EVALUATION OF TYPE-2 DIABETES MELLITUS AMONG HEPATITIS B AND C PATIENTS IN PENANG GENERAL HOSPITAL, MALAYSIA

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by

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Dedication

I would like to dedicate my thesis

To

My Country…

My Father…

My Mother…

My Wife…and

My Family…

For their unconditional love, encouragement, patience and sacrifice during my study.

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ABBREVIATIONS

ALP	Alkaline Phosphotase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
β-cell	Beta cell
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
GAD	Glutamic Acid Decarboxylase
GLUT-4	Glucose Transporter Type 4
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HOMA	Homeostatic Model Assessment
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IL-6	Interleukin-6
MC	Mixed Cryoglobulinemia
NHANES III	Third National Health and Nutrition Examination Survey
NHMS 1	First National Health and Morbidity Survey
NHMS 2	Second National Health and Morbidity Survey
OGTT	Oral Glucose Tolerance Test
RNA	Ribonucleic Acid
sTNFR1	Soluble Tumor Necrosis Factor Alpha Receptor Type 1
sTNFR2	Soluble Tumor Necrosis Factor Alpha Receptor Type 2
TNF-α	Tumor Necrosis Factor Alpha
TNFR1	Tumor Necrosis Factor Alpha Receptor Type 1
TNFR2	Tumor Necrosis Factor Alpha Receptor Type 2
WHO	World Health Organization

PENILAIAN DIABETES MELLITUS JENIS-2 DALAM KALANGAN PESAKIT HEPATITIS B DAN C DI HOSPITAL PULAU PINANG, MALAYSIA

ABSTRAK

Diabetes mellitus (DM) dan infeksi virus hepatitis kronik C (HCV) dan B (HBV) secara relatifnya merupakan gangguan biasa dan dianggap sebagai masalah utama kesihatan awam di seluruh dunia, dengan meningkatnya komplikasi dan kadar mortaliti. Kaitan epidemiologi antara infeksi virus hepatitis kronik dan diabetes mellitus telah dilaporkan. Banyak kajian terdahulu menunjukkan prevalens DM yang amat tinggi dalam kalangan pesakit HCV- berpenyakit hati kronik, jika dibandingkan dengan pesakit berpenyakit hati kronik yang berpunca daripada etilogi lain. Banyak kajian lain melaporkan perkaitan yang sama antara diabetes dan infeksi virus hepatitis B, tetapi dengan kekerapan yang lebih rendah. Matlamat kajian ini adalah untuk menilai keberlakuan diabetes jenis-2 dalam kalangan pesakit infeksi virus hepatitis B atau C dan mengkaji faktor risiko yang berkaitan dengan perkembangan diabetes jenis-2 dalam populasi hepatitis. Kajian silang retrospektif telah dijalankan di Hospital Pulau Pinang, Malaysia. Seramai 520 pesakit hepatitis B dan C terlibat dalam kajian ini berdasarkan kriteria yang ditetapkan. Daripada 520 pesakit, 269 mengalami infeksi hepatitis B dan 251 lagi mengalami infeksi hepatitis C. Rekod pesakit diteliti untuk mendapatkan data kajian, contohnya kewujudan diabetes jenis-2, jenis hepatitis virus kronik, data makmal, data demografi dan keputusan klinikal. Kajian ini melibatkan 331 pesakit lelaki dan 189 pesakit perempuan. Daripada jumlah tersebut, 177 berbangsa Melayu, 319 Cina dan 24 India. Terdapat perkaitan yang signifikan antara diabetes jenis-2 infeksi hepatitis kronik, yang prevalens diabetes secara signifikannya lebih tinggi dalam infeksi hepatitis C (25.9%) daripada dalam infeksi hepatitis B (16.4%) (p = 0.008). Selepas pemboleh ubah

diselaraskan dengan menggunakan regresi logistik, kejadian diabetes dikaitkan dengan bangsa (OR = 3.16, 95% CI = 1.90-5.24, nilai p = 0.001), kumpulan umur (OR = 2.53, 95% CI = 1.41-15.45, nilai p = 0.002), sejarah diabetes keluarga (OR = 3.51, 95% CI = 1.73-7.10, p = 0.001) dan jenis hepatitis (OR = 1.70, 95% CI = 1.07-2.70, nilai p = 0.023). Dalam kalangan pesakit yang dijangkiti hepatitis B, kejadian diabetes dikaitkan dengan faktor bangsa dan kumpulan umur dalam kehadiran faktor lain. sementara, selepas factor penyelarasan dalam kalangan pesakit yang dijangkiti hepatitis C dikawal, kejadian diabetes dikaitkan dengan bangsa dan sejarah diabetes keluarga. Dapatan kajian menunjukkan bahawa jenis hepatitis secara signifikannya berkaitan dengan kejadian diabetes dalam kalangan pesakit hepatitis B dan C, daripada populasi kajian. Selanjutnya, pesakit dengan infeksi hepatitis C adalah berisiko tinggi untuk mengalami diabetes jenis-2 daripada pesakit dengan infeksi hepatitis B. Kajian ini merumuskan bahawa pesakit berbangsa Melayu, berumur (lebih tua), serta dengan sejarah diabetes keluarga yang positif, dianggap sebagai faktor risiko bebas bagi perkembangan diabetes mellitus jenis-2 dalam kalangan pesakit yang dijangkiti virus hepatitis. Kajian selanjutnya diperlukan untuk mengkaji perkaitan ini serta faktor-faktor yang risiko lain. Di samping itu, kajian ini juga mencadangkan agar penyaringan ketidaknormalan glukosa dijalankan dalam kalangan pesakit dengan infeksi hepatitis C.

EVALUATION OF TYPE-2 DIABETES MELLITUS AMONG HEPATITIS B AND C PATIENTS IN PENANG GENERAL HOSPITAL, MALAYSIA

ABSTRACT

Diabetes mellitus (DM) and chronic hepatitis C (HCV) and B (HBV) virus infections are relatively common disorders and considered as worldwide, major public health problems with increasing complication and mortality rates. An epidemiologic link between chronic hepatitis virus infection and diabetes mellitus has recently been reported. Many of previous studies have revealed a higher prevalence of DM in patients with HCV-related chronic liver disease when compared to patients with chronic liver disease resulting from other etiologies. Many other studies have reported similar relationship between diabetes and hepatitis B virus infection but with lower frequencies. The aims of this study are to evaluate the occurrence of type-2 diabetes among patients with chronic hepatitis B or C virus infections and to investigate the risk factors which are associated with the development of type-2 diabetes in hepatitis population. A retrospective cross-sectional study was conducted in Penang General Hospital, Penang, Malaysia. A total of 520 patients with hepatitis B and C were enrolled in this study according to the inclusion criteria of the study. Among 520 patients, 269 were diagnosed with chronic hepatitis B and 251 with chronic hepatitis C infection. The patients' records were reviewed to select the required data for the study such as the presence of type-2 diabetes, type of chronic viral hepatitis, laboratory data, demographic data and clinical outcomes. This study included 331 males and 189 females. Out of those, 177 patients are Malay, 319 Chinese and 24 Indian. There was a significant association between chronic hepatitis infection type-2 diabetes, in which, the prevalence of diabetes was significantly higher in hepatitis C (25.9%) than in hepatitis B (16.4%) infection (p = 0.008). After adjusting the

confounding variables by applying logistic regression, diabetes occurrence was associated with race (OR = 3.16, 95% CI = 1.90-5.24, *p* value = 0.001), age group (OR = 2.53, 95% CI = 1.41-15.45, *p* value = 0.002), family history of diabetes (OR = 3.51, 95% CI = 1.73-7.10, *p* = 0.001) and type of hepatitis (OR = 1.70, 95% CI = 1.07-2.70, *p* value = 0.023). Among hepatitis B infected patients, diabetes occurrence was related to the race and age group factors in the presence of other factors. While after controlling of confounding factors among hepatitis C infected patients, diabetes occurrence was associated with the race and family history of diabetes. The study findings revealed that type of hepatitis was significantly associated with the diabetes occurrence among hepatitis B and C patients of the study population. Furthermore, patients with hepatitis C infection were at a higher risk to develop type-2 diabetes than patients with hepatitis B infection. This study concluded that the Malay race, older age and positive family history of diabetes are considered as independent risk factors for type-2 diabetes mellitus development among viral hepatitis infected patients. Further studies are needed on this field to investigate this association and the other possible risk factors. In addition, this study suggests that screening for glucose abnormalities should be indicated in patients with hepatitis C infection.

Chapter One
Introduction

1.1 Viral Hepatitis

Hepatitis is defined as an inflammation of the liver. There are many causes of hepatitis including viruses, medicines and alcohol. However, the hepatitis which is caused by a virus is usually called viral hepatitis**.** There are two phases of viral hepatitis; acute hepatitis which is found in all types of hepatitis, and chronic hepatitis which is observed in hepatitis B, C and D infection only (Horn, 2005). Most forms of hepatitis can clear up spontaneously within few months, while other cases having certain types of hepatitis can develop chronic and fatal liver diseases (Carlson *et al.*, 2004).

Chronic hepatitis is considered as a heterogeneous group of diseases of different etiologies, pathogenesis and degree of activity as well as stage of progression (Kuntz and Kuntz, 2008). The numbers of hepatitis infection cases (especially B and C) are staggering since both are common infectious diseases with many ways of virus transmission among the general population. Moreover, the diagnosis and treatment of hepatitis represent the most active part of medicine related to the liver disease, and this is due to the development of basic molecular biology and the large numbers of infected people. The knowledge of viral hepatitis infection is increasing especially for hepatitis C virus which was discovered about 15 years ago. The recent available information of viral hepatitis makes it possible to understand the majority of hepatitis viruses and the related diseases (Worman, 2006).

1.2 Hepatitis Classification

There are many types of human hepatitis viruses namely: hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, and hepatitis E virus and the diseases which caused by these viruses are known as hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E, respectively (Hollinger *et al.*, 2002).

Different types of human hepatitis viruses cause different types of liver diseases and there many ways to classify these viruses. The classification may depend on the viruses DNA and RNA or could be based on the families of viruses that they belong to. On the other hand, the clinicians may divide them according to the types of hepatitis they can cause. While for epidemiologists, they more interested in the transmission ways of hepatitis viruses (Worman, 2006).

Hepatitis B and C viral infections are considered the most important types of hepatitis and major health problems in the world. These two viruses are mostly associated with chronic hepatitis, liver cirrhosis and hepatic failure and sometimes may progress to hepatocellular carcinoma. Moreover, they are known to cause infections with significant morbidity and mortality especially in developing countries (Haider *et al.*, 2006).

1.2.1 Hepatitis B Infection

Hepatitis B is an infectious disease and it is caused by hepatitis B virus (HBV) which can attack the humans liver leading to transient or chronic infection (Seeger and Mason, 2000). HBV was discovered in 1966 (Lee, 1997).

The infection of HBV was firstly known as “serum hepatitis” (Yap, 2004). This virus can replicate itself inside the hepatocytes causing an overlapping with the normal functions of the liver (Tong *et al.*, 1999). HBV infection is considered as a world health problem especially in Asia and its progression can lead to significant morbidity and mortality. However, HBV can be transmitted by contact to the infected blood or body fluids (Lavanchy, 2004). HBV infection can be in acute or chronic phases, in which, the symptoms of acute HBV infection include vomiting, abdominal pain, nausea, fever, jaundice, dark urine and hepatomegaly. Around 90% of perinatal acute hepatitis B infection cases are asymptomatic. The typical symptoms are well reported in about 5 – 15% of recently infected young children (1–5 years of age) and in 33-50% of older children adolescents and adults (Shepard *et al.*, 2006). The majority of acute hepatitis B infected individuals are capable to clear the viral infection without medicines and they virtually have immunity to the HBV (Maddrey, 2000). Among these infected individuals, approximately 5-10% of people with acute infection will develop chronic HBV infection (Jonas *et al.*, 2010).

The infected individuals with chronic HBV have a higher risk to develop liver cirrhosis, end stage liver disease and hepatocellular carcinoma which can occur as a result of immune-mediated inflammatory response. Approximately 12% of patients with chronic HBV infection have been reported to develop cirrhosis annually (Pungpapong *et al.*, 2007; Yin and Tong, 2006). Moreover, patients with chronic HBV infection have higher risk for hepatocellular carcinoma in about 300-fold when compared with the general population (Wong *et al.*, 1995).

Chronic HBV infection causes many complications and it bears the burden of several diseases which are virtually associated with HBV. Many studies have reported that cirrhosis and hepatocellular carcinoma can lead to premature death in 5-15% of chronic HBV infected patients. Hepatic manifestations which are related to HBV infection can still be asymptomatic until the diagnosis or until they present the acute hepatitis signs (Shepard *et al.*, 2006).

Approximately 2 billion people have been infected with HBV in the world. Among them, there are 350 million people who are diagnosed with chronic HBV infection, and about 30% of them will develop chronic infection complications leading to death (André, 2000). The prevalence of HBV infection can be divided into low, intermediate and high endemicity (Rots *et al.*, 2010). In Asia, the prevalence is considered high and it is estimated to be less than 8% in many countries like China, Indonesia, Korea and Philippine (Yin and Tong, 2006).

The situation does not differ so much in Malaysia since the viral hepatitis is considered as a serious public problem and it is estimated that 1 million people are infected with chronic HBV. Moreover, the prevalence of HBV infection is 4.7% and it constitutes about 75% of all viral hepatitis in the Malaysian population. Approximately 80% of the hepatocellular carcinoma cases are attributed to chronic HBV infection in Malaysia (Khairullah and Merican, 2004; Yin and Tong, 2006).

There are many routes by which HBV can transmit among the people. Blood transfusion is considered as the main route followed by sexual transmission. While in the endemic regions, the perinatal vertical transmission is a common way of spread. On the other hand, there are many other potential routes of virus transmission including needle stick, dialysis and transplacental spread (Lamoreux, 2008).

The drugs that are used in the treatment of HBV infection have been reported to reduce the liver damage by stopping virus replication but not to clear the infection (Dienstag, 2008). In acute HBV infection, the majority of patients do not need a treatment because they can clear the infection without any treatment especially in adults (Hollinger and Lau, 2006).

HBV infection drugs include mainly interferon which is defined as an immune system modulator. The other type of chronic HBV infection drugs of antiviral agents included lamivudine, adefovir, tenofovir and entacavir (Dienstag, 2008). However, the antiviral therapy of HBV infection is expensive, therefore, it is not easy for the treatment to be available for the majority of the infected patients in the developing countries (Wong *et al.*, 1995).

The prevention of hepatitis infection by the vaccine is the most meaningful way to avoid the occurrence of viral hepatitis. Thus, all the infants have to obtain the hepatitis vaccine. Since 1982, the vaccine of HBV infection was used worldwide and about 1 million doses have been used. In several countries, the percentage of children who have chronic HBV infection is about 8-15% and the vaccination has minimized the chronic

infection rate in immunized children to less than 1% (WHO, 2008). Malaysia has a successful program of vaccination, therefore, the incidence of viral hepatitis infection has been reduced significantly (André, 2000).

1.2.2 Hepatitis C Infection

Hepatitis C virus (HCV) causes hepatitis C which is considered as a blood liver disease, this virus was first discovered in 1989. Initially, the disease was known as "non-A non-B". HCV is transmitted primarily by direct contact with the blood or body fluids of the infected individuals. However, HCV infection is considered as a cause for chronic liver disease such as liver cirrhosis (Sy and Jamal, 2006).

Moreover, HCV leads to liver inflammation that interferes with normal liver functions. Eventually, HCV can lead to severe, persistent liver damage, cirrhosis and may be complicated by liver cancer. The initial symptoms of HCV infection are mild and because of that the infection often goes unnoticed until the damage of the liver is discovered after years of infection (WHO, 2003).

Approximately more than 170 million of the world's population is currently diagnosed with chronic HCV infection and it is also responsible for 100000 cases of liver cancer per year (Poynard *et al.*, 2003). Therefore, World Health Organization (WHO) has considered HCV infection as a global health problem. Because of this high prevalence of HCV infection and to recognize its epidemiology, there is a global concern of the disease in order to identify the specific health care measures to provide disease prevention and control (Chen and Morgan, 2006).

Primary exposure to HCV causes an acute infection which is often relatively mild. Most patients who have chronic HCV infection do not show the symptoms and they live with a normal life. In 10-25% of people, the infection develops over the course of 10-40 years (Alter *et al.*, 1998). Some of infected individuals with acute hepatitis might have mild flu-like symptoms, including loss of appetite, fever, headaches, abdominal pain, muscle or joint pain, nausea and fatigue (Villano *et al.*, 1999). On the other hand, some others with chronic infection, though not common, they showed more severe flu-like symptoms, itching and dark urine (Hoofnagle, 1997). About 20-30% of infected persons develop clinically acute HCV infection in their attempt to resolve the infection, while 70-80% of patients with acute HCV infection do not resolve the infection but lead to permanent viral infections (Immunobiology, 2005).

Over time, people with chronic HCV infection may report various symptoms related to liver damage (Chen and Morgan, 2006). Chronic HCV infection accounts for at least 25% of all cases of chronic liver disease. However, a significant proportion of infected individuals with chronic HCV infection are asymptomatic, in which, patients have normal liver enzymes and normal liver histology. Progression of HCV is slow in infected patients, and they may remain asymptomatic for many years (Desenclos *et al.*, 2001). The prognosis of chronic HCV infections may be liver cirrhosis and hepatocellular carcinoma (Bonkovsky and Mehta, 2001). Moreover, HCV-related liver cirrhosis is currently considered as the main cause of liver transplantation among liver diseases (Berenguer and Wright, 1999).

However, most of the chronic HCV cases eventually develop to liver disease, therefore, the crucial aim is to prevent the progression of HCV infection in order to minimize its morbidity and mortality among the infected patients (Jaeckel *et al.*, 2001).

Given the lack of HCV infection symptoms and definitive liver histology, the liver enzymes levels are currently considered as the main indicator of liver progression to cirrhosis (Hu *et al.*, 2004). Many studies reported that severe hepatic fibrosis, as well as a severe inflammation activity, due to high levels of liver enzymes may be related with liver progression to cirrhosis over 10 years. When the fibrosis is mild, the progression to cirrhosis has been slowed and limited (Desenclos *et al.*, 2001). Hence, persons with high levels of liver enzymes progress heading more quickly toward the disease than those with normal levels of the same liver enzymes (Hu *et al.*, 2004). The HCV has a serological association with end-stage liver disease that needs for liver transplantation (Resnick and Koff, 1993). HCV infection accounts for 20% of cases of acute hepatitis, 70% of cases with chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of cases with liver transplant (Mchutchison *et al.*, 2000).

HCV infection prevalence is not well known in several countries and that may be due to the HCV detection process which has practical difficulties involving the detection of HCV-RNA in the infected persons' serum. However, based on several studies, approximately 3% of the total population is infected with HCV infection in the world (WHO, 2006). The HCV infection prevalence rate is estimated fewer than 2.5% in most populations in Europe, Americas, and South-East Asia.

The prevalence rates in Western Pacific regions and parts of South America are higher ranging between 2.5- 4.9% while in the Middle East and Africa the HCV infection prevalence rate has been reported with range between 1- 12% (WHO, 2000).

In Malaysia, HCV infection prevalence is estimated 1.6% of the population (Sultan *et al.,* 2010) and 0.3% is positive for anti-HCV among blood donors. Blood donation screening has started since 1991 in the National Blood Bank (Zawawi, 2004). HCV infection is a growing problem in the Malaysian population as many people are found to have HCV infection through routine screening. In 2000, around 550 cases were reported to have hepatitis C infection in Malaysia with an incidence rate of 2.5/100,000 population. In 2004, about 741 cases were with an incidence rate of 2.9/100,000 population. Most of these cases reportedly have had blood transfusions or blood products previously. Like hepatitis B, hepatitis C has high risk to develop to chronic liver diseases including cirrhosis and hepatocellular carcinoma in up to 85% of cases in Malaysia (Ministry of Health Malaysia, 2005).

There are many routes of HCV transmission including blood transfusion which is considered as the current risk of infection by HCV. Moreover, an important percentage of the infected people can acquire the virus by drug use through injections. Direct exposure to infected blood, sex with multiple partners, tattoos, perinatal transmission and hemodialysis are considering important routes in HCV transmission. Moreover, it is estimated that 2% of people are infected with HCV through the needle stick injury (Lamoreux, 2008).

Preventing the progression to severe liver disease by the early eradication of the HCV is the main goal of hepatitis C treatment (Strader *et al.*, 2004). The majority of infected people are mostly unable to clear the infection because there is no known drug which can eradicate the HCV. Nevertheless, HCV infection treatment includes antiviral and immunomodulatory agents that modify the immune response and suppress the viral replication. Interferon is the only potential treatment that can be used effectively to inhibit the viral replication and minimize liver injury in a minority of patients but the improvement is usually transient. The most successful treatment has been measured by its ability to improve the liver histological findings and normalization of ALT levels in the serum (Sharara *et al.*, 1996). Using a combination treatment of ribavarine and interferon may improve the patients' response and the therapy effectiveness (Armas-Merino *et al.*, 1999).

1.3 Diabetes Mellitus

In 2000, according to the WHO, the estimated number of people diagnosed with diabetes mellitus (DM) was approximately 177 million worldwide and the expectations predict an increase in diabetic patients to at least 300 million by 2025. Thus, according to these statistics, there will be 165% increase in the DM incidence in the next 25 years (American Diabetes Association, 2004). In developing countries, most of people with DM belong to age group of 45 – 65 years. The DM management costs are ranging from 2.5% to 15% of the annual national health care budgets (American Diabetes Association, 2005).

It was reported that 5.1% of people with ages ranging between 20 -79 years in all International Diabetes Federation (IDF) member countries have DM in 2003 (American Diabetes Association, 2004). The highest numbers of people with DM are in the European Region and Pacific Region and these numbers are about 48 and 43 million respectively. The prevalence rate of DM in the North American region is considered as the highest rate which is 7.9% followed by the European region (7.8%) (American Diabetes Association, 2005).

In Asia, China and India are considered the most populous countries in the world in which give these two countries the prime importance to the epidemiology of DM. WHO predicts that the number of diabetic cases will increase in these two countries substantially. The majority of these cases will be in China (50 million) and India (57 million), therefore, more than 30% of people with DM will be in these two countries alone in 2025 (Cockram, 2000).

In Malaysia, the First National Health and Morbidity Survey (NHMS 1) was conducted in 1986 and reported the DM prevalence of 6.3%, while in the Second National Health and Morbidity Survey (NHMS 2) in 1996 the prevalence elevated to 8.2%. In a recent study, the prevalence had been noted to be higher at 10.5%. The WHO has predicted that Malaysia would have a total number of 2.48 million diabetics in 2030 compared to 0.94 million in 2000 increased by 164% (Mafauzy, 2006).

Malaysia is a multiethnic population and it consists of three main races Malay, Chinese and Indian and all these races are well represented in this country. Therefore, taking all together, Malaysian population would be at a higher risk to develop DM phenomenally like other countries in Asia (Zaini, 2000).

There are two types of DM; type-1 (insulin dependent diabetes mellitus i.e. IDDM) and type-2 (non-insulin-dependent diabetes mellitus i.e. NIDDM). Type-1 diabetes occurs mostly in children and young adults and can be noted in different ages. Approximately 4.9 million people are diagnosed with IDDM in various age groups, in which, its prevalence in the world's population is about 0.09%. The European Region has the highest number of IDDM cases 1.27 million, while the number in the North American Region is 1.04 million and in the South East Asian Region is 0.91 million patients with IDDM (Tabibiazar and Edelman, 2003).

NIDDM is the most common form of DM in the world and approximately 90% of DM patients are with NIDDM (Vijan *et al.*, 2000). The main factors that can be associated with the NIDDM occurrence are older age, family history, obesity, previous history of gestational diabetes, ethnicity and physical inactivity. The nature of the epidemic of DM still affects an increasing number of people worldwide, while global awareness remains low. In developed countries, NIDDM composes about 85% to 95% of all cases with DM and it constitutes for a higher percentage in the developing countries (International Diabetes Federation, 2003).

The NIDDM symptoms progress gradually in the diabetic patients and their onset does not suddenly happen like in IDDM. The symptoms of NIDDM may include nausea, polyuria, fatigue, weight loss, unusual thirst, frequent infections, blurred vision and slow healing of wounds, while other people may have no symptoms at all (Misra and Vikram, 2004).

In many countries, most of the DM cases are intensified in the urban areas. This feature will be destined to increase especially in countries with fast industrialization in the future (American Diabetes Association, 2005). In the developing countries, the situation is considered as a significant predictor for the projected increasing in numbers of DM cases. DM prevalence is higher in the developed world countries than in the developing countries, it is predicted to remain so till 2025. Therefore, the developing world will bear the burden of the increasing epidemic in the future. This problem should be addressed and solved, otherwise, the DM prevalence in the developing countries is predicted to rise by 170% in 2025 while the rise in the developed countries is at 41% over the same period (American Diabetes Association, 2004).

1.4 Association of Chronic Viral Hepatitis Infection and Type-2 Diabetes

The occurrence of DM has been reported to be higher in patients with chronic hepatitis that resulted from different etiologies when compared with the general population (Huang *et al.*, 2010). The liver's role in the carbohydrate metabolism is considered as substantial and important, so any defects in the liver functions may cause glycemic homestasis abnormalities as a complication of chronic liver disease (Custro *et al.*, 2001).

Clinically, the risk of having NIDDM in chronic HCV infected patients is important even though it is small. The liver disease progression is noticed to be deteriorated in the presence of DM and the effectiveness of viral hepatitis treatment agents can be less. NIDDM has been considered as an extrahepatic manifestation of HCV infection based on early clinical observations. Although the mechanism by which the HCV lead to DM are still not well determined, the direct virus action or cytokine stimulation are considered as suggested mechanisms that enhance the HCV infection to develop NIDDM in the infected patients (White *et al.*, 2008).

Further investigation into the pathophysiologies of that association may help to find out the main process by which NIDDM can occur in HCV infected patients (Wilson, 2004). Based on investigations which have reported that NIDDM occurrence will be decreased as a result of curing of HCV infection, clinical trials of chronic HCV infection treatment have shown that HCV may interact with the carbohydrates metabolism in the infected people (Negro and Clément, 2010). Many studies have revealed that the frequency of NIDDM in patients infected with chronic HCV is higher as compared with chronic HBV or other chronic liver diseases. Moreover, this higher prevalence of DM is not linked

exclusively to liver cirrhosis as it is increased in non-cirrhotic patients with HCV infection when compared to non-cirrhotic patients with HBV infection (Petit *et al.*, 2001). The prevalence of NIDDM is estimated 9-50% among HCV infected patients (Mavrogiannaki *et al.*, 2009). At a conservative estimation, approximately 12 million patients with HCV-induced cirrhosis and 28 million with chronic HCV have DM, therefore, HCV infection can develop DM in about 40 million individuals leading to a major public health problem (Lecube *et al.*, 2004).

Many risk factors can be involved to exaggerate the expression of NIDDM in HCV infected patients like age, body mass index, race, family history of DM and liver cirrhosis. Furthermore, people who they are 40 years old and above with HCV infection were reported to have NIDDM three times than those without HCV infection according to the Third National Health and Nutrition Examination Survey (NHANES III) (Mehta *et al.*, 2000).

Recent studies have suggested that liver transplantation which has been caused by HCV infection is substantially associated with post-transplant NIDDM occurrence (Mugo *et al.*, 2006). Moreover, approximately 40-64% of HCV infected liver transplantation recipients have developed post-transplant NIDDM and this prevalence is higher than that of transplanted patients for other liver diseases. In other words, hepatitis C infection has been reported to be a significant independent risk factor for occurrence of post-liver transplant DM (Lecube *et al.*, 2006).

On the other hand, many other studies have revealed that HBV infection may also cause DM, but the frequencies of this connection are less than in HCV infection (Mason *et al.*, 1999). Although there is a link between HCV infection and NIDDM and it has been recognized, there is correlation between chronic HBV infection and NIDDM can still be detected. However, since chronic viral hepatitis has been caused by both HBV and HCV, and in addition to the high prevalence of HBV infection as well as DM, combined with HCV- NIDDM link, it is possible that chronic HBV infection can develop NIDDM in HBV infected patients (Li-Ng *et al.*, 2007). In spite of there are several data which have shown that HBV infection has less significance association with NIDDM than HCV infection, chronic HBV infection can have a significant role in the development of NIDDM (Lao *et al.*, 2007). Based on several studies, the association between HBV infection and NIDDM can be attributed to the complications of HBV infection including liver fibrosis or cirrhosis (Huang *et al.*, 2010). While in other studies, the NIDDM occurrence can be detected in chronic HBV infected patients in the absence of liver cirrhosis with DM prevalence estimated 2-14% among the HBV population (Mavrogiannaki *et al.*, 2009).

1.4.1 Pathophysiological Mechanisms for Development of Type-2 Diabetes in Hepatitis C Virus Infection

The specific mechanisms responsible for the development of NIDDM in HCV infected patients are still unknown. The main mechanisms that may be proposed in the HCV infection-DM association could be the direct damage to the pancreatic beta cell, the triggering of beta cell autoimmunity by HCV and/or the increased in the insulin resistance (Noto and Raskin, 2006).

1.4.1.1 Beta Cell Autoimmunity

HCV is associated with extrahepatic events of autoimmune origin such as the glomerulonephritis membranoproliferative and essential mixed cryoglobulinemia. HCV infection may trigger an autoimmune reaction against pancreatic beta cells leading to DM. HCV can also stimulate these cells by having a region of its amino acid sequence shows a strong homology with glutamic acid decarboxylase (GAD) which is the most important pancreatic islet cell antigen. This mechanism can contribute in the occurrence of DM in HCV infected patients but it is not considered as the main pathophysiology of HCV infection and DM association (Honeyman *et al.*, 1998).

1.4.1.2 Direct Injury of the Beta Cell

Although HCV mainly affects the liver (Aria *et al.*, 1993), its occurrence in other tissues confirms that viral replication can also infect other organs. It has been able to detect multiple replications in extrahepatic sites such as mononuclear cells, Lymph nodes, brain, adrenal gland, heart, kidney, intestine, thyroid, bone marrow, spleen and pancreas (Vargas *et al.*, 2002). Virtually, an active replication of HCV in has been reported in the acinar cells of exocrine pancreas and in the epithelial cells of the pancreatic ducts. However, it is possible that HCV can infect the pancreatic beta cells and interfere in the synthesis and secretion of insulin leading to DM (Yan *et al.*, 2000).

1.4.1.3 Insulin Resistance in Hepatitis C Infection

It stands to reason that HCV infection leads to increase the insulin resistance because it is an infectious process that produces liver injury (Konrad *et al.*, 2000). However, there must be some specific mechanisms associated with HCV infection causing a higher

prevalence of DM compared to other liver diseases. Although the pathophysiology of insulin resistance has been reported as the basic mechanism for developing NIDDM in chronic HCV infected patients, it is not confirmed that production of proinflammatory cytokines could be responsible for the greatest potential DM in HCV infected patients (Lecube *et al.*, 2006).

It is well known that insulin resistance is associated with increased proinflammatory activity with elevated cytokine such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (Bugianesi *et al.*, 2005). The TNF-α promotes serine phosphorylation of the substrate-1-insulin receptor, decreasing the activity of this receptor tyrosine kinase (Hotamisligil *et al.*, 1996), and its expression is directly related to insulin resistance and hypertriglyceridemia (Kern *et al.*, 2001). The TNF-α exerts its biological effects through interaction with two types of receptors that are expressed in the cell membrane, type 1 (TNFR1) and type 2 (TNFR2) (Tartaglia and Goeddel, 1992). Quantification plasma of the two receptors is the best indicator of the overall system activation, having a longer half-life, higher plasma levels and less variability than TNF-α (Straczkowski *et al.*, 2002).

For its part, the IL-6 is a multifunctional cytokine produced by a variety of cell types, including immune system, liver and adipose tissue. It mediates both the inflammatory reaction and in the response induced by stress (Papanicolaou *et al.*, 1998). The IL-6 promotes the insulin resistance through inhibition of transcription of the glucose transporter GLUT-4 which is a substrate of the insulin receptor (Rotter *et al.*, 2003). Circulating levels of IL-6 are associated with insulin resistance in human with

NIDDM (Vozarova *et al.*, 2001) and predict the risk of developing DM (Hotamisligil *et al.*, 1996). In comparison with the healthy individuals, patients with chronic HCV infection have showed extra concentrations of both TNF-α and its soluble receptors (sTNFR1 and sTNFR2) and IL-6 (Knobler and Schattner, 2005; Malaguarnera *et al.*, 1997). In addition, it has reported that the concentration of these cytokines is associated with the severity degree of liver injury (Neuman *et al.*, 2002). However, to date no studies have evaluated the relationship between TNF-α, sTNFR1, sTNFR2 and IL-6 with insulin resistance and/or DM in patients infected with HCV infection compared with patients with other liver diseases (Lecube *et al.*, 2006).

In summary, HCV infection by direct virus action and induce liver inflammation, cause releasing and activation of TNF-α and IL-6, then by mechanisms above, leading to insulin resistance then to NIDDM. Other factors of the host including age, obesity and positive family history of DM, may help in insulin resistance develop by increasing the level of TNF-α or by other different mechanisms (Schattner and Knobler, 2008).

1.4.2 Risk Factors for Hepatitis C Infection-Diabetes Association

Patients with chronic hepatitis infection are considered at high risk to develop NIDDM substantially (Qureshi *et al.*, 2002). In addition, there are many predisposing factors which can aggravate the occurrence of DM in hepatitis patients such as age, obesity, race, positive family history and severe hepatic histology (Schattner and Knobler, 2008). In chronic HCV infected patients, NIDDM occurs more frequently in persons who are older, with high BMI and non-white (Mehta *et al.*, 2000). The trend of the recent studies is to focus on the association of HCV infection and NIDDM and the independent risk

factors for DM development in patients with chronic HCV infection. According to these studies, many factors were reported to develop NIDDM and others were found not affecting on its occurrence (Fartoux *et al.*, 2005).

According to clinical evidences, age can play an important role in the occurrence of NIDDM in HCV infected patients and it can be as a predisposing factor for getting DM in general population, as well as in HCV infected patients. Obesity is considered as one of the important risk factors leading to DM, and it was also found to be one of the contributors in developing NIDDM in HCV infected population. Many studies have shown that obesity was highly associated with NIDDM occurrence (Knobler and Schattner, 2005).

In addition, HCV infected patients with positive family history of DM will be at a higher risk of having NIDDM. It was noticed that the family history of DM was the most significant predictor for NIDDM occurrence in patients with chronic HCV infection (Chehadeh *et al.*, 2009). Furthermore, patients with acute alcoholic consumption may be at a risk of having DM by the reduction in insulin-mediated glucose uptake. While the chronic drinking of alcohol will lead to damage of the pancreatic islet β-cells causing NIDDM (Garcia-Compean *et al.*, 2009).

The other risk factor which is leading to NIDDM in HCV infected patient is race. Many data have recognized that patients who are black can develop NIDDM that associated with HCV infection. Moreover, the prevalence of NIDDM has been shown to be increased significantly in blacks with HCV infection. Additionally, HCV infection may

increase the occurrence of NIDDM in blacks since this race is at a higher risk due to insulin resistance, dysfunction of islet cell and the genetics interplay. Accordingly, HCV infection- NIDDM link was measured in different ethnic group like Japanese, American Indian, Chinese and Italian. As a result of the environmental factors effect, the association of HCV and NIDDM can be differed in these ethnic groups (Mugo *et al.*, 2006).

Recently, the importance of risk factors identification is to reveal by which mechanism this association happens (Petit *et al.*, 2001). Furthermore, HCV infection is considered as an important factor to cause liver cirrhosis and the latter was found to be highly associated with glucose intolerance. Approximately 10-20% patients with cirrhosis may have DM as one of the liver cirrhosis complications (Schattner and Knobler, 2008).

1.4.3 Complications of Hepatitis C Infection and Diabetes Comorbidity

The association of HCV infection and NIDDM has several clinical consequences regardless of the association pathogenesis (Leandro *et al.*, 2006). Moreover, the stage of liver cirrhosis severity depends on many cofactors including gender, age, obesity and clinical conditions. NIDDM is considered as one of these cofactors which may affect on the HCV infection and modify its course leading to worsen the prognosis of HCV infection (Negro and Clément, 2010). DM morbidity is severe and affects on people life seriously due to many complications including fibrosis, liver failure, minimum response to the antiviral therapy and development of hepatocellular carcinoma. According to recent studies, DM can cause severe hepatic encephalopathy in HCV cirrhotic patients compared to patients without DM (Lonardo *et al.*, 2007).

Furthermore, DM has been reported to develop liver cancer in cirrhotic patients with chronic HCV infection. These evidences show that the DM interacts with other traditional risk factors and with HCV infection to increase the risk of hepatocellular carcinoma occurrence (Lonardo *et al.*, 2007). In addition, many factors may be included in liver cancer development such as HCV infection, HBV infection, cirrhosis as well as NIDDM which all of these are more frequent in patients with primary liver cancer. DM can cause a primary liver cancer in the existence of other risk factors including HBV, HCV infection and liver cirrhosis, i.e. that DM has increased the possibility for developing hepatocellular carcinoma in patients with chronic liver disease. Other risk factors such as gender, age and alcohol intake may contribute to develop hepatocellular carcinoma in the presence of DM and HCV infection (Mugo *et al.*, 2006).

Moreover, HCV infected patients are at a high risk of insulin resistance, which in turn, may consider as independent risk factor for liver fibrosis, since fibrosis grades were significantly linked to insulin resistance. Recently, evidence has confirmed that insulin resistance occurs at early stages of HCV infection and it is considered as an independent predictor for liver fibrosis degree (Hui *et al.*, 2003). According to this observation, patients who were infected with HCV and developed DM may have severe hepatitis complications based on their liver enzymes and liver biopsy findings (Petit *et al.*, 2001).

In general, DM is well known to cause microvascular and macrovacular complications, therefore, HCV patients with DM will be more risked to develop these complications. It has been reported that patients with DM may develop severe renal dysfunction in the presence of HCV infection than in patients without HCV infection (Soma *et al.*, 2000).

In addition, hemodialysis has been shown to be required in one third of chronic hepatitis patients. Recently, both DM and atherosclerosis can be attributed to inflammatory cause and the occurrence of both can be increased and worsened as a result of severe inflammation (Pradhan *et al.*, 2001). Moreover, the increase in the TNF level has been recognized to be related with recurrent vascular events and atherosclerosis (Ridker *et al.*, 2000). Since the chronic hepatitis infection is associated with TNF level increasing in the liver and serum, the association of HCV and DM can be significantly linked to more deteriorated vascular complications than in each disorder alone (Schattner and Knobler, 2008).

1.4.4 Clinical Management

The understanding of treatment concepts of HCV- NIDDM association is still unclear and partially understood**.** There are two main purposes of treating the DM in HCV infection: to minimize the fibrogensis, thus, the progression of liver disease and to improve the response to antiviral therapy (Negro and Clément, 2010). Similarly, the eradication of HCV by antiviral therapy such as interferon can decrease the insulin resistance and improve the insulin sensitivity. However, the reported response is below the required level, therefore, further studies are needed in order to improve the response to antiviral therapy (Strader *et al.*, 2004). One of the most important therapy concepts is to correct the insulin resistance, since HCV infection has been reported to increase the insulin resistance which can predispose for development of DM and interfere with the course of liver disease. Thus, the clearance of HCV infection is leading to decrease the insulin resistance and reduce the possibility of DM occurrence and liver complications (Alaei and Negro, 2008).

Furthermore, the insulin resistance must be reduced in patients with HCV infection who are not responding to interferon therapy in order to increase the response to the antiviral therapy upon retreatment. However, the improvement of response to interferon therapy has been recognized by insulin sensitizing agents (Overbeck *et al.*, 2008).

Other evidences have shown that weight loss in chronic HCV infected patients may contribute to the decrease the liver enzymes and reduce liver fibrosis (Hickman *et al.*, 2002). While in other studies, it has been reported that insulin sensitivity can be increased by TNF-α inhibition (Shintani *et al.*, 2004). Further studies are needed to investigate the proper treatment used for insulin sensitivity improvement and to evaluate the association of these insulin sensitizing agents with HCV infection by various pharmacological intervention (Schattner and Knobler, 2008).

1.5 Problem Statement

For many years, people have debated about the chronic viral hepatitis and DM association. Patients with chronic viral hepatitis infection can be under a great risk to develop DM especially in those patients with pre-diabetes factors. However, the ignorance of this problem may lead to serious complications with increased mortality rate among the hepatitis population. All these prompt the efforts to investigate the occurrence of DM and the associated risk factors among the chronic viral hepatitis infected Malaysian patients.

1.6 Rationale of the Study

The link between chronic viral hepatitis and DM occurrence is considered substantial, therefore, many questions must still be addressed related to this association between these two common public health problems. To current date, there is no published data that investigate the association between NIDDM and chronic viral hepatitis in Malaysia. Based on this fact, the current study is aimed to evaluate the epidemiological connection between chronic HBV and HCV with NIDDM occurrence among the Malaysian population. In addition, this study investigates the associated factors with the development of NIDDM among the HBV and HCV population of the study.

1.7 Significance of the Study

The results of this study could be used as a baseline for future studies that focused on the association between chronic viral hepatitis and NIDDM. Furthermore, this study may support the background of the practitioners about the possibility of NIDDM occurrence in chronic viral hepatitis patients, especially HCV infection. It could also help to reduce the DM occurrence in chronic hepatitis patients by attracting the attention of the involved individuals to prevent the NIDDM development among the chronic viral hepatitis patients and to avoid the clinical complications of the HCV infection- NIDDM association. On the other hand, this study will give an idea for the HCV infected patients, especially those who they have other associated risk factors, about the possibility of having NIDDM and severe clinical consequences due to that combination.