EVALUATION OF CORONARY HEART DISEASE RISK AMONG PATIENTS WITH TYPE 2 DIABETES IN HOSPITAL PULAU PINANG, MALAYSIA

by

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LIST OF ABBREVIATIONS

ACE inhibitor	Angiotensin Converting Enzyme inhibitor
ADA	American Diabetes Association
BHS	British Hypertension Society
BMI	Body Mass Index
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
FBS	Fasting Blood Sugar
HbA1c	Haemoglobin A1c
HDL-cholesterol	High Density Lipoprotein Cholesterol
JBS	Joint British Societies
LDL-cholesterol	Low Density Lipoprotein Cholesterol
NICE	National Institute for Health and Clinical Excellence
NHMS III	Third National Health and Morbidity Survey
NSF	National Service Framework
SBP	Systolic Blood Pressure
TC	Total Cholesterol
UKPDS	United Kingdom Prospective Diabetes Study
VLDL-cholesterol	Very Low Density Lipoprotein
WHO	World Health Organization

PENILAIAN RISIKO PENYAKIT JANTUNG KORONARI DALAM KALANGAN PESAKIT DENGAN DIABETES JENIS 2 DI HOSPITAL PULAU PINANG, MALAYSIA.

ABSTRAK

Prevalens diabetes mellitus meningkat dengan begitu ketara sekali dalam kalangan penduduk Malaysia sejak beberapa dekad yang lalu. Di samping itu, penyakit kardiovaskular (CVD) merupakan penyebab utama bagi morbiditi dan kematian / kematian di Malaysia. Pesakit diabetes mudah mendapat penyakit jantung koronari (CHD) daripada mereka yang tidak menghidap diabetes. Tambahan pula, pesakit diabetes yang tiada bukti klinikal CHD berisiko mengalami CHD yang sama seperti pesakit tanpa diabetes tetapi menghidap CHD. Faktor risiko klasik CHD memainkan peranan penting dalam usaha menganggar atau menentukan risiko CHD dalam kalangan pesakit diabetes. Faktor tersebut adalah umur, jantina, tabiat merokok, hiperglisemia, hipertensi, dislipidemia dan obesiti.

Kaedah epidemiologi dan biostatistik dibangunkan untuk meramal CHD. Enjin risiko UKPDS (United Kingdom Prospective Diabetes Study) menggabungkan persamaan matematik ke dalam suatu model untuk mengira risiko mutlak insidens CVD. Kalkulator risiko UKPDS digunakan khusus bagi pesakit diabetes jenis 2. Selanjutnya, ia memasukkan HbA1c (glycated haemoglobin) sebagai satu pembolehubah berterusan dan masa, semasa diagnosis diabetes.

Penyelidikan ini bermatlamat menilai risiko 10-tahun CHD dalam kalangan pesakit diabetes jenis 2, dengan menggunakan kalkulator enjin risiko UKPDS khusus dan faktor yang berkaitan. Di samping itu, dikaji juga natijah sasaran faktor risiko CHD berdasarkan Garis Panduan Diabetes Malaysia. Akhir sekali, kajian ini turut

mengkaji perkaitan di antara kawalan glisemia dengan faktor risiko CHD. Untuk mencapai matlamat ini, suatu kajian rentas silang retrospektif dijalankan di Klinik Pesakit Luar Diabetes, Hospital Pulau Pinang. Pesakit kajian didiagnosis dengan diabetes jenis 2, berumur dalam lingkungan 25-65 tahun; tempoh menghidap diabetes di antara 1-20 tahun. Kajian ini tidak melibatkan pesakit dengan sejarah CHD atau sejarah CHD keluarga dan pesakit dengan diabetes gestasi (gestational diabetes). Kajian ini merekrut seramai 1000 orang pesakit (529 lelaki dan 471 perempuan). Ramalan risiko 10-tahun CHD dikira menggunakan enjin risiko UKPDS.

Kebanyakan daripada populasi kajian (43.9% Cina, 32% Melayu dan 24.1% India) berumur dalam lingkungan 50-59 tahun. Ramai pesakit menghidap hipertensi dan dislipidemia. Faktor risiko CHD tidak dikawal dengan baik oleh kebanyakan pesakit. Total 10-tahun CHD dianggar adalah 17.81% ±10.9 dan kebanyakan pesakit tergolong dalam kumpulan berisiko tinggi dan sangat tinggi. Pesakit lelaki, berumur dalam lingkungan 50-56 tahun, mempunyai berat badan berlebihan atau yang terlampau gemuk mempunyai risiko yang lebih tinggi mendapat CHD daripada yang lain. Perokok tegar (active smokers) mempunyai risiko yang lebih tinggi daripada mereka yang bukan perokok (24.30 vs 16.41, $p < 0.001$). Selanjutnya, pesakit dengan tempoh menghidap diabetes yang lebih panjang mempunyai risiko yang lebih tinggi daripada pesakit yang baru didiagnosis. Jenis terapi hipoglisemia oral yang digunakan mempunyai kesan yang signifikan terhadap perkembangan risiko CHD. Penentu risiko CHD dalam kalangan populasi diabetes di Malaysia adalah HbA1c, gula-darah puasa (fasting blood sugar), trigliserida, HDL-kolesterol, LDLkolesterol, dan total kolesterol. Keputusan kajian menunjukkan bahawa min HbA1c bagi total populasi adalah 8.36% ± 2.3. Lelaki mempunyai tahap glisemia yang lebih baik

daripada perempuan (8.22 vs 8.53, $p < 0.001$). Cina mempunyai tahap glisemia yang lebih baik daripada bangsa lain (7.92 vs 8.69 bagi Melayu dan 8.74 bagi India). Pesakit yang mempunyai berat badan yang berlebihan dan yang terlampau gemuk secara signifikannya mempunyai tahap glisemia yang lebih tinggi daripada pesakit lain. Pesakit dengan gabungan terapi menunjukkan tahap glisemia yang lebih tinggi daripada pesakit yang lain. Pesakit dengan kawalan glisemia yang tidak begitu baik secara signifikannya mempunyai risiko yang lebih tinggi mendapat CHD dalam kalangan populasi kajian.

Kajian merumuskan bahawa perkembangan CHD dalam kalangan populasi diabetes jenis 2 di Malaysia adalah tinggi. Kebanyakan pesakit tidak dirawat dengan aspirin dan / atau statin. Faktor penentu yang memberi kesan pada risiko perkembangan CHD adalah gender, penuaan, indeks jisim badan (body mass index, BMI), dislipidemia, tempoh menghidap diabetes dan jenis agen hipoglisemia oral yang digunakan.

Kajian ini juga menunjukkan bahawa faktor risiko CHD tidak dikawal dengan baik dalam kalangan kebanyakan pesakit diabetes jenis 2 di Malaysia. Di samping itu, glisemia tidak dikawal dengan baik dalam kalangan populasi diabetes di Malaysia dan terlalu sedikit pesakit yang berusaha mengawalnya dengan baik. Di samping itu, kajian melaporkan bahawa glisemia dikaitkan dengan risiko perkembangan CHD.

EVALUATION OF CORONARY HEART DISEASE RISK AMONG PATIENTS WITH TYPE 2 DIABETES IN HOSPITAL PULAU PINANG, MALAYSIA

ABSTRACT

The prevalence of diabetes mellitus had increased tremendously in the Malaysian population during the last decade. In addition to that, cardiovascular disease (CVD) reported to be an important cause of morbidity and mortality in Malaysia. Patients with diabetes are more likely to develop coronary heart disease (CHD) than a non diabetic population. Moreover, patients with diabetes but without clinical evidence of CHD own the same risk for CHD events as patients without diabetes but with CHD. The classical risk factors for CHD play an important role in the CHD risk estimation among patients with diabetes. These risk factors are age, gender, smoking status, hyperglycaemia, hypertension, dyslipidaemia and obesity.

The prediction of CHD goes back to the development of epidemiological and biostatistical methods. The United Kingdom Prospective Diabetes Study (UKPDS) risk engine incorporates mathematical equations into a model which calculates the absolute risk of incident cardiovascular disease (CVD). The UKPDS risk calculator is used specifically for patients with type 2 diabetes. Furthermore, it includes glycated haemoglobin (HbA1c) as a continuous variable and the time since diagnosis of diabetes.

This research aimed to estimate the predicted 10-year CHD risk among patients with type 2 diabetes using the diabetes specific UKPDS risk engine calculator and the factors associated with it. It also examined the target outcome for the CHD risk factors according to the Malaysian Diabetes Guideline. Finally, it investigated the

association of glycaemic control with CHD risk. To achieve this, a retrospective cross sectional study was conducted at the Outpatient Diabetes Clinic in Hospital Pulau Pinang. The patients included in the study were diagnosed with type 2 diabetes, between 25-65 years; their diabetes duration was between 1-20 years. The study excluded patients with the history or with family medical history of CHD and patients with gestational diabetes. One thousand patients (529 male) were recruited in the study. The 10-year predicted CHD risk was calculated using the UKPDS risk engine.

The age of the study population (43.9% Chinese, 32% Malay and 24.1% Indian) was mostly between 50-59 years. Most of the patients were hypertensive and dyslipidaemic. The CHD risk factors were poorly controlled among a majority of the patients. The total 10-year estimated CHD was 17.81% ±10.9 and most of the patients were within the high (44.7%) and very high risk (12%) groups. Patients who were male, between 50-56 years in age, overweight or obese had a higher risk of developing CHD than others. Active smokers had higher risk than non smokers (24.30% vs 16.41%, $p < 0.001$). Moreover, patients with longer diabetes duration had a higher risk than newly diagnosed patients. The type of oral hypoglycaemic therapy used had significant effect on CHD risk development. The determinants of CHD risk among Malaysian diabetes population were HbA1c, fasting blood sugar, triglyceride, high density lipoprotein (HDL-cholesterol), low density lipoprotein (LDL-cholesterol) and total cholesterol. The study results showed the mean HbA1c of the total population was 8.36% ± 2.3. Males had better glycaemia levels females (8.22 vs 8.53, $p < 0.001$). Chinese had better glycaemia than other races (7.92 vs 8.69 for Malay and 8.74 for Indians, $p < 0.001$). Overweight and obese patients had significantly higher glycaemia than others. Patients with combination therapy

showed a higher glycaemia than others. Patients with poor glycaemic control had significantly higher risk of developing CHD among the study population.

The study concluded that the risk of developing CHD among type 2 diabetes Malaysian population was high. The study also showed that the CHD risk factors were poorly controlled among most of the Malaysian patients with type 2 diabetes. Furthermore, glycaemia was very poorly controlled among the Malaysian diabetic population and very few patients showed an adequate control.

In addition, the study reported that glycaemia was associated with the risk of developing CHD. The determinant factors that had an effect on the risk of developing CHD were gender, aging, body mass index (BMI), dyslipidaemia, smoking status, diabetes duration and the type of oral hypoglycaemic agents used.

CHAPTER ONE: INTRODUCTION

1.1 Diabetes mellitus

Diabetes is a disease characterized by the relative or absolute lack of insulin. This chronic disease is known by its symptomatic increase in lipid, protein metabolism and blood glucose concentration (Koda-Kimble *et al.*, 2005). Hyperglycaemia and the other metabolic abnormalities associated with diabetes contribute to the development of complications such as cardiovascular complications, retinopathy, nephropathy and neuropathy (Fowler, 2008). Lately, it is well recognized that diabetes mellitus can be classified in to different types with different etiologies, in spite of the similarity that could occur in their pathologic sequences, after the onset of disease (Koda-Kimble *et al.*, 2005).

Type 1 diabetes is also known as insulin-dependent diabetes. It results from autoimmune pancreatic beta-cells destruction which causes an absolute insulin deficiency. It most commonly afflicts individuals around the time of puberty (Koda-Kimble *et al.*, 2005). Type 1 diabetes is treated by insulin, diet and exercise (Poretsky, 2002).

Type 2 diabetes is also known as non-insulin-dependent diabetes mellitus. It results when insulin secretion is insufficient for maintaining glucose homeostasis, although pancreas preserves some beta-cell function. Type 2 diabetes is also known as adult-onset diabetes (Howlett *et al.*, 2003). Moreover, the development of type 2 diabetes is affected by genetic factors, environmental factors, obesity, physical activity, birth weight and diabetic pregnancy (Alberti and Zimmet, 1998).

Type 2 diabetes is treated by diet, exercise and oral anti-diabetic agents; insulin is used when the oral anti-diabetic agents fail to sustain glycaemic control. Oral anti-diabetic drugs that are used in type 2 diabetes include: sulfonylurea, biguanides, α-glucosidase inhibitors, thiazolidinediones and non-sulfonylurea insulin secretogogues (Koda-Kimble *et al.*, 2005).

Type 2 diabetes considered as a main public health problem in both developed and developing countries. In developing countries, the growing prevalence of type 2 diabetes presents both a health and an economic challenge (Apparico *et al.*, 2007).

1.2 Coronary heart disease

Coronary heart disease (CHD) is a condition characterized by the accumulation of plaque inside the coronary arteries. Coronary arteries responsible for cardiac muscle supply with oxygen-rich blood. Plaque consists of fat, cholesterol, calcium, and other substances found in the blood. The accumulation of plaque in the arteries is called atherosclerosis. The blood flow to the cardiac muscle is reduced due to the partial or complete block by the plaque. The low oxygen-rich blood supply to the cardiac muscle causes angina pectoris. Angina is characterized by chest pain or discomfort. If the chest pain persists without medical interruption for prolonged periods this causes irreversible myocyte damage which is known as myocardial infarction (Kasper *et al.*, 2005; McPhee *et al.*, 1997).

Cardiovascular diseases' (CVD) prevalence is increasing rapidly in developing countries because of the increase in the adoption of western diet and lifestyle (Ghali, 1991, Manton, 1988). In Malaysia, CVD is an important cause of morbidity and mortality. CVD is considered for about a fifth of the total burden of disease in Malaysia by the year 2000. CHD is considered for 50 % of the cardiovascular burden

(Ministry of Health Malaysia, 2004b). In 2006, CVD was the commonest cause of deaths in government hospitals accounting for 24.2 % of total deaths (Ministry of Health Malaysia, 2008c). Management of CHD includes modification of risk factors, lifestyle changes, medical therapy and revascularization procedures (Ministry of Health Malaysia, 2009a). High diabetes and hypertension prevalence have a major contribution to the worsening of cardiovascular health in the developing countries (Zaini, 2000).

1.3 Type 2 diabetes and coronary heart disease

Type 2 diabetes is considered as a significant risk factor for CHD (Haffner *et al.*, 1998). This problem is amplified by the total number of individuals with diabetes; approximately 246 million people worldwide (Adler, 2008a). Although that there is no record of absolute time specific risk levels of CHD among diabetic population, it is well known that diabetic population are capable of developing CHD 2-4 times more likely than patients without diabetes (Haffner *et al.*, 1998). Furthermore, it is recommended to consider patients with diabetes and no clinical evidence of CVD have the same risk for CHD events as patients without diabetes but with established CHD (Expert Panel on Detection Evaluation, 2001).

Presently, about 20 % of patients with diagnosed CHD have an underlying disease of diabetes (Malmberg *et al.*, 2000; Lowel *et al.*, 2000; McGuire *et al.*, 2000; Mukamal *et al.*, 2001; Laskey *et al.*, 2002), and the prevalence of undiagnosed diabetes is also high among patients with CHD (Norhammar *et al.*, 2002). Coronary heart and cerebrovascular disease are a serious cause of morbidity and mortality (Kannel *et al.*, 1976; Fuller *et al.*, 1983). Most importantly, the mortality of patients with diabetes having an acute coronary event is 50 % greater than in patients without diabetes (Malmberg and Ryden, 1988; Malmberg *et al.*, 2000).

The classical risk factors for CHD which is age, smoking status, hypertension, and dyslipidaemia play an important role in the prediction of CHD risk in patients with diabetes (Turner *et al.*, 1998b; Davis *et al.*, 1999). Clinical trials showed that risk factor interventions cause reduction in CHD risk in diabetic and non-diabetic individuals. But the absolute advantage for the diabetic population is even greater due to higher absolute CHD risk (Adler, 2008b). Such evidence is available on blood-pressure-lowering drugs (Curb *et al.*, 1996; Hansson *et al.*, 1998; Tuomilehto *et al.*, 1999), lipid-lowering drugs (Pedersen *et al.*, 2000; Rubins *et al.*, 1999; Lindholm, 2003), anti platelet drugs (Antithrombotic Trialists' Collaboration, 2002), beta-blockers (Gundersen and Kjekshus, 1983) and ACE-inhibitors (Moye *et al.*, 1994; Torp-Pedersen *et al.*, 1996; Zuanetti *et al.*, 1997). Joint British Societies (JBS) have recommended that primary prevention of CHD should be based on the assessment of absolute CHD risk (Jackson, 2000).

1.4 Epidemiology and prevalence

Population studies have clearly showed that the enormous rose in type 2 diabetes prevalence all over the world make it very likely that the situation is heading towards epidemic levels. From 1985 to 1995, the estimated diabetes population in the world rose from 30 million to 135 million. Based on this, epidemiologists predict that the diabetic population will bulge to 300 million by the year 2025, with nearly half of them will be in the Asia and Oceania region alone. It has been pointed out that there will be an expected rise of about 42% in developed countries while developing countries will escalate to 170% (King *et al.*, 1998).There will be a huge rise of the disease in Asia and many of these will be seen in China (40 million) and India (55 million) according to the vast numbers of people in these countries. However, the other rapidly developing countries in Asia such as Malaysia, Singapore, and Thailand

will experience the surge (Zaini, 2000). Diabetes and its complications is a major threat and expected to cause escalation to the public health resources, economic and social costs (Chuang *et al.*, 2002).

Malaysia is one of the countries that will be highly affected due to the major shift in the patterns of life and longevity of the population. It is clear that Malaysia has the right elements to set the scene for the outburst of diabetes like the rest of Asia. Malaysia, which has a multiethnic population, is expected to reach around 33.7 million by the year 2020. The three principal races of Malaysia are Chinese, Indians and Malays. So, if China and India countries are on the verge to exceed the international prevalence rate of type 2 diabetes, their respective counterparts in Malaysia will be much worse. The diabetes prevalence in Malaysia has steadily risen from 0.6% in 1960, to 2.1% in the 1982, and 6.3% in 1986 (Zaini, 2000). The Third National Health and Morbidity Survey (NHMS III) showed that the prevalence of the type 2 diabetes rose to 14.9% , which is almost 79.5% in the space of 10 years from 1996 to 2006 (Ministry of Health Malaysia, 2009b). The Indians had the highest prevalence of 19.9% followed by Malays 11.9% and Chinese 11.4% (Letchuman *et al.*, 2010). The demographic pattern has also changed to a large extent. Over the last few decades, Malaysia had experienced a rapid demographic and socio-economic change due to the inevitable migration from rural to urban areas (Ali *et al.*, 1993).

CVDs are the leading cause of death for 16.7 million people around the globe according to the WHO estimates. Deaths from CVD are twice now in developing countries. In addition, there is a concern regarding high CVD deaths among early age compared with those in the developed regions. By 2020, WHO predicts almost 25 million CVD deaths worldwide (Mackay *et al.*, 2004). CHD has no gender, geographic, or socioeconomic boundaries (World Health Organization, 2011).

In Malaysia, chronic diseases accounted for 71% of all deaths and by 2002, 30% of them died because of CVD (National Heart Association of Malaysia, 2008). It is estimated that by 2020, CHD and other non communicable diseases are predicted to account for seven out of every ten deaths in the Asia-Pacific countries. Malaysia is experiencing a rise in heart diseases despite improvement in health services and facilities. Heart diseases are considered as the second leading cause of death in 2006, accounting for 15.5% of those who died in government hospitals (National Heart Association of Malaysia, 2008).

Epidemiologic studies have indicated that the mortality from CVDs is more than double in patients with diabetes compared to patients without diabetes. In addition, the premature death from cardiovascular complications is very common among patients with type 2 diabetes (Leiter, 2005).

1.5 Pathophysiology

Type 2 diabetes mellitus is a heterogeneous group of metabolic disorders. The metabolic disorders are a result of the combination of resistance to insulin action and inadequate insulin secretion with varying prevalence among different ethnic groups. These disorders are characterized by hyperglycaemia and associated with microvascular (i.e., retinal, renal, possibly neuropathic), macrovascular (i.e., coronary, peripheral vascular), and neuropathic complications (Mahler and Adler, 1999).

Patients with type 2 diabetes differ from patients with type 1 diabetes mellitus, as they are not absolutely dependent upon insulin for life. However, many patients with type 2 diabetes are eventually treated with insulin, because they maintain the ability

to secrete some endogenous insulin, so they are require, but do not depend, on insulin (Mahler and Adler, 1999).

The pathophysiology of type 2 diabetes mellitus is characterized by impaired regulation of hepatic glucose production, and declining ß-cell function, ultimately leading to ß-cell failure. Furthermore, primary events are characterized by combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. In addition to the elevated levels of free fatty acids in plasma, insulin resistance also decreases glucose transport into muscle cells. Moreover, elevated hepatic glucose production and increased lipolysis is mainly attributed to insulin resistance. Type 2 diabetes develops when insulin secretion cannot increase sufficiently to compensate the insulin resistance. The insulin concentrations may be high, yet inappropriately low for the glycaemia level (Mahler and Adler, 1999; McPhee *et al.*, 1997; Epstein *et al.*, 1992; Lilly, 2003).

Atherosclerosis is the main cause of CHD. The process of developing atherosclerosis begins from the endothelial function disruption. This occurs through lipoprotein droplets accumulations in the coronary vessels intima. The replication of the cells leads to the formation of the fatty streak which considered as the earliest visualized lesion of atherosclerosis (Libby and Theroux, 2005). Then, the fatty streak is then transformed into the fibrous plaque. Fibrous plaque is made up mainly by collagen and proteoglycan secreted by the smooth muscle cells. At this point the lesion starts affecting the vessel lumen (Lilly, 2003; Libby and Theroux, 2005; McPhee *et al.*, 1997; Kanjilal *et al.*, 2008). The characteristics of coronary lesions in patients with diabetes compared with non-diabetics have several important distinctions. Lesions in patients with diabetes have more extensive and diffuse atherosclerosis, smaller vessels containing longer lesions, impaired vascular remodeling with greater luminal

encroachment, impaired collateral vessel formation and higher coronary calcification scores (Lilly, 2003).

The coronary plaque in patients with diabetes seems more liable to rupture owing to a thin fibrous cap, more inflammatory cells and smooth muscle cells. It has been reported that patients with diabetes without MI had higher levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1), markers of hypofibrinolysis and hypercoagulability that are also associated with atherosclerosis and MI, when compared with non-diabetic patients with MI (Lilly, 2003).

The major CHD risk factors in patients with type 2 diabetes are hyperglycaemia, insulin resistance syndrome, hypertension, dyslipidaemia, smoking, obesity and lack of exercise, gender, age, family medical history of heart disease and enlarged heart (Turner *et al.*, 1998b; Krentz *et al.*, 2005) .

1.6 Coronary heart disease risk factors

1.6.1 Hyperglycaemia

The measurement of glycaemia in the form of glycated haemoglobin (HbA1c) is now accepted as a benchmark of glycaemic control of patients with diabetes (The Diabetes Control Complications Trial Research Group, 1993). There is also an indication that HbA1c provides important information to providers and patients considering both health status and medical care charges in future (Gilmer *et al.*, 1997). Glycated haemoglobin is made up of the slow, non-enzymatic reaction between haemoglobin and glucose (Bunn, 1981). The rate of synthesis of glycated haemoglobin is mainly related to the plasma glucose concentration. Glycated haemoglobin measurement is broadly used for routine monitoring of long-term glycaemic status in patients with diabetes. Glycated haemoglobin is a clinically

useful indicator of mean glycaemia during the preceding 120 days, which is the average erythrocytes life span (Goldstein *et al.*; 2004, Bunn, 1981; Jovanovic and Peterson, 1981; Nathan *et al.*, 1984; Cefalu *et al.*, 1994).

Hyperglycaemia is the biochemical hallmark of diabetes. However the links between hyperglycaemia and excess CVD remain incompletely delineated (De Fronzo, 2004). In spite of that, chronic hyperglycaemia as evaluated by the level of HbA1c has been shown to relate tightly to the microvascular complications development of diabetes (Klein *et al.*, 1996). Researchers showed that patients with diabetes with the highest blood glucose level have the highest complications incidence (Stratton *et al.*, 2000). A meta-analysis reported that there is 18% (95% CI 10%-26%) increase in risk for CVD outcomes for every 1% increase in HbA1c (Selvin *et al.*, 2004).

Several potential pathogenic suggest a casual association between hyperglycaemia and vascular disease. Hyperglycaemia leads to accelerated formation of advanced glycation end products (AGE), formation by AGE of irreversible abnormal deposits in the subintimal layers of blood vessels, interference by these deposits with cellular interactions and generation of toxic reactive oxygen species modification of LDL-cholesterol particles through glycation, making them more susceptible to oxidation, thickening and leakage of the vasculature due to cross-linking of vascular proteins by AGE, activation of protein kinase-C leading to increased vascular permeability and hyperglycaemia could cause activation of the pylol pathway with secondary cellular osmotic and ionic changes (Voulgari *et al.*, 2010; Hoffbrand *et al.*, 2005).

1.6.2 Hypertension

Hypertension considered as a silent disease and simply an absence of routine check-up lead to many undiagnosed hypertensive cases (Akter *et al.*, 2010). In addition, hypertension may also interrelate with other CHD risk factors to speed up CHD development (Ministry of Health Malaysia, 2008a). The prevalence of hypertension in Malaysia is between 14.0 - 24.1% (National Health and Morbidity Survey III, 2006). Around 65% of patients with type 2 diabetes of more than 30 years duration have hypertension (El-Atat *et al.*, 2003). It is thought that high blood pressure accounts for up to 75 % of added cardiovascular risk in people with diabetes, contributing significantly to the overall morbidity and mortality (Epstein, 1997). In addition, a combination of hypertension and diabetes causes a high risk of CVD (Morrish *et al.*, 1990; Prevost *et al.*, 2005).

Sustained blood pressures of 120-139 mmHg systolic, or 80-90 mmHg diastolic are now regarded as “pre-hypertension” for patients with no diabetes. For any given level of blood pressure, however the clinical impact is greater in the presence of diabetes and especially when accompanied by nephropathy (Chobanian *et al.*, 2003).

The pathophysiological mechanisms of hypertension-mediated tissue damage in patients with diabetes include impaired vascular auto regulation which allows transmission of high systemic blood pressure to the microvasculature, decreased vascular compliance (decreased compliance of major vessels, for example the aorta, perhaps resulting from non-enzymatic glycation of vessel wall proteins) which may tend to higher central pressures, endothelial dysfunction which is associated with impaired endothelial responses and sodium retention which reflects hyperinsulinaemia effects of renal ion handling. Hypertension in patients with type 2 diabetes tends to be characterized by sodium retention and volume expansion. Severe

hyperglycaemia which is a risk of insulin therapy may be associated with acute changes in blood pressure (Stern *et al.*, 2004; Sobel and Schneider, 2002).

1.6.3 Dyslipidaemia

The risk of any level of lipid profile variables is higher in the diabetic population than general population (Kon, 2005). Patients with type 2 diabetes tend to have the same lipid profile as individuals with atherogenic profile having abdominal obesity and insulin resistance (Carr and Brunzell, 2004). Patients with treated diabetes do not usually have raised absolute levels of total or LDL-cholesterol (Krentz, 2003). Patients with type 2 diabetes more often have raised levels of fasting and postprandial triglycerides; this is generally accompanied by a low plasma concentration of cardio protective healthy HDL-cholesterol. A high plasma triglyceride concentration is a risk factor for CHD (Austin *et al.*, 1998).

Triglyceride could be directly associated to the development of coronary atheroma. Therefore, low triglyceride could be the key feature underlying the development of CHD in patients with insulin resistant (Austin *et al.*, 1998; Ginsberg, 2000).

Low levels of HDL-cholesterol are closely associated with increased risk of CHD in both diabetic and non-diabetic populations. There are several reasons for these apparent protective properties of HDL-cholesterol. There are many reasons behind the protective features of HDL-cholesterol. The main function of HDL-cholesterol is to deliver cholesterol to the liver for excretion, it may also have anti-inflammatory and antioxidant properties, protecting against atheromatous disease (Barrett Connor *et al.*, 1982).

The pathophysiology of dyslipidaemia in diabetic population revolves around circulating insulin which is in healthy people responsible for adipocyte lipid

metabolism. The fatty acids liberated by impaired actions of insulin in adipocytes have been implicated in a diverse range of defects in type 2 diabetes, ranging from hypertriglyceridaemia to impaired insulin secretion and endothelial dysfunction. Insulin causes the suppression of intra-adipocyte hormone-sensitive lipase in the postprandial period, preventing lipolysis and result in the release of fatty acids. Higher insulin levels stimulate intravascular lipoprotein lipase which accompany the early postprandial period. This increases triglyceride clearance from chylomicrons and very low density lipoprotein (VLDL-cholesterol) particles into adipocytes and minorly into myocytes. Consecutively insulin stimulates intra-adipocyte esterification of fatty acids forming new intra-adipocyte triglyceride stores (Stern *et al.*, 2004).

The defects that are encountered in type 2 diabetes include increased hepatic synthesis and secretion of large VLDL-cholesterol particles, increased residence time of triglyceride rich particles, increase triglyceride –cholesterol ester exchange, relatively cholesterol-depleted HDL-cholesterol and LDL-cholesterol (Stern *et al.*, 2004; Sobel and Schneider, 2002).

1.6.4 Gender

Males and females share a lot of CHD risk factors such as age, dyslipidaemia, hypertension, smoking, diabetes, obesity and physical inactivity. But the use of contraceptives and the reduction of ovarian function with age considered as an additional risk factors for females (Bush *et al.*, 1988).Women with diabetes had a CVD events risk similar to those without diabetes but with prior CHD. For men with diabetes, the CV events risk was half for men without diabetes who had known CHD (Becker *et al.*, 2003).The alterations in triglycerides and HDL-cholesterol observed among patients with type 2 diabetes tend to be more marked in women than men.

This may be part of the explanation for the greater relative risk for women with diabetes (Juutilainen *et al.*, 2004). Middle aged women with diabetes are more likely to have high blood pressure than men (Hypertension in Diabetes Study, 1993).

1.6.5 Obesity

Obesity is rapidly becoming one of the most important problems globally and in Malaysia as well. It is an important contributory factor to diabetes. The worldwide prevalence of overweight (body mass index (BMI) ≥25.0 kg/m^2) and obesity (BMI ≥ 30.0 kg/m^2) is estimated at more than 1.1 billion. Newly, the risk of obesity related diseases among Asian have rises from a lower BMI of 23 kg/m^2 (James *et al.*, 2002). In Malaysia, the prevalence of obesity (BMI>30 Kg/m^2) in 1996 was 4.4% and overweight (BMI 25– 30 Kg/m^2) was 16.6%. Moreover, urban areas showed higher prevalence rates of overweight individuals (17.4%) compared to their rural counterparts (15.5%) (Zaini, 2000). This indicates the high prevalence of overweight and obesity in Malaysia which is much more serious than what has been reported in countries around the region. Singapore and Malaysia had the highest levels of overweight and obesity within the region. Malay ethnic origin shows significantly higher body weights than those of Chinese or Indian background (Gill, 2006). The National Health and Morbidity Survey in Malaysia 1996 reported that in adult females showed higher prevalence rates of overweight and obesity than male adults (Lim *et al.*, 2000).

When the energy intake from food and drink exceeds energy expenditure from physical activity and other metabolic processes, weight gain and obesity develop. The economic transition that has been developed in recent years causes a rapid change in lifestyle which represents the most likely cause for the increase in population weight in Asia. Diet and levels of physical activity have changed due to

modernization throughout Asia. Traditional foods such as fresh fish, meat, and local fruits and vegetables of past generations have been replaced by rice, sugar, flour, canned meats, canned fruits and vegetables, soft drinks and beer (Gill, 2006). Definitely the consuming of larger amounts of fats, oils, meat, sugar and less vegetables and cereals happened more than in the past (Drewnowski and Popkin, 1997). In addition, the leisure time activities have been changed from the past by which television; computers and videos are becoming the preferred activities throughout the region. Furthermore, motorized transport has replaced bicycles (Bell *et al.*, 2002).

The increase in BMI causes an increase in the risk of hypertension (Ascherio *et al.*, 1996). The association between hypertension and obesity is characterized by an increase in vascular volume. Many pathological mechanisms could be associated in the development of hypertension in individuals with obesity which is increased renal sodium and water absorption, sympathetic nervous system activation, changes in Na+/H+-ATPase activity, and growth factor–mediated structural changes to the vascular wall. Hyperinsulinemia considered a contributing factor in each case (Redon, 2001).

Increased free fatty acids observed in individuals with obesity contribute to the defects in glucose use and storage. The increase in body fat causes an increase in the rate of lipolysis. This leads to increased free fatty acid mobilization and consequently to increased free fatty acid oxidation in muscle and liver. As a consequence, glucose use by muscle decreases because of the use of free fatty acid as an alternate energy source, and hepatic glucose production increases in response to the higher free fatty acid oxidation. These actions result in hyperglycaemia and impaired glucose tolerance (Jensen *et al.*, 1989).

It also affects lipid metabolism by increasing very-low-density lipoprotein production by the liver, reducing HDL-cholesterol levels, and increasing the number LDL-cholesterol particles. These changes in lipoprotein profile and glycaemia are associated with increased risk of CHD (Despres, 1994).

1.6.6 Age

Age is the one of the strongest predictors of CHD risk. Most men by age 65 have a 20% risk of a CHD event during the next 10 years (Booth *et al.,* 2006). Clinical guidelines recommend that type 2 diabetes individuals be regarded as a high-risk for CHD if they are older than 40 years of age (American Diabetes Association, 2009).

1.7 Prevention

It has been clarified that vascular complications risk increases constantly with rising of risk factors in patients with type 2 diabetes, in spite of the absence of the natural thresholds by which vascular complications risk are prevented completely. The microvascular and macrovascular complications are developed by the synergistic contribution of poor glycaemic control, hypertension and hyperlipidaemia in patients with type 2 diabetes (Adler *et al.*, 2000; Stratton *et al.*, 2000).

Harmonization between effective risk factor management plans for patients with diabetes is very important. The management includes steps to maintain glycaemic control, lower blood pressure, reduce LDL-cholesterol levels, smoking cessation and increase physical activity (O'Connor *et al.*, 1998; American Diabetes Association, 2003). Vascular protective measures such as statins, angiotensin-converting enzyme (ACE) inhibitors and lower blood pressure targets, are advised for all patients with high risk of CHD. For intermediate CHD risk, pharmacological measures depend upon the severity of the associated risk factors. Moreover, low risk population has

less advantages from pharmacological vascular protection, as the treatment hazards may exceed the advantages and unlikely to be cost effective (National Cholesterol Education Program Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2001; McPherson *et al.*, 2006).

In spite of the arguments regarding the 10 year predicted risk level (>15%, or >30%) at which primary prevention of CHD, using aspirin and/or statins, should be started (Collins *et al.*, 2003; Jackson, 2000). The National Institute for Health and Clinical Excellence (NICE) guidance and supported by the National Service Framework (NSF) for diabetes have lowered the calculated 10-year CHD risk level threshold for pharmacological intervention to 15% in patients with diabetes as opposed to the 30% 10-year CHD risk level applied in the general population (Guzder *et al.*, 2005; National Institute for Clinical Excellence, 2002).

1.7.1 Role of diet and exercise

A combination of weight loss and increased exercise levels are the most effective strategies to help patients reaching their targets of lowest risk of progression. Physical activity may lead to improvements in blood pressure, lipids profile, insulin sensitivity and body weight. In addition, it may improve endothelial function, coronary blood flow, reduce levels of inflammatory markers and thrombotic risk. Regular exercise also plays an important role in cardiac rehabilitation after Ml and in the treatment of intermittent claudication. Obesity is a most important cause of acquired insulin resistance. In addition, obesity aggravates many risk factors for CHD. In spite of the advantages of weight loss on glycaemia, lipids, blood pressure, inflammatory markers and other risk factors, treatment generally stays far from satisfactory. Low-carbohydrate diets and anti-obesity drugs (like orlistat) are important solutions to be considered with obesity (Krentz *et al.*, 2005).

1.7.2 Hyperglycaemia management

Hyperglycaemia influences the biochemical parameters and affects the progression of CHD and mortality rates in individuals with diabetes (Van der Does *et al.*, 1998; Herman, 1999). The results from the United Kingdom Prospective Diabetes Study (UKPDS) indicated that by lowering the concentration of blood glucose, the risk of diabetic complications reduces (Stratton *et al.*, 2000). Controlling hyperglycaemia by aggressive treatment is much more effective in lowering the number of complications than standard treatment (Van der Does *et al.*, 1998; Herman, 1999).

There are important oral anti-diabetic agents that are used for controlling the glycaemia such as sulphonylureas (first generation e.g. tolbutamide, chlorpropamide and second generation e.g. glibenclamide glipizide gliclazide glimepiride), rapid acting insulin secretagogues (e.g. repaglinide, nateglinide), biguanides (e.g. metformin), alpha-glucosidase inhibitors (acarbose, miglitol, thiazolidinediones e.g. rosiglitazone, pioglitazone) (Ministry of Health Malaysia, 2009b).

1.7.3 Hypertension management

Recent clinical trials have informed target blood pressures and have helped to identify the drugs that are most advantageous in diabetes population (Galzerano *et al.*, 2010). For achieving blood pressure targets in many patients, it is recommended to use two or more drugs from different classes. The important issue that should be considered is the level of blood pressure attained, rather than the drugs selection with particular modes of action (Brown *et al.*, 2003). The 2004 American Diabetes Association (ADA) guideline (Adams *et al.*, 2008; Arauz-Pacheco *et al.*, 2004), 2004 British Hypertension Society (BHS) (Ramsay *et al.*, 1999; Williams *et al.*, 2004) and the Joint National Committee Report (Chobanian *et al.*, 2003) recommend a target of <130/80 mmHg for patients with diabetes. The ADA recommends using an

angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blockers as first-line therapy. While in practice, the first choice for many physicians would be a low-dose of diuretic.

Non-pharmacological measures are regarded as the cornerstone of therapy, although its benefits are often underestimated and rarely attained. Reduction in body weight for obese and overweight patients by having a regular aerobic physical exercise could be beneficial. Reduced dietary salt intake and increased potassium intake through eating fresh fruit and vegetables would be very helpful. If drug therapy is necessary for most patients; non-pharmacological measures would be very useful for limiting the need for medication (Sobel and Schneider, 2002).

1.7.4 Dyslipidaemia management

Lipid lowering should have a significant place in the primary prevention of CVD in patients with diabetes. Most of the evidence favoring lipid-lowering relates to the use of statins (Vijan and Hayward, 2004). Trials that involved participants with diabetes and CHD have shown that cholesterol lowering with statins substantially lowers the risk of subsequent cardiovascular events (Welch, 2004).

However, in spite of increasing evidence and knowledge of the lipid lowering value, a recent survey of diabetes specialists showed that many patients with diabetes still remain untreated or undertreated. Moreover, the current lipid lowering prescription rates in patients with diabetes remain low, even in patients with CVD (Leiter, 2005). An estimated 70–97% of patients with type 2 diabetes have a dyslipidaemic profile (Fagot-Campagna *et al.*, 2001). It has been clarified that statins therapy is very beneficial in both primary and secondary prevention of cardiovascular events

especially in those with diabetes (Sacks *et al.*, 2000; Collins *et al.*, 2003; Lindholm, 2003; Goldberg *et al.*, 1998).

Non-pharmacological measures involves dietary measures which is attaining ideal body weight, reducing saturated fat consumption to around 30% of total calories, increasing intake of monounsaturated, avoiding trans-fatty acids. Excessive alcohol consumption may exacerbate hypertriglyceridaemia (Krentz *et al.*, 2005). The UKPDS showed that three months' diet therapy in newly diagnosed patients with diabetes resulted in a reduction in mean plasma triglycerides with minor improvements in total cholesterol. Body weight was reduced by a mean of 5% and fasting plasma glucose was reduced (Manley *et al.*, 2000).

1.8 Prediction engines

The prediction of CHD goes back to the development of epidemiological and biostatistical methods. These methods permitted the evaluation of the factors that can identify the risks of a specific outcome over time. They also involve a suitable study design that recruits individuals who are free of the particular vascular event of interest, acquiring baseline data on factors that might influence risk for the outcome, and following the participants prospectively for the clinical outcome development under investigation (Wilson *et al.*, 1998). By 1991, Framingham CHD risk score were published to assess the risk of CHD by predicting the total CHD (Anderson *et al.*, 1991b) and a variety of first cardiovascular occurrences (Anderson *et al.*, 1991a). Specialized models were developed for subjects with type 2 diabetes that consider additional potential predictor variables. The authors have suggested that the main predictor variables for initial CHD events were sex, age, ethnicity, smoking status, HbA1c, time since the diagnosis of diabetes, systolic blood pressure, and the levels for lipids (Stevens *et al.*, 2001).

Currently, there are many risks tables and equations have been proposed for the purpose of CHD prediction; the most famous and most commonly used is that derived from the Framingham (Kannel *et al.*, 1976), SCORE (Systematic Coronary Risk Evaluation) (Conroy *et al.*, 2003), and United Kingdom Prospective Diabetes Study (UKPDS) studies (Stevens *et al.*, 2001; Kothari *et al.*, 2002), and the last has been developed specifically for diabetic sub-populations.

Clinicians are capable of using CHD risk score models to help them to estimate the absolute risk of CHD in a given patient. Risk estimation allows a more defined estimate than 'high risk' as well as risk communication to patients may itself encourage health (Roach and Marrero, 2005). Patients with type 2 diabetes have a higher risk of CHD than general population which makes the intervention increasingly important in diabetic population (Koskinen *et al.*, 1992; MRC Working Party, 1992; Turner *et al.*; 1998a).

The U.K. Prospective Diabetes Study (UKPDS) is randomized landmark controlled trial. It indicated that both intensive treatments of blood glucose and of blood pressure in diabetes can decrease the risk of diabetes-related complications in newly diagnosed patients with type 2 diabetes (Unnikrishnan, 1998; UKPDS Group, 1998). In addition to giving answers to questions related to therapy issue, 5102 cohort UKPDS patients were followed for a median of 10.7 years, providing excellent opportunity for a natural history description of treated disease (Adler *et al.*, 2000; Stratton *et al.*, 2000). In quantitative terms, UKPDS investigators described the connection between risk factors and the over time presence of diabetic complications. The UKPDS risk engine corporate mathematical equations into a model which calculates the absolute risk of incident CVD (Adler, 2008b).

1.9 Rational of the study

Diabetes is known to increase the risk for CHD 2- to 3-fold and when patients with diabetes develop overt CHD, the prognosis will be much worse than it is for patients without diabetes (Barrett-Connor *et al.*, 1991; Koskinen *et al.*, 1992; Manson *et al.*, 1991). The most effective management of diabetes revolves around prevention, so CHD risk estimation is recommended as a strategy to identify high-risk patients who would be the major beneficiaries of priority interventions (Kannel *et al.*, 1976; Fuller *et al.*, 1983). Although advances in recent years in CHD prevention and the associated decrease in mortality from the disease, patients with type 2 diabetes have had a lower reduction and an increase in mortality rate (Gu *et al.*, 1999). To date, the assessment of CHD risk in patients with type 2 diabetes has been very limited worldwide (Winocour and Fisher, 2003). Furthermore, there is no published data in Malaysia that evaluates CHD risk among type 2 diabetes and addresses CHD risk in type 2 diabetes as a problem. Based on that, the present study evaluates the absolute levels of 10-year CHD risk among patients with type 2 diabetes in Hospital Pulau Pinang using the diabetes specific UKPDS risk engine. In addition, this study investigates target outcome for the cardiovascular risk factors according to the Malaysian Diabetes Guideline among type 2 diabetes population of the study.

The results of this study could be used as a baseline for future studies that focused on cardiovascular complications in patients with type 2 diabetes. It could also support the background of the practitioners about the risk factors and the importance of assessing CVD in patients with type 2 diabetes. It could help to prevent cardiovascular development since the most effective management of diabetes revolves around prevention.

1.10 The study objectives

The objectives of this study are to:

1-Estimate the predicted 10-year CHD risk among patients with type 2 diabetes using the diabetes specific UKPDS risk engine calculator.

2-Examine the target outcome for the CHD risk factors in patients with type 2 diabetes according to the Malaysian Diabetes Guideline.

3-Evaluate the factors associated with the predicted 10-year CHD risk score among patients with type 2 diabetes.

4-Investigate the association of glycaemic control with CHD risk.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Patients with type 2 diabetes have high prevalence of CHD than the general population (Barrett-Connor *et al.*, 1991; Koskinen *et al.*, 1992; Manson *et al.*, 1991). Interventions are strongly important and proved to be beneficial in general populations and mostly in diabetic populations (Pyorala *et al.*, 1997; MRC Working Party, 1992; Shepherd *et al.*, 1995; Turner *et al.*, 1998a; Mann, 2000). Patients with type 2 diabetes should have their CHD risk assessment checked routinely for determining the optimal care (Brown *et al.*, 2000).

2.2 Literature review

The U.K. Prospective Diabetes Study (UKPDS) is a prospective observational study cohort of 5102 patients in 23 hospital based clinics in England, Scotland and Northern Ireland, followed for a median of 10.7 years (Adler *et al.*, 2000; Stratton *et al.*, 2000). It aimed to test whether type 2 diabetes complications occurrence is reduced by allocated treatment for diabetes (Unnikrishnan, 1998; UKPDS Group, 1998). As a conclusion the trial showed that both intensive treatments of blood glucose and of blood pressure in diabetes can reduce the risk of diabetes-related complications in newly diagnosed subjects with type 2 diabetes. It also participated essentially to understand the prognosis of diabetic complications by recording the clinical characteristics, and then outcomes (Unnikrishnan, 1998; UKPDS Group, 1998).

UKPDS reported that the risk of CHD increases approximately 11% for each 1% (1 unit) increase in glycated haemoglobin (HbA1c) which reflects the glycaemia

contribution itself. In addition to hyperglycaemia, high levels of LDL-cholesterol, low levels of HDL-cholesterol, hypertension and smoking status had been proposed by UKPDS as modifiable predictors.

The association between risk factors and the occurrence of diabetic complications over time was described in quantitative terms (Turner *et al.*, 1998b; Barrett-Connor and Wingard, 1983). The UKPDS risk engine combined mathematical equations into a model that estimates CHD and stroke risk (Stevens *et al.*, 2000; Stevens *et al.*, 2004; Stevens *et al.*, 2001; Kothari *et al.*, 2002).

There are other models that existed before UKPDS risk engine but are different by which they may not have considered a measure of glycaemia (Anderson *et al.*, 1991a), or the estimates derived from the model was from small, localized populations, which probably were not appropriate for the populations to which it was applied (Eastman *et al.*, 1997).

Moreover, Coleman *et al.* suggested in his report that Framingham, SCORE, and DECODE (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe) risk equations are not reliable for the estimation of cardiovascular risk in patients with type 2 diabetes (Coleman *et al.*, 2007). The widely-used Framingham models are not specifically designed for subjects with type 2 diabetes and derived from a population with only 337 patients with type 2 diabetes (Anderson *et al.*, 1991a; Anderson *et al.*, 1991b). It employs dichotomous variables for glycaemia, presence or absence of diabetes which implies that CHD risk increases in patients with diabetes similarly despite of glycaemic control or diabetes duration (Myers *et al.*, 2000), while UKPDS includes glycaemia as a continuous variable and time since diagnosis of diabetes (Feher and Elkeles, 1999).

In addition, there is the Prospective Cardiovascular Munster (PROCAM) model which is derived only from men data in that study and this score includes triglycerides, LDL-cholesterol and HDL-cholesterol, but not total cholesterol or glucose concentrations (Assmann *et al.*, 1999). The 10-year European SCORE project included the classic risk factors which are sex, age, systolic blood pressure, smoking status and either total cholesterol or total HDL-cholesterol but diabetes was not included because of lack of comparable data in the individual studies (Balkau *et al.*, 2004). DECODE equation recruited over two thousand patients with diabetes in the study, but fasting plasma glucose was incorporated in a categorical manner which therefore does not adequately consider the effect of glycaemia different levels (Balkau *et al.*, 2004; Coleman *et al.*, 2007).

Mafauzy *et al.* conducted a study in Kelantan enrolling 2508 participants. The study aimed to determine the prevalence of type 2 diabetes and impaired glucose tolerance and their association with cardiovascular risk factors. The patients were asked to come to the local health clinic for interviewing and physical examining. Blood was collected for glucose, triglyceride, total cholesterol, LDL-cholesterol, HDL-cholesterol, urea, creatinine and uric acid determination. The results of the study showed that patients with type 2 diabetes had significantly higher mean BMI, systolic blood pressure, diastolic blood pressure, serum urea, triglyceride, cholesterol and LDL-cholesterol and lower mean serum HDL-cholesterol than the normal subjects. Females showed significantly a higher obesity than males. As a conclusion, the study indicated that patients with type 2 diabetes showed a high prevalence of obesity, hypertension and hypercholestrolaemia (Mafauzy *et al.*, 1999).

In Trinidad, a study was conducted to evaluate the long-term glycaemic control and risk of CVD in multi-ethnic groups for patients with type 2 diabetes (Ezenwaka and