the liver cell or extensive fibrosis associated with regenerative nodules as results in chronic inflammation of the liver) which may progress into hepatocellular carcinoma (HCC) (Akcam, Boyaci, Pirgon, Koroglu, & Dundar, 2013), so that NAFLD is considered the main cause of liver failure and is shown to increase mortality (Adams et al., 2010; Duan, Qiao, & Fan, 2012). In light of that, a study by Adams et al., (2005) showed that 37% of patients with NAFLD have developed to the liver fibrosis. About 12-40% of patients with simple fatty liver would progress to NASH and which further would develop to fibrosis within 8-13 years. Moreover, 15% of patients who have NASH and early stage of fibrosis would progress to cirrhosis. Current studies also confirmed that the presence of portal tracts fibrosis in obese patients was significant predictive factor of fibrosis development. Furthermore, around 7% of patients with NAFLD and associated cirrhosis would progress to HCC after 10 years, whereas about 50% would require liver transplant or succumb to liver related condition. Interestingly, higher incidence of HCC is associated with NAFLD related cirrhosis as compared to those related to hepatitis or alcoholics (de Alwis, Nimantha Mark Wilfred & Day, 2008). To date, NAFLD is considered the most common cause of abnormal liver function (Targher et al., 2007). Elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are the most common occurrence in NAFLD (E. J. Kim et al., 2014). Several studies have also indicated that NAFLD is associated with rising prevalence of cardiovascular disease (CVD) regardless of the presence or absence DM (Kotronen & Yki-Jarvinen, 2008). Hence, Kim, (2014) and his colleagues confirmed that NAFLD is not only a risk factor for progressive liver diseases, but also is considered an independent risk factor of CVD.

Table 1.1 : Clinical symptoms, signs, and laboratory picture of NAFLD

Frequently asymptomatic	High ALT (2-4x)
Vague and unspecific symptoms	High GGT (2-6x)
Abdominal right upper quadrant discomfort	Mild elevation of AST(can be elevated in cirrhosis)
Fatigue	Blood glucose > 100 mg/dL
Dyspepsia	TG > 150 mg/dL
Overweight (BMI ≥25 kg/m^2)	TC > 200 mg/dL
High blood pressure	HDL-C < 45 mg/dL
Hepatomegaly (in 50%)	LDL-C > 130 mgldL
Splenomegaly (in 25%)	

(Adapted from Oliveira, de Lima Sanches, de Abreu-Silva, & Marcadenti, 2015). ALT: Alanine aminotransferase, GGT: Gamma-Glutamyl Transferase, TG: Triglyceride, TC: Total Cholesterol, HDL-C: High-Density Lipoprotein-Cholesterol, LDL-C: Low-Density Lipoprotein-Cholesterol

1.4 Significant of the Study

NAFLD is considered as the pandemic liver disease from the twenty-first century and it is increasing worldwide, in line with pandemic of obesity (Machado & Cortez-Pinto, 2014). There are around one billion persons worldwide as having NAFLD (Loomba & Sanyal, 2013). It is also considered as the third cause of the liver transplantation in United States. NAFLD is correlated with increased overall mortality by increasing CVD mortality (Adams et al., 2005; Rafiq et al., 2009; Söderberg et al., 2010).

The proposed topic warrants examination as the findings from the present study would supply insights to our understanding of the association of different factors such as demographic factors (age, sex and ethnicity), anthropometric measurements (BMI and WHR), lifestyle (dietary pattern and physical activity), lipid profile (TC, TG, HDL-C and HDL-C), and medical history of diseases (DM and hypertension) with NAFLD. The study would also highlight on the differences of subcutaneous tissue thickness and hepatic echo–intensity attenuation between subjects with and without NAFLD. On top of that, this study would identify the risk predictors of NAFLD. Hence, the main reason for conducting this study is to determine the contributing factors of NAFLD amongst Malaysian adults.

In summary, it is predicted that the findings from our study would involve to the body of knowledge with respect to preventive measures of the predictive factors of and NAFLD.

1.5 Conceptual Framework of the Study

Cobceptual framework (Figure 1.2) provides detailed description about the present study. There are several factors which can lead to NAFLD. These factors were set as independent variables and NAFLD as dependent variable.

However, hepatic echo-intensity attenuation rate might be affected by the dependent variable (NAFLD) (Xia et al., 2012).

1.5.1 Dependent Variable

The dependent variable of the present study is NAFLD which has been sonographically diagnosed.

1.5.2 Independent Variables

NAFLD is mostly affected by the following factors, including the demographic factors (age, gender and race), anthropometric measurements (BMI and WHR), lifestyle factors (dietary pattern and physical activity), lipid profile (TC, TG, HDL-C and LDL-C), medical history of diseases (DM and hypertension) and subcutaneous tissue thickness (Fan et al., 2005b; Wong et al., 2010). All the factors mentioned above were listed as independent variables in this study. All independent variables were analyzed to determine their association with dependent variable.

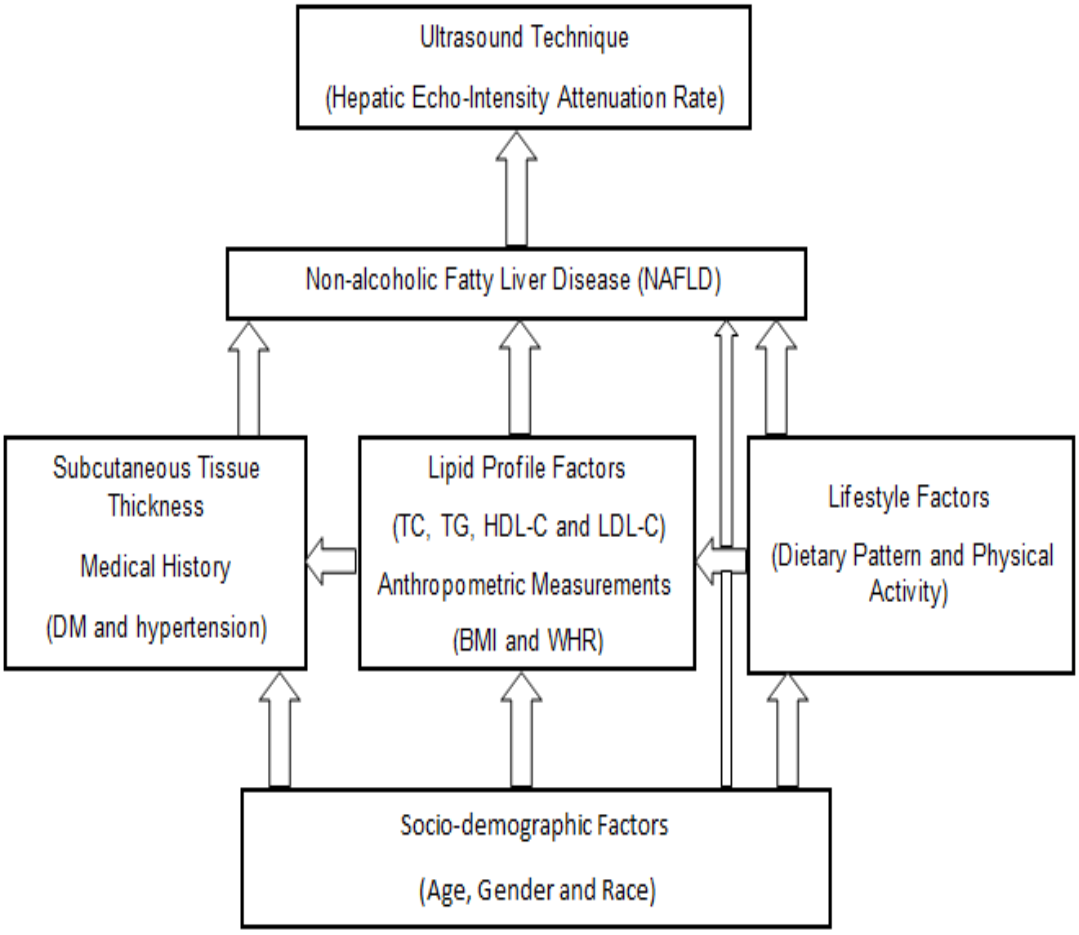

Figure 1.2 : Conceptual framework of the study

1.6 Study Objectives

General Objective

To determine the contributing factors associated with sonographic findings of NAFLD amongst Malaysian adults at Golden Horses Health Sancturay in Selangor.

Specific Objectives

1. To determine the proportions of demographic factors (age, sex and ethnicity) and NAFLD grades, anthropometric measurements (BMI and WHR), lifestyle (dietary pattern and physical acivity), lipid profile (TC, TG, HDL-C, LDL-C), and medical history of diseases (DM and hypertension) amongst a study population.
2. To determine the association of demographic factors (age, sex and ethnicity), anthropometric measurements (BMI and WHR), lifestyle (dietary pattern and physical activity), lipid profile (TC, TG, HDL-C and LDL-C), and medical history of diseases (DM and hypertention) with NAFLD.
3. To compare the differences of mean hepatic echo-intensity attenuation rate and subcutaneous tissue thickness between NAFLD patients and normal subjects.
4. To determine the association of demographic factors (age, sex and ethnicity), anthropometric measurements (BMI and WHR), lifestyle (dietary pattern and physical activity) and medical history of diseases (DM and hypertension) with grading of NAFLD.
5. To determine the predictors (age, sex, ethnicity, dietary pattern, physical activity, BMI, WHR, TC, TG, HDL-C, LDL-C, DM, hypertension and subcutaneous tissue thickness) of NAFLD.
6. To compare the differences of mean TC, median TG, HDL-C and LDL-C, between different grading of NAFLD.
7. To compare the differences of mean hepatic echo-intensity attenuation rate and subcutaneous tissue thickness between different grading of NAFLD.

1.7 Study Hypotheses

1. There is significant association of demographic factors (age, sex and ethnicity), anthropometric measurements (BMI and WHR), lifestyle (dietary pattern and physical activity), lipid profile (TC, TG, HDL-C and LDL-C), and medical history of diseases (DM and hypertention) with NAFLD.
2. There are significant differences of mean hepatic echo-intensity attenuation rate and subcutaneous tissue thickness between NAFLD patients and normal subjects.
3. There is significant association of demographic factors (age, sex and ethnicity), lifestyle (dietary pattern and physical activity),

anthropometric measurements (BMI and WHR) and with grading of NAFLD.

4. Age, female gender, Malay and Indian races, excess of fat and carbohydrate intake, active physical activity, obese and severe obese, high WHR, high TC, high TG, low HDL-C, high LDL-C, DM and hypertension are risk predictors of NAFLD.
5. There are significant differences of mean TC, median TG, HDL-C and LDL-C, between different grading of NAFLD as well as a significant association between medical history (DM and hypertension) and grading of NAFLD.
6. There are significant differences of mean hepatic echo-intensity attenuation rate and subcutaneous tissue thickness between different grading of NAFLD.

1.8 Definition of Terms

NAFLD: It is defined as excessive deposition of fat in the liver cell with abscent alcohol intake. On biopsy, it is described by excess amount of fat over 5% of wet liver weight (Dai et al., 2009). On ultrasound, it is identified by increased liver parenchyma echogenicity more than adjacent organs such as right renal cortex or spleen (Hamer et al., 2006).

NAFLD grading: It represents disease severity which are divided into three grades (I or mild, II or moderate and III or severe). Thses three grades can be diagnosed depending on increasing echogenicity of liver parenchyma as well as visibility of portal vein branches walls and diaphragm.

BMI: It is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

WHR: It is defined as the waist circumference measurement divided by hip circumference measurement multiplied by 100%. Waist circumference (WC) is measured at the level of the umbilicus between the lowest rib and iliac crest. In contrast, hip circumference is measured at the widest points around buttocks.

Physical Activity: It is defined as any bodily movement carried out by skeletal muscles that requires energy expenditure

Vigorous Physical Activity: It is referred to heavy duty activity which requires a person to breath harder than normal such as running, swimming and tennis (single).

Moderate Physical Activity: It is referred to activities of intermediate effort that make a person breaths less than that in vigorous but slightly harder than normal such as cycling slower than 10 miles per hour and tennis (double).

Lipid Profile: Being panel of blood tests that serves as an initial medical examination tool for abnormalities in lipids, like TC, TG, HDL-C and LDL-C. Lipid profile results are used as diagnostic reference for many diseases such as CVD and genetic diseases.

Odds ratio (OR): It is the ratio of the probability that an event (disease or exposure) will occur divided by the probability that the event will not occur.

Response rate: It refers to the number of subjects who answered the survey divided by the number of subjects in the sample.

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