THE IMPACT OF COMPLIANCE OF THE PRESCRIBERS TO THE MALAYSIAN CONSENSUS FOR TYPE 2 DIABETES MELLITUS MANAGEMENT FOR HOSPITALIZED PENANG HOSPITAL'S PATIENTS AND THEIR SELF MANAGEMENT

By

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DEDICATION

In the name of Allah the Most Compassionate and Most Merciful. I dedicate this thesis

To my lovely country.... Sudan

To this great land .....Malaysia

.. .. .. *To the memory of....*

My beloved, father Adam A.elkarim, who hasn't saved any efforts to bring me up in the best way. My dearest uncle, Ahmed Sharief, who owes and offers me all the invaluable care

Both of them have provided me with the best life and best education abroad to attain my expectations.

May Allah (SWT) forgive them and make the paradise their permanent residence.

.....to the most essence in my life

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My dearest aunt, Halima Salih

For their prayers, love, suffers, pain and tolerance of my absences .....Their support and encouragement have pulled me through my difficult times and enlighten my way to the right path.

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List of Abbreviations

DM	Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
MC	Malaysian Consensus
H PP	Hospital Pulau Pinang
BMI	Body Mass Index
HPT	Hypertension
BG	Blood Glucose
BP	Blood Pressure
HDL-C	High-Density Lipoprotein Cholesterol
RM	Ringget Malaysian
ADH	Anti-Diuretic Hormone
ADA	American Diabetes Association
WHO	World Health Organization
T1DM	Type 1 Diabetes Mellitus
NIDDM	Non-Insulin Dependent
GDM	Gestational Diabetes Mellitus
IGTT	Impaired Glucose Tolerance Test

IFG	Impaired fasting glucose
B-cells	Beta-cells
MODY	Maturity onset diabetes of the young
CVDs	Cardiovascular diseases
USA	United State of America
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases.
CHD	Coronary heart disease
MI	Myocardial infarction
DN	Diabetic neuropathy
BS	Blood Sugar
ESRD	End-stage renal disease
IDF	International Diabetes Federation
FPG	Fasting Plasma Glucose
FBG	Fasting Blood Glucose
APR	Asia-Pacific Region
Aus Diab	Australian Diabetes
GPs	General Practitioners
OHAs	Oral Hypoglycaemic Agents
MUFA	Mono-unsaturated Fatty Acids

ATP	Adenosine Tri-phosphate
K_{ATP}	Potassium Adenosine Tri-phosphate
PKC	Protein Kinase C
TZDs	Thiazolidinediones
AA	Amino Acids
FDA	Food and Drug Administration
SQ	Subcutaneous
AACE	American Association of Clinical Endocrinologist
CDA	Canadian Diabetes Association
Diabetes UK	Diabetes United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
1DF-WPR	The International Diabetes Federation -Western Pacific Region guidelines
CAN	Canadian
US$	United State Dollar
HbA1c	Glycosylated Haemoglobin
HCPs	Health care Practitioners
AUDIT	Analysis and Understanding of Diabetes and Dyslipidemia: Improving Treatment
JEU	Joint European guideline

NCEP	National Cholesterol Education Program guideline
CVRF	Cardiovascular Risk Factor
SSED	Swiss Society of Endocrinology-Diabetology
LDL	Low Density Lipoprotein-Cholesterol
NCEPATP 111	National Cholesterol Education Program Adult Treatment Pane l111 guideline

List of Publications and Seminars

KESAN KEPTUHAN PRESKRIBER KEPADA KONSENSUS MALAYSIA BAGI PENGURUSAN DIABETES MELLITUS JENIS-2 UNTUK PESAKIT YANG DIMASUKKAN KE HOSPITAL PULAU PINANG DAN PENGURUSAN DIRI

ABSTRAK

Diabetes mellitus ialah penyakit tak menular yang paling biasa ditemui di merata dunia yang dikaitkan dengan pelbagai komplikasi serius. Pengurusan yang betul akan dapat menangguhkan perkembangan komplilkasinya. Banyak negara telah menerbitkan panduan amalan bagi pengurusan diabetes untuk membantu pakar perubatan memberikan penjagaan yang terbaik bagi pesakit- pesakit diabetes. Kajian ini bertujuan untuk menilai pematuhan para preskriber terhadap pengurusan panduan amalan klinikal bagi Diabetes Mellitus Jenis ke 2 (T2DM) (the Malaysian Consensus MC, 1996) bagi pesakit-pesakit dewasa T2DM yang dimasukkan ke Hospital Pulau Pinang (HPP) kerana belum ada kajian yang meniliti kepatuhan ini di Malaysia. Di samping itu ia bertujuan untuk menilai pengetahuan umum tentang pesakit-pesakit T2DM dari segi swarawatan penyakit mereka. Pengumpulan data prospektif telah dijalankan bersama-sama dengan sesi temuduga pesakit dan kajian retrospektif. Pendekatan "dari bawah ke atas" telah digunakan bagi menganggar kos perubatan langsung dan kos tempoh rawatan di hospital bagi setiap pesakit. Natijahnya kepada pesakit dan kosnya dinilai dan dianalisa bagi kesemua subjek dan dibandingkan dengan pematuhan dengan garispanduan MC. Daripada maklumat kseluruhan 154 pesakit, 46.8% terdiri daripada

lelaki, 53.2% wanita dan majoriti pesakit (55.8%) tidak obes. Diabetes yang tak terkawal digambarkan dalam bentuk hipoglisemia (39.0%) atau hiperglisemia (33.7%) merupakan sebab paling biasa pesakit dimasukkan ke hospital, manakala hipertensi (HPT) merupakan komorbiditi yang pradominan (66.2). Lima puluh dua pesakit (33.8%) dianggap pesakit yang baru dikesan kerana mereka baru dikesan mengalami diabetes dalam tempoh beberapa hari sehingga ≥ 3 tahun. Pesakit yang bakinya, 66.2% telah dikesan dalam tempoh 3 sehingga ≥ 10 tahun daripada tarikh panduan MC dikeluarkan sehingga tempoh pengumpulan data. Daripada pesakit- pesakit ini, 50 orang telah dirawat dengan mematuhi garispanduan MC, manakala 104 orang pesakit lagi diurus dengan cara tidak mematuhi garispanduan MC. Bilangan dan kekerapan pengubatan yang ditetapkan adalah lebih tinggi dalam kalangan kumpulan yang tak patuh, namun perbezaannya tidak signifikan secara statistic (nilai $P > 0.05$). Merskipun tidak ada perbezaan signifikan dalam BG purata semasa dimasukkan ke hospital dan semasa dibenarkan pulang pada kedua-dua kumpulan tersebut, bilangan pesakit yang mempunyai tahap BG yang baik semasa dibenarkan pulang lebih tinggi dalam kalangan kumpulan yang patuh. Purata jumlah kos rawatan hospital dalam kalangan kumpulan yang tak patuh didapati jauh lebih tinggi (RM 643.09) berbanding dengan kumpulan yang patuh (RM 593.62). Kajian ini mendapati majoriti preskriber tidak patuh dengan panduan MC untuk mengurus pesakit-pesakit T2DM di HPP. Walaupun keputusan menunjukkan tidak ada perbezaan signifikan di antara kumpulan yang dirawat dengan patuh dan yang tak patuh, kumpulan yang patuh mengalami pembaikan yang lebih baik

dalam kawalan glisemia dan juga kos purata rawatan hospital yang lebih rendah. Kohort temuduga pula menunjukkan mereka kekurangan pengetahuan tentang pengurusan diabetes dan terlalu sedikit daripada mereka yang didapati mematuhi program penjagaan diri yang dicadangkan.

THE IMPACT OF COMPLIANCE OF THE PRESCRIBERS TO THE MALAYSIAN CONSENSUS FOR TYPE 2 DIABETES MELLITUS MANAGEMENT FOR HOSPITALIZED PENANG HOSPITAL'S PATIENTS AND THEIR SELF MANAGEMENT

ABSTRACT

Diabetes mellitus, (DM) is the most common non-communicable disease worldwide which is associated with various serious complications. Proper management delays the development of complications. Various countries have developed practice guidelines for the management of diabetes to assist physicians in providing the best care for diabetic patients. This study was aimed to evaluate the prescribers' compliance with the clinical practice guideline for Type 2 Diabetes Mellitus (T2DM) management (the Malaysian Consensus MC, 1996) for adult T2DM patients admitted to Hospital Pulau Pinang (HPP), because there was no previous studies investigated the compliance in to the MC in Malaysia and to assess the general knowledge of T2DM patients regarding self-management of their disease. A prospective data collection was carried out in combination with patient interviews and retrospective study. The "bottom up" approach was used to estimate the direct medical costs and average hospitalization cost per patient stay. Patients' outcomes and costs were evaluated and analyzed for the whole subjects and in comparison to compliance with the MC. Of these 154 patients, 46.8% were male, 53.2% were female and the majority of patients (55.8%) were not obese. Uncontrolled diabetes

manifesting as hypoglycaemia (39.0%) or hyperglycaemia (33.7%) were the most common causes of admission, whereas hypertension (HPT) was the predominant co-morbidity (66.2%). Fifty two (33.8%) patients were considered newly diagnosed, as they had been diagnosed with diabetes within days to ≤ 3 years. The remaining 66.2% patients had been diagnosed for 3 up to ≥ 10 years, from the MC issued until the data collection period. Of these patients, 50 were treated in compliance with the MC guidelines, whereas 104 patients were managed in a manner that was not compliant with the MC. The number and frequency of prescribed medications was higher among the non-compliance group, but the difference did not attain statistical significance (P value > 0.05). Although there was no significant difference in the average BG during hospitalization and upon discharge between the two groups, the number of patients with a good BG level at discharge was higher in the compliance group. The average total cost of hospitalization for the non-compliant group was considerably higher (RM 643.09) than the compliant group (RM 593.62). This study found that majority of the prescribers did not comply with the MC for the management of T2DM patients at HPP. Although the results showed non-significant differences between the compliant and non-compliant treated groups, the compliant group experienced better improvements in glycaemic control as well as a lower average cost of hospitalisation. Patient interviews of the cohort revealed that, there was a lack of general knowledge about diabetes management and minimal adherence to the recommended self-care program was also observed in this cohort.

CHAPTER ONE

INTRODUCTION

1.1 Background

Diabetes is a general name for the illness characterised by an excessive excretion of urine (polyuria). The word "diabetes" was derived from a Greek word "diabainein" which means "to siphon" or "to pass through" (http://www.whfhhc.com/diabetes/). Diabetes also means "the legs are spreading" (due to the strengthened urine), which refers to the increase in the frequency of urination. The word "Mellitus" comes from the Latin word "mellitus", which means "honey sweet". Thus the name "diabetes mellitus", or "honey sweet flow" refers to the sweet taste of patient's urine and blood (http://www.blurtit.com/q526150.html).

There are two main diabetic conditions: diabetes mellitus and diabetes insipidus. Both are associated with increased thirst and an increased production of urine. Diabetes insipidus is a disease caused by decreased production, secretion or function of the anti-diuretic hormone (ADH), which leads to excessive loss of water from the kidney. The term "diabetes insipidus" refers to the quantity and quality of the urine (Corwin, 2000).
In the past, these two types of diabetes were distinguished by tasting patient urine: in the case of diabetes mellitus, the urine has a relatively sweet taste due to its sugar content, while in the case of diabetes insipidus the urine has a dilute and watery taste or "copious amount" of dull, or tasteless urine (Roberts, 1866). In this thesis, the word diabetes always refers to diabetes mellitus.

1.1.1 Definition

Diabetic mellitus (DM) is a group of metabolic disorders characterised by hyperglycaemia due to a relative or absolute lack of insulin, or cellular insensitivity to insulin (American Diabetes Association' (ADA), 2007). DM is characterized by abnormalities in carbohydrate, fat and protein metabolism. In the long term, DM results in chronic complications including micro-vascular, macrovascular and neuropathic changes that manifest in organ damage. If not effectively treated DM in its most acute and severe form can lead to confusion, loss of consciousness and death (Mealey and Ocampo, 2007).

1.1.2 Diabetes Mellitus Classification

A 1999 report from the World Health Organization (WHO) classified DM and other categories of hyperglycaemia according to their various clinical stages and aetiological types. As well as, the American Diabetes Association (ADA), (2005), categorised DM into four different classes according to its clinical and aetiological characteristics.

1.1.2 (a) Type 1 DM

Type 1 DM (T1DM) is often referred to as immune-mediated, insulin-dependent, or juvenile onset diabetes. It accounts for only 5-10% of diabetes cases (Daneman, 2006). T1DM results from the destruction of the β-cells of the pancreas, which drastically lowers or eliminates the secretion of insulin.

1.1.2 (b) Type 2 DM

Type 2 DM (T2DM) is the most common form of DM, and accounts for 90-95% of those with diabetes (Broadhurst and Domenico, 2006). It is also referred to as non-insulin dependent (NIDDM) or adult onset diabetes. T2DM can affect individuals of any age; even children may be diagnosed with T2DM (Pinhas-Hamiel and Zeitler, 2005). Hyperglycaemia, insulin resistance and a relative impairment of insulin secretion are the hallmarks of this condition.

1.1.2 (c) Gestational DM

Gestational DM (GDM) is a condition of glucose intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. It occurs normally in the third trimester of pregnancy (Buchanan and Xiang, 2005), and women with GDM are at high risk for developing diabetes.

1.1.2 (d) Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

The IGT and/or IFG are known as "pre-diabetes", which is an intermediate condition of high blood glucose levels that does not meet the specific criteria for a diagnosis of diabetes, but is a risk factor for diabetes and cardiovascular disease (Valensi *et al.,* 2005). A patient with IGT and IFG has a higher chance of developing DM in the later stages of their life.

1.1.2 (e) Other specific types of DM

This category includes the less common causes of DM, such as several conditions associated with monogenetic defects in β-cell function (ADA, 2007). It includes diabetes caused by a specific and identified underlying defect, such as genetic defects of β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies and drug or chemical induced disease. These types of DM are characterized by early onset of hyperglycaemia (before age of 25 years). They are referred to as maturity onset diabetes of the young (MODY), and are characterized by impaired insulin secretion with minimal or no defects in insulin action.

1.1.3 Pathophysiology

DM is a disease of hyperglycaemia, which is defined as a blood glucose level higher than normal. Hyperglycaemia is usually caused by an insulin deficiency, such as in T1DM, or as a result of decreased cellular responsiveness to insulin, such as in T2DM. (Corwin 2000).

1.1.3 (a) Pathogenesis

The autoimmune destruction of the insulin producing β-cells in the pancreatic islets of Langerhans leads to loss of insulin secretion (Rabinovitch and Suarez-Pinzon, 1998). This destruction may be due to environmental factors such as viruses or toxins, or genetic factors (Lefebvre *et al.,* 2006). The resulting absolute insulin deficiency is characteristic of T1DM.

Impaired insulin secretion and/or resistance to insulin action characterises T2DM. This insulin resistance decreases tissue uptake of glucose, causing an excessive accumulation of glucose in the circulation, which known as hyperglycaemia (Goldstein, 2003). This hyperglycaemia stimulates the pancreas to produce more insulin in an attempt to overcome insulin resistance. If pancreatic insulin secretion is not sufficient for the metabolic needs of the body, the final consequence is uncontrolled hyperglycaemia.

Patients with T2DM exhibit various degrees of tissue resistance to insulin, impaired insulin secretion and increased basal hepatic glucose production. Persistent or prolonged hyperglycaemia is associated with multiple disorders including obesity, atherosclerosis, hyperlipidaemia, hypertension, renal failure, blindness and other cardiovascular diseases (Golden *et al.*, 2007). The specific causes of T2DM are unknown; however, there does seem to be a genetic component as patients with T2DM have been shown to have a stronger family history of diabetes compared with T1DM patients (Koda Kimble, *et al.*, 2001; Katz and Abraham, 2006; Linn, *et al,* 2008).

1.1.3 (b) Signs and symptoms

Each type of diabetes presents differently. T1DM, which develops due to damage of insulin-producing β.islet cells in the pancreas, presents most commonly at a younger age. T1DM patients are likely to have hyperglycaemia, develop serum ketoacidosis and require exogenous insulin for blood glucose control (McAnulty, *et al.*, 2000). On the other hand, T2DM develops only when insulin is either dysfunction or inadequate. It may develop at any age, although it is usually develops in adults. Although T2DM is

usually associated with obese patients, it may also affect non-obese people (Fujita *et al.*, 2009). T2DM can be treated with oral agents, and ketoacidosis is uncommon, therefore exogenous insulin is not essential for its treatment.

Both T1DM and T2DM present with similar symptoms, such as increased thirst with frequent urination, unexpected weight loss, weakness and fatigue, extreme hunger and blurred vision. Other symptoms of T2DM include an increased frequency of infections and cuts, or bruises that do not heal quickly (Berl *et al.*, 2007). In the early stages, T2DM may not exhibit any signs or symptoms, or they may be so mild that they go unnoticed. Compared to T1DM, the evident symptoms of T2DM take a much longer time to develop http://www.johnshopkinshohealthallert.com). Although majority cases of T2DM may experience the symptoms of DM, patients are often not aware that their symptoms are related to DM, and they may avoid seeing their medical practitioner (Preshaw, 2008). Very often patients are not aware that they have T2DM until they have developed its complications, such as blurry vision or chest pain as a warning sign of ischemia. In 2007, Unger found that many macrovascular and microvascular complications may be noticeable on first diagnosis due the slowly progressive nature of T2DM and the development of chronic hyperglycaemia. Unfortunately, oral pharmacologic therapies are becoming less effective for minimizing the effects of chronic hyperglycaemia due to the deterioration of β-cell function and serious insulin resistance over time.

1.1.4 General complications

DM, if left untreated, can result in various complications. Excessive circulating blood glucose may cause damage to nerves and blood vessels. Blood vessel damage may be both macro- and microvascular, and can cause damage to multiple organs (Pessina, 2007). The microvascular complications of DM include neuropathy, nephropathy, and retinopathy. The macrovascular complications of DM may lead to the development of various cardiovascular diseases (CVDs), such as hypertension, ischemic heart disease, acute myocardial infarction and heart failure. In addition, DM is also one of the main causes of stroke in the United States according to the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, 2004).

1.1.4 (a) Cardiovascular disease - heart disease and increased risk of stroke

Macrovascular complications, such as CHD, stroke and peripheral vascular disease usually occur at a younger age in the majority of diabetic patients, (Koda Kimble *et al.,* 2001). Winer and Sowers reported in 2002 that the risk of developing CVD is higher in diabetic patients compared with non-diabetic patients in the general population. Cardiovascular diseases (CVDs) are the main cause of diabetes related death, contributing to 65% of all diabetes mortality (Grundy *et al.,* 1999). At present, diabetes is considered the main risk factor for several forms of CVD since approximately 75 to 80% of all diabetic patients develop a severe form of those complications, (Koda Kimble *et al.,* 2001). The incidence of CHD and myocardial infarction (MI) are about two to three times higher in diabetic than non-diabetic patients. Of all premature deaths in diabetic patients from CHD, 50% were squeal of T2DM. The CVD risk in diabetic

patients is aggravated by the presence of other co-morbidities such as smoking, hypertension, high serum cholesterol and obesity (Solano and Goldberg, 2005).

1.1.4 (b) Neuropathy

Diabetic neuropathy (DN) is heterogeneous collection of nerve damage conditions caused by uncontrolled BG. They are a consequence of metabolic disturbances in the neurons, microangiopathy affecting the capillary supply to neurons, or an autoimmune process (Koda Kimble *et al.,* 2001). Neuropathy most commonly presents as a diffuse, symmetric sensorimotor syndrome such as carpal tunnel syndrome or as autonomic neuropathy. In 2008, The U.S. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) demonstrated that DN occurs as a consequence of decreased blood flow and high blood sugar (BS) levels; hence, diabetic patients with uncontrolled blood sugar levels have a higher incidence of this complication. About 60-70% of diabetic patients have some form of neuropathy, and the risk of experiencing this complication increases with age and duration of diabetes. However, Vinik and Mahayana reported in 2004 that the true prevalence of DN is not known. Various reports suggest that DN is present in 10% to 90% of diabetic patients, depending on the criteria and methods used to define neuropathy.

Autonomic neuropathy is defined as the diabetes-related damage caused to the nerves that control the bladder, digestive tract and reproductive organs. The 2007 National Diabetes Fact Sheet reported that about two-thirds of diabetic patients are susceptible to have mild to severe forms of autonomic nervous system damage such as impaired

sensation or pain in the feet or hands, decreased rate of digestion of food in the stomach, carpal tunnel syndrome, erectile dysfunction, or other forms of nerve problems.

Peripheral neuropathy affects the nerves controlling the extremities, especially the feet and legs. Numbness and tingling, sensitivity to touch or muscle weakness are signs of such a neuropathy (Vinik and Mahayana, 2004; Diabetes UK, 2008). About one third of diabetic patients aged 40 years or older have impaired sensation or a total lack of feeling in their feet. This decreased sensation can contribute to foot injuries and infections, which can develop into foot ulcers, as patients are unable to feel them. These foot ulcers are the major contributing cause of lower-limb amputations in diabetic patients (Apostolou and Ram, 1999; Illa, 1999).

1.1.4 (c) Nephropathy - kidney damage and kidney failure

Prolonged elevation of BS levels will also affect the microvasculature of the kidney, thus interfering in its normal filtration function. This deterioration is known as kidney disease of diabetes, or diabetic nephropathy (Christensen, 2004). Diabetic nephropathy develops in both T1DM and T2DM patients. T2DM is the more common cause of End-Stage Renal Disease (ESRD), and approximately 40% of all T2DM patients develop diabetic nephropathy (Tourah, 2008). This prevalence is expected to increase significantly world-wide due to the epidemic-like expansion of number of T2DM cases (Rossing *et al.*, 2004). Diabetic nephropathy is characterised by continual albuminuria, elevated blood pressure and a progressive decline in kidney function, which eventually leads to ESRD. Deteriorations in renal function also exacerbate any existing cardiovascular disease,

which can further aggravate renal failure. Kidney damage and the development of end-stage renal disease usually take years to develop (Kidney failure), (International Diabetes Federation (IDF), 2003).

1.1.4 (d) Retinopathy - vision problems and blindness

Diabetic retinopathies are DM related complications that are characterised by progressive microvascular complications including micro-aneurysms, which are swellings and blockages of the vessels supplying the retina. As the number of blocked blood vessels increase, a condition known as severe non-proliferative retinopathy develops (Leiter, 2005). In 2006 and 2008 studies, the U.S. National Eye Institute reported that the growth of new abnormal and fragile vessels (proliferative retinopathy) occurs at a more advanced disease stage, and when these vessels leak, severe vision loss and blindness can occur. A Florida study by Chalam *et al.,* in 2005 found that about 25-80% of T1DM patients develop retinopathy within five to fifteen years after diagnosis. This rate of incidence is higher in T2DM patients nineteen years after diagnosis, but varies between patients who are taking insulin (40-84%) and those who are only on oral hypoglycaemics (24-53%). Furthermore, 2007 National Diabetes Statistics reported that diabetes is the leading cause of new cases of blindness among adults aged 20 to 74 years in the US.

1.2 Epidemiology

1.2.1 World wide prevalence

The prevalence of diabetes mellitus (DM) is increasing throughout the world due to aging, accelerated population growth, urbanisation, the high prevalence of obesity and

inactive lifestyles. In 2007, Herman illustrated that the prevalence of DM increases considerably over time nationwide, and that it is one of the main causes of morbidity and mortality worldwide. This study also found a significant difference in the prevalence of DM among different racial and ethnic groups. Abate and Chandalia (2003) found important differences in the incidence of DM and its complications between countries as well as between ethnic, cultural and even age groups within the same country.

Although diabetes has been recognized clinically for thousands of years, rigorous scientific study of its epidemiology has only been conducted within the past several decades. The WHO Global Burden of Disease Report estimated that there were over 177 million adults worldwide suffering from diabetes in 2002. About two thirds of these people were reported to live in developing countries (WHO, 2003).

The prevalence of DM in the United States continues to increase, with a staggering toll in acute and chronic complications, as well as disability and death. Diabetes is the sixth most common cause of death in the US (Steinbrook, 2006). The Centre for Disease Control and Prevention estimated in 2005 that 20.8 million persons in the USA, representing about 7% of the population, had diabetes. This estimate may only represent about two thirds of diagnosed diabetic patients in the USA, as many cases have never been diagnosed (Ekoe *et al.,* 2001). The incidence of diabetes is expected to double by the year 2030. In 2004, Segal and Karen reported that T2DM had become one of the most serious health concerns in the U.S., affecting an estimated 18.2 million Americans.

The prevalence of DM is increasing, particularly among youth and young adults, in parallel with the continuing rise in obesity.

Studies in 2003 by Aguilar-Salinas *et al.,* were reported similar trends for DM in Mexico. Over the past 30 years, diabetes has become a public health problem in Mexico with considerable medical, social and economic consequences. The mortality rate due to diabetes has increased gradually since 1940s. Over the past 40 years, diabetes has risen to become the fourth leading cause of death in Mexico, after cardiovascular problems, neoplastic diseases and accidents and violence (Ekoe *et al.,* 2001).

An epidemiological review and study of DM in Europe conducted by in 2000 by Ozturk *et al.,* reported that DM affected 30 million people out of the entire European population of 850 million people, including Turkey. Out of these, four million had a diagnosis of insulin-dependent diabetes mellitus (IDDM) and 26 million were suffering from non-insulin-dependent diabetes mellitus (NIDDM). A 2002 study conducted by Ciardullo *et al.,* found that the prevalence of diabetes in the general population of Italy was estimated to be 3-4% and increasing with age. Of all diabetes patients, 90% have T2DM, which presents in adulthood. In Sweden, the prevalence of DM is about 3-4% of the total population. Although the current absolute numbers are unknown, it is estimated that about 300,000 Swedish suffer from the disease, which may be a conservative estimate because of the rapid increase in T2DM prevalence (Henriksson and Jonsson, 1998; King *et al.,* 1998).

A number of epidemiological studies have been carried out since the early 1960s to explain the prevalence and nature of diabetes in African populations. The prevalence of DM in Africa has paralleled the sharply rising international trends (Motala, 2002). The majority of patients in African countries who suffer from diabetes are between the ages of 45 and 64, which is similar to other developing countries (Wild *et al.,* 2004). About 70-90% of African diabetic patients have T2DM and 25% have T1DM (Abdelgadir, 2006). The reported prevalence of T2DM among the adult population in Northern Sudan is 10.4%, while the prevalence of T1DM in all ages ranges from 0.3/1000 in Nigeria to 0.95/1000 in Sudan (Motala *et al.,* 2003).

There are no studies to reflect the current situation of DM in the Eastern Mediterranean/Middle East region, because not all countries have data from nationwide health surveys. However, consistent with global trends, it is estimated that these countries will also experience a rapid increase in the rates of obesity and diabetes. In these regions, majority of health problems arise because of inconsistent levels of care between rural and urban centres as well as emphasis on treatment instead of prevention (Bouguerra *et al.,* 2007).

The Asia-Pacific region (APR) represents the most important region for any epidemiological study of diabetes, as it is the most populated area of the world. Its largest country, China, contains 20% of the world population (1.2 billion), followed by India with its population of 1 billion, and Indonesia with a population of about 200 million people. The combined population of this region is extremely high and has been

experiencing a rapidly rising prevalence of diabetes (Cockram, 2000). For example, in 1998 it was estimated that approximately 140 million people suffered from diabetes, throughout the world (Cockram, 2000). The WHO predicts that this figure will rise to 300 million people by the year 2025, with more than 150 million of these patients residing in Asia, 90 million of whom will be in China and India (Yoon *et al.,* 2006). Another study (Gimeno *et al.,* 2002) reported that the prevalence of DM has worsened in Japanese-Brazilians over the past 7 years such that they have one of the highest prevalence rates in the world. The recent Australian Diabetes, Obesity and Lifestyle Study (AusDiab) conducted in 2002 by Hilton *et al.,* found that 7.5% of the Australian population aged 25 years and older suffered from T2DM. Over 90% of undiagnosed Australian diabetes patients had recognizable risk factor during their visit to the general practitioners (GPs) each year. Therefore, the Australian GPS identified about 300,000 to 500,000 Australians suffer from undiagnosed diabetes. This study concluded that early diagnosis is a major factor for minimizing the risk of micro- and macrovascular complications.

1.1.2 Prevalence in Malaysia

A study published in 2000 by Zaini concluded that Malaysians were living an improved life expectancy, yet sedentary lifestyle with high intake of carbohydrates and fatty foods because of improved socio-economic conditions and stress. This trend represents multiple risk factors that will undoubtedly lead the Malaysian population into a diabetes epidemic. The estimated number of adults with DM in Malaysia in 2000 was 940,000, a figure that is expected to rise to 2.48 million people by 2030 (Cruez, 2008). According

to 2008 Ministry of Health Malaysia statistics, Malaysia has a population of just over 25,000,000 people; thus, nearly 17% of the general population of Malaysia suffers from DM.

The recently published Third National Health and Morbidity Survey of 2006 (NHM 3) found that the prevalence of the most common chronic diseases in Malaysia had increased compared to the last survey in 1996. The prevalence of DM was found to have increased from 8.3% to 14.9%, and the prevalence of HPT was increased to 43% from 33% (Rashid, 2008).

1.3 Diagnosis of diabetes mellitus

The 1999 Malaysian Consensus (MC) practice guidelines for Type 2 Diabetes mellitus (T2DM) management 2nd edition, recommend that any individual who displays symptoms such as weight loss, tiredness, lethargy, polyuria, polyphagia, polydipsia, pruritus vulvae and banalities be screened for DM. Moreover, individuals who present to a primary health care facility for any reason with any of the following characteristics should be screened for diabetes, regardless of whether they display symptoms: aged 35 years and over, obesity (BMI $\geq$ 30), history of gestational DM, history of big baby (birth $\geq$ 4.0 kg.), family history of diabetes, hypertension and hyperlipidaemia, (total cholesterol > 6.5 m mol/l and fasting triglyceride > 2.3 m mol/l). All pregnant women should be screened at least once at $\geq$ 24/52 period of gestation.

If the symptoms of a patient are suspicious for diabetes, urine and blood glucose tests are used to confirm the diagnosis (Cutler, 2003). The presence of ketones and protein in the urine helps diagnose diabetes and evaluate kidney function. However, a study by Kuzuya *et al.,* in 2002 reported that the diagnoses of diabetes and pre-diabetes are done definitively by measuring BG or fasting plasma glucose (FPG) levels. Individual with either a borderline or normal FPG level that present with some symptoms of diabetes may require an oral glucose tolerance test (OGTT) to confirm the diagnosis of diabetes (Kuzuya *et al.,* 2002). OGTT is a special test that measures the ability of the body to utilize glucose.

Several different criteria exist for the diagnosis of hyperglycaemia and diabetes based on FPG and OGTT results. These criteria include the 1997 American Diabetes Association (ADA) criteria as well as the 1985 and 1999 WHO criteria (Gabir *et al.,* 2000). In the 1985 WHO criteria, diabetes could be diagnosed by either a fasting plasma glucose (FPG) $\geq$ 7.8 mmol/l (140 mg/dl) or a 2-hour post load plasma glucose (2-h PG) $\geq$ 11.1 mmol/l ($\geq$ 200 mg/dl) after a 75-g OGTT load (Gabir *et al.,* 2000), while the ADA 1997, criteria stated that both T1DM and T2DM could be confirmed by a FPG level $\geq$7.0 mmol/l ($\geq$ 125 mg/dl) on two separate occasions (Gabir *et al.,* 2000; the US Expert Committee Report, 2002). On the other hand, the WHO 1999 criteria recommends an OGTT if the FPG is $\geq$ 7.0 mmol/l, and states that the diagnosis of diabetes is confirmed if the 2-h PG is $\geq$ 11.1 mmol (Vaccacro *et al.,* 1999; Lindstrom *et al.,* 2003).

1.4 Management of diabetes mellitus

Management of diabetes is designed to maintain BG levels within a normal range, termed euglycaemia. Currently, there is no cure for diabetes (Halban, 2006); however, appropriate management of patients with DM will help delay the progression of the disease, reduce the development of its complications, and improve clinical outcomes (Wyne and Bell, 2004). T1DM patients require regular injection of insulin to adjust BG levels, as their bodies cannot produce enough insulin. The first line for T2DM management is diet modification and exercise. If these manoeuvres fail to control BG, an oral hypoglycaemic agent (OHA) could be added. A 2002 study by Assal *et al.*, stated that regular blood glucose monitoring, medication compliance and careful self-management of the disease are important to stabilize blood glucose levels and eliminate the symptoms of hyperglycaemia. Hence, proper T2DM management is important in order to achieve the long-term goals of treatment, which are prolonged life, symptom relief and prevention of long-term DM complications such as heart disease and kidney failure.

1.4.1 Non-drug therapies

The most important non-drug therapy is behaviour modification for a healthier life-style. Diabetic patients are encouraged to modify their daily diet such that it is well balanced, and to perform regular exercise (Franz *et al.*, 2002).

1.4.1 (a) Dietary therapy

Nutritional recommendations for diabetic patients are the same as for non-diabetic individuals. A 2007 study by Dedoussis reported that diet management is a main factor for maintaining long-term health and quality of life for people with T2DM. General intake guidelines include 50-60% of daily energy requirements derived from carbohydrates, low glycaemic index foods, foods containing cereal fibre and a protein intake of least 0.86 g/kg/day. The consumption of added sugars can be up to 10% of daily energy requirements. Also, guidelines recommend a limited intake of total fat, especially saturated fats and monounsaturated fatty acids (MUFA) where possible, appropriate use of nutritive and non-nutritive sweeteners, and a daily vitamin and mineral supplement.

1.4.1 (b) Exercise

Increased physical activity and regular exercise is an important element of diabetes management. Exercising muscles require more glucose to meet their energy requirements, and therefore regular exercise removes excessive sugar from the body and improves insulin sensitivity (Quesada, 2003). Though a healthy, nutritious diet and a moderate exercise regimen represent the foundations of T2DM management, weight loss is another important tool for diabetes control (Flood, 2007). Therefore, patients with mild to moderate disease may initially utilize diet and exercise alone to restore effective glycaemic control.

1.4.2 Drug therapies

As diabetes progresses, the pharmacologic interventions are required to achieve euglycaemia. The choice for first line drug therapy depends on the type of diabetes. Exogenous insulin is needed for T1DM, while in T2DM different classes of oral hypoglycaemic agents (OHAs) are used. A 1999 study by Damsbo *et al.,* and a 2007 study by Modi both stated that OHAs have variable mechanisms by which they normalize BG. These include either promoting insulin secretion by the pancreas, increasing insulin sensitivity or delaying the rate at which glucose is absorbed from the gastrointestinal tract (GIT). Insulin may be required for T2DM therapy if a patient does not attain glycaemic goals by oral therapy.

1.4.2 (a) Oral hypoglycaemic agents (OHA)

There are five classes of oral hypoglycaemic agents (OHAs) approved for the treatment of T2DM. These drugs vary in their mechanism and site of action as well as their duration of action and reduction in HbA1c levels. These OHAs include sulfonylureas and meglitinides, which are also known as secretagogues, biguanides and thiazolidinediones, which are also known as sensitizers, and alpha-glucosidase inhibitors, which help to delay the absorption of carbohydrates in the GIT (Geng *et al.,* 2007).

The ability of an OHA to reduce BG levels varies depending on the aetiology of the diabetes. A non-obese patient usually receives sulfonylureas as first line therapy, whereas an obese patient usually responds better to metformin (biguanides). A combination of OHAs is used if one OHA is insufficient to control BG effectively.

Some patients may even need a combination of more than two drugs to maintain euglycaemia.

(ii) Sulfonylureas

Sulfonylureas have been used as first-line oral anti-hyperglycaemic agents for T2DM since 1954 (Vagula and Devi, 2008). Historically, sulfonylureas have been most widely used to start oral drug therapy for non-obese T2DM patients, while metformin has been preferred for obese patients (Baily and Day, 2003). Sulfonylureas are thought stimulate insulin release from the beta cells of pancreatic islets by inhibition of potassium sensitive adenosine triphosphate (ATP) channels (K_{ATP} channels) in the β-cell membrane. When sulfonylureas bind to their receptors, they presumably close the K_{ATP} channels, which lead to a decrease in the K^+ permeability of the β-cell membrane. This change depolarizes the cell, triggering a calcium influx that activates the insulin secretion machinery. Sulfonylureas also promote insulin exocytosis by direct interaction with the secretory machinery, without closing the plasma membrane K_{ATP} channels. This effect is dependent on protein kinase C (PKC), and was observed at therapeutic concentrations of sulfonylureas, which properly contributes to their hypoglycaemic action in diabetics (Eliasson *et al.,* 1996; Geng *et al.,* 2007). Sulfonylureas are classified into first-generation and second-generation compounds. They vary in their potency, safety, and pharmacokinetic characteristics. The second-generation agents, including glipizide (Minidiab, Glucotrol $^{(R)}$), glibenclamide, known as glyburide in USA, (Daonil, Diabeta, Micronase, Glynase $^{(R)}$), gliclazide (Diamicron$^{(R)}$), and glimepiride (Amaryl$^{(R)}$), are characterized by their high potency as well as improved pharmacokinetic and safety

profiles (Modi, 2007). The first-generation sulfonylureas include acetohexamide (Dymelor(R)), tolbutamide (Rastinon, Orinase(R)), tolazamide (Tolinase(R)) and chlorpropamide (Diabinese(R)). Chlorpropamide and tolbutamide are the most commonly utilized first generation sulfonylureas. A 2007 study from Meyer and DalPan and a 2005 study from Bastaki stated that the choice of sulfonylurea depends on the propensity of the patient to develop hypoglycaemia as a result of different pharmacokinetics, since the long-acting sulfonylureas can induce hypoglycaemia while the short-acting agents may not cause euglycaemia.

Sulfonylureas are generally taken one to two times a day, before meals. Their dosing schedule is included in (Appendix C). They are well tolerated and have a low incidence of side effects. The most common sulfonylurea side effect is hypoglycaemia, which can occur due to an unnecessarily high dose, excessive physical activity or improper diet. Hypoglycaemia manifests as hunger, nausea/vomiting, fatigue, headache, tremor, finger tingling, mouth numbness and muscle weakness (Inzucchi *et al.,* 2005). Furthermore, sulfonylureas are contraindicated in T1DM, people with sulfa allergies, and patients with advanced liver or kidney disease. Sulfonylureas are not recommended in pregnancy due to the studies that showed adverse effects on animal foetuses. There are no adequate studies regarding the effects of sulfonylureas on the human foetus. It is also important to note that second generations sulfonylureas have less drug-drug interactions than first generation compounds.

(ii) Meglitinides

These agents enhance insulin release from the pancreas over a short period of time only if blood glucose levels are high. Therefore, they are classified as short-acting secretagogues (Lewis, 2002). Meglitinides first became available in 1997 for the treatment of T2DM patients. Their brand names are Prandin(R) (repaglinide) and Starlix(R), and they are taken orally two to four times per day with meals. As for side effects, they have a low risk of hypoglycaemia, but may cause weight gain.

(iii) Biguanides

Biguanides, (metformin, phenformin and buformin) reduce hepatic glucose output and stimulate the transportation of glucose into muscle in the presence of insulin. This class of drugs is ineffective for non-insulin dependent (NIDDM) treatment (Modi, 2007). Biguanides must be used with caution in patients with impaired liver or kidney function.

Metformin hydrochloride is one of the most commonly used first-line oral agents for the treatment of T2DM (Bastaki, 2005). Metformin lowers blood glucose levels primarily by decreasing the amount of glucose produced by the liver. It also helps to lower blood glucose levels by improving the sensitivity to insulin, such that glucose can be absorbed. The usual starting dose of metformin hydrochloride tablets is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses. Metformin as a monotherapy is usually not accompanied by hypoglycaemia, and has been used safely in patients with pre-diabetic hyperglycaemia (Nathan, *et al.*, 2006).

The major non-glycaemic effect of metformin is either weight stability or modest weight loss, which is in contrast to many of the other blood glucose–lowering medications that can cause weight gain. The common side effects of metformin include nausea and diarrhoea, but these are improved over time when taken with food.

(iv) Thiazolidinediones

Thiazolidinediones (TZDs, also known as glitazones) are insulin sensitizers now widely used for the treatment of T2DM. Three TZDs have been used in clinical practice, namely troglitazone, pioglitazone, and rosiglitazone (Vagula and Devi, 2008). TZDs have been used to treat T2DM since the late 1990s and the normal dose is once or twice daily.

Glitazones can be useful in patients who are at high risk of cardiovascular disease, as they have been demonstrated to improve patient lipid profiles (Nass and Blumenthal, 2000; Black, 2003; Wilding, 2006). Common side effects of TZDs include upper respiratory infections, sinus infections, headaches and mild anaemia. Serious side effects include fluid retention, heart failure, muscle pain and weight gain.

(v) Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (acarbose, miglitol and voglibose) delay digestion and absorption of carbohydrates at the intestinal lining (Krentz and Baily, 2005). They may be used as monotherapy in conjunction with an appropriate diabetic diet and exercise or as adjunctive therapies with other anti-diabetic drugs for T2DM. Acarbose is the most

commonly used drug in this class. Side effects of this drug class include episodes of hypoglycaemia and gastrointestinal disturbances such as flatulence and diarrhoea.

1.4.2 (b) Insulin

Insulin is a hormone produced by the β-cells of pancreas that is released into the portal vein and reaches peripheral circulation. It is considered as one of the most potent regulators of blood glucose level, in addition to, its extensive effects on both metabolism and several other body systems (e.g., vascular compliance). Insulin increases glucose utilization by cells in the liver, muscle and fat tissue by converting excess glucose to glycogen for storage in the liver and muscle. Insulin also inhibits the catabolism of fat and amino acids (AA) for energy production (Yang, 2004). A deficiency or absence of insulin creates a defect in the insulin central metabolic control mechanism (transfer of lipids from adipose tissue to the liver for mobilization as an energy source), a defect in its status as control signal to other body systems (such as amino acid uptake by body cells) and a defect in the anabolic effects throughout the body. Hence, a decrease in the amount of insulin released results in DM. (Turner *et al.*, 1999).

The amount and type of insulin required depends on the height, weight, age, food intake, and activity level of a diabetic patient (Vagula and Devi, 2008). Some patients with T2DM may also need to use insulin injections if their diabetes cannot be controlled with diet, exercise, and oral medication. Insulin, derived from the pancreas of animals, was first available for diabetic patients in the 1920s. This extracted insulin would vary with the animal species it was obtained from, such as cows and pigs. Recently, the genetically