A PHARMACOEPIDEMIOLOGICAL EVALUATION OF GLYCAEMIC CONTROL AMONG DIABETES PATIENTS RECEIVING DIFFERENT TREATMENT REGIMENS AT PENANG GENERAL HOSPITAL

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By

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DEDICATION

I dedicate my thesis to my parents, whom I owe my entire life: my father, lawyer Abd Al-Rida Al-Baroodi, and my mother, engineer Zahra Abu Al-Maali. I would like to thank them from the deepest part of my heart for helping me to reach the place where I stand. Without their prayers, tolerance, understanding, support, encouragement, and care, I would not be where I am today. I wish to express my deepest gratitude and extreme appreciation to my beloved husband, Mohammad Faiz Eessa. I also dedicate my thesis to my lovely two-year-old son Elias Abu Al-Maali. His innocent, childish way of laughing, kissing, playing, and growing right in front of my eyes has helped to give me the power to complete my studies. I would like to dedicate my thesis, in particular, to my sister, Hala Al-Baroodi, for the years she has spent encouraging and understanding me. I also thank her daughter, Jude Al-Jumaily, and her husband, Zaid Al-Jumaily, for encouraging me to achieve my goals and finish what I had started. I also express my appreciation to my sister Weam Al-Baroodi and her husband Baseem, my sister Elham Al-Baroodi, her husband Haider Al-Ali, my lovely nieces Dania and Shams, and my darling brother Salaam Al-Baroodi, who passed away to God's highest heaven. I wish he was here at this sweet moment of my life. I dedicate my thesis to my lovely sister-in-law Daad Al-Baroodi, my darling nephews Samir and Bisher, my darling brother Weasam Al-Baroodi, his wife Ban, and my sweet nephews Humam, Haya, and Hala for their wonderful encouragement, care, and support during my studies.

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LIST OF ABBREVIATION

AACE	American association of clinical endocrinologists
ACCORD	Action to control cardiovascular risk in diabetes
ACE	American college of endocrinology
ADA	American diabetes association
ADVANCE	Action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CIRS	Cumulative illness rating scale
CRC	Clinical research centre
CVD	Cardiovascular disease
DCCT	Diabetes control and complications trial
DPP-4	Dipeptidyl peptidase-4 inhibitors
EDIC	Epidemiology of diabetes interventions and complications
FBS	Fasting blood sugar
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GLP1	Glucagon-like peptide-1
HDL	High density lipoprotein

HIV	Human immunodeficiency virus
IDDM	Insulin-dependent diabetes mellitus
IDF	International diabetes federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
JDDM	Japan diabetes clinical data management
LDL	Low-density lipoprotein
NHANES	National health and nutrition examination survey
NHMS	National health and morbidity survey
NIDDM	Non-insulin-dependent diabetes mellitus
NPH	Neutral protamine hagedorn
OGTT	Oral glucose tolerance test
OHAs	Oral hypoglycaemic agents
PCOS	Polycystic ovarian syndrome
RR	Relative risk
SD	Standard deviation
SU	Sulfonylurea
TG	Triglycerides
TZD	Thiazolidinediones
UKPDS	United Kingdom prospective diabetes study
VHA	Veterans health administration
VLDL	Very low density lipoprotein
WHO	World health organization

PENILAIAN FARMAKOEPIDEMIOLOGIKAL UNTUK PENGAWALAN GLISEMIK DI KALANGAN PESAKIT DIABETES YANG MENERIMA PELBAGAI REGIMEN DI HOSPITAL PULAU PINANG

ABSTRAK

Secara umum, penyakit diabetes mellitus jenis 2 tidak boleh dirawat dengan menggunakan satu jenis drug atau dengan cara mengubah gaya hidup sahaja. Tambahan agen antidiabetes atau peningkatan dos disarankan untuk mengawal keadaan penyakit tersebut daripada menjadi bertambah teruk. Tujuan kajian ini dijalankan adalah untuk menilai drug antidiabetes yang digunakan di Hospital Pulau Pinang dan hubungannya dengan dapatan klinikal rawatan penyakit. Juga untuk menentukan bilangan pesakit diabetes yang boleh mencapai sasaran klinikal yang ditetapkan. Hubungkait di antara tempoh masa seseorang pesakit menghidap diabetes dengan strategi rawatan, bilangan komplikasi lain yang dihidapi, komorbiditi dan dapatan klinikal juga turut dinilai. Kajian ini merupakan kajian pemerhatian retrospektif keratan silang melibatkan 1014 pesakit diabetes mellitus jenis 2 yang menghadiri klinik diabetes pesakit luar di hospital berkenaan. Kajian ini turut meneliti rekod perubatan setiap pesakit bermula pada tahun 2005 hingga 2007. Dapatan klinikal secara primer dan sekunder untuk rawatan diabetes yang disarankan untuk pemantauan termasuklah plasma glukosa sewaktu berpuasa, HbA1c, tekanan darah (BP) dan profil lipid. Data yang diperolehi dikumpul dan dianalisa menggunakan pakej perisian SPSS versi 15.0 (SPSS Inc., chicago, IL) dan *Microsoft Excel*. 54% daripada jumlah pesakit adalah wanita dan 54.1% daripadanya

adalah kaum Cina. Hasil kajian mendapati terdapat perbezaan secara signifikan dalam kawalan glisemik bagi beberapa strategi rawatan yang digunakan. Pesakit yang menerima rawatan mono agen hipoglisemik oral (OHA) mempunyai tahap HbA1c yang paling rendah. Walaupun penambahbaikan rawatan sama ada melalui penambahan agen antidiabetes atau peningkatan dos dilaksanakan, didapati paras glukos di kalangan pesakit masih tinggi (p<0.001). Hampir separuh daripada pesakit diabetes yang menjalani terapi mono OHA tidak mengalami sebarang komplikasi. Sebaliknya, majoriti (92.8%) daripada pesakit diabetes tidak terkawal mengalami komplikasi walaupun mereka mengikuti pengubatan antidiabetes. Terdapat hubungan di antara tempoh diabetes dengan strategi rawatan, bilangan komplikasi dan komorbiditi (p<0.001). Berdasarkan keputusan kajian yang diperolehi, rumusan telah dibuat iaitu terapi mono menggunakan OHA memberikan dapatan klinikal yang lebih baik berbanding regimen rawatan lain. Lebih daripada separuh pesakit yang menerima terapi mono OHA mempunyai jangka masa rawatan yang lebih pendek. Perbezaan ini tidak semestinya menggambarkan kegagalan regimen rawatan seperti yang disarankan dalam Garis Panduan Amalan Klinikal Malaysia. Hal ini mungkin disebabkan oleh keadaan penyakit yang bertambah teruk dan masalah komplians pesakit terhadap pengambilan ubat antidiabetes. Kajian ini akan memberikan input kepada Kementerian Kesihatan Malaysia dalam mengambil langkah perlu untuk meningkatkan kualiti hidup pesakit diabetes.

Kata kunci: OHA, diabetes jenis 2, kawalan glisemik, tempoh penyakit, komorbiditi, komplikasi

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ABSTRACT

Generally, type 2 diabetes mellitus cannot be managed with a single drug or lifestyle changes alone; therefore, adding anti-diabetic agents or increasing the dose is recommended to control the disease progression. This study aimed to evaluate the anti-diabetic drugs used at Penang General Hospital in relation to the clinical outcomes of the disease management and to determine the proportions of diabetic patients who achieved the target levels. The association between diabetes duration and each of: treatment strategies, number of complications, comorbidities and clinical outcomes was also evaluated. This was a cross-sectional retrospective observational study involving 1014 patients with type 2 diabetes mellitus who attended the outpatient diabetes clinic at the Penang General Hospital in Malaysia. Each patient's medical record from 2005 to 2007 was reviewed. The primary and secondary clinical outcomes for treatment of diabetes that are recommended to be monitored include fasting plasma glucose, haemoglobin A1c (HbA1c), blood pressure (BP) and the lipid profile. All the collected data were analysed using the SPSS (version 15.0) software package (SPSS Inc., Chicago, IL) and Microsoft Excel. Female patients constituted 54% of the study population, and 54.1% of the sample was Chinese. There were significant differences in glycaemic control between the treatment strategies, and patients receiving monotherapy with oral

hypoglycaemic agents (OHA) had the lowest HbA1c level. Furthermore, high glucose levels were observed in spite of the treatment intensification either by addition of anti-diabetic agents or increment of the drug dose (p <0.001). About half of the diabetic patients who were on monotherapy with OHAs had no complications. A large proportion (92.8%) of the study population had uncontrolled diabetes even though they were receiving anti-diabetic medications. There was an association between the diabetes duration and each of the following: treatment strategies, number of complications, and co-morbidities (p <0.001). On the basis of these results, we conclude that monotherapy with OHAs therapy had better outcomes (glycaemic control, BP, high density lipoprotein cholesterol, and the number of complications) than the other treatment regimens. Moreover, more than half of those who were on monotherapy with OHA therapy had relatively shorter treatment period. The differences observed in the study outcomes may not necessarily reflect the failure of the other treatment modalities recommended by the Malaysian Clinical Practice Guidelines. Rather, these findings could be due to the progression of the disease and possibly inadequate patient compliance to the anti-diabetic medications. These findings provide an input to the Malaysian Ministry of Health to take steps for improving the management and quality of life of patients with type 2 diabetes.

Keywords: OHAs, type 2 diabetes, glycaemic control, disease duration, co-morbidities, complications.

CHAPTER 1

INTRODUCTION

This study attempts to evaluate the medications used for the treatment of type 2 diabetes and the clinical outcomes achieved at Penang General Hospital, Malaysia. This chapter indicates the problem of uncontrolled diabetes in spite of the patients taking anti-diabetic medications. It also contains the research questions, and the study objectives which have been investigated.

1.1 Introduction

Diabetes mellitus is a costly disease for both the diabetic patient and the healthcare sector, because of the severity and chronic nature of its complications (Ooyub *et al.*, 2004). On the other hand, many studies including the United Kingdom Prospective Diabetes Study (UKPDS) have reported a significant reduction in microvascular complications associated with tight glycaemic control (Stratton *et al.*, 2000). On the other hand, the effect of the glycaemic control on the macrovascular complications is incompletely understood (American Diabetes Association, 2002). Guidelines for the management of type 2 diabetes mellitus outline many treatment strategies depending on the HbA1c level, starting by the diet therapy which is intensified by initiating pharmacotherapy (Ministry of Health Malaysia *et al.*, 2004; Rodbard *et al.*, 2007).

Pharmacological treatment of diabetes mellitus type 2 begins with an oral agent, usually metformin or sulfonylurea (SU). If proper glycaemic control is not achieved with a single drug, the combination of these two drugs is recommended

(American Diabetes Association, 2008c; Edwards *et al.*, 2008). Over time, most diabetic patients will require three or more oral anti-diabetic medications, and they may even have to use insulin. Although the American Diabetes Association (ADA) recommends metformin for the initiation of monotherapy, there are no guidelines to help physicians select the second or third drug, if additional medication is required (American Diabetes Association, 2008c). Guidelines from the American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE) recommend several therapy options, depending on the patient's HbA1c level (American College of Endocrinology and American Association of Clinical Endocrinologists, 2002). Similarly, Malaysian guidelines recommend the treatment strategies depending on the screening of the HbA1c level. Moreover, modification of the treatment regimen would be recommended if the current regimen failed to achieve the target level (Ministry of Health Malaysia *et al.*, 2004).

1.2 Problem Statement

Diabetes mellitus is becoming a worldwide epidemic (World Health Organization, 2000). Epidemiologists estimate that by 2025 diabetes will affect 300 million people (King *et al.*, 1998), with about half of them from the Asia Oceania region alone. During this time, there will be three-fold increase of this disease in Asia, both in developed countries like China and India, and in the rapidly developing countries, such as Malaysia and Singapore (King *et al.*, 1998). In the last two decades, Malaysia has undergone rapid growth, registering an improved quality of life, a reduced mortality rate, and an increased median age. Unfortunately, this great progress also makes Malaysia highly prone to the diabetes epidemic (Yun *et al.*, 2007).

In order to properly manage the disease, patients with diabetes must comply with both dietary and pharmacologic therapy. Furthermore, given the chronic and costly nature of diabetes, it is important to know the best treatment strategy that leads to the best glycaemic control, i.e., the most dramatic reduction in HbA1c level. As the oral hypoglycaemic agents (OHAs) have limited range of HbA1c reduction, the combination of OHAs or concurrent therapy of OHAs with insulin is recommended to reduce the HbA1c level as far as possible (Kuritzky, 2006). The majority of type 2 diabetic patients, start bed time insulin because of the high morning fasting glucose levels, which related to the excessive glucose production overnight. Some elderly patients who have the higher levels during the afternoon may have better response to the morning insulin (Cutfield, 2009). The tight control will prevent or reduce the incidence of macrovascular and microvascular complications, thereby decreasing the burden on both the patients and the healthcare sector (Beck-Nielsen and Henriksen, 2007; Mathieu, 2009). The ratio of the diabetic patients who can achieve the target glycaemic control is varied from one population to another. This depends on many factors; the treatment and the patients compliance to the treatment are part of these factors. In Malaysia, there is a high proportion of patients with uncontrolled diabetes despite taking anti-diabetic therapy (Ismail *et al.*, 2000; Eid *et al.*, 2004; Sulaiman *et al.*, 2004; Mafauzy, 2006; Tan *et al.*, 2008). Two studies conducted elsewhere (Japan and the U.S) reported that the proportions of patients with good glycaemic control were more than those with poor glycaemic control (Kobayashi *et al.*, 2006; Wahba and Chang, 2007).

1.3 Research Questions

i. Are there any differences in the clinical outcomes (glycaemic control, blood pressure (BP), and lipid profile) achieved by the type 2 diabetic patients on different pharmacological regimens?

ii. Do complications and co-morbidities have effects on the clinical outcomes (glycaemic control, BP and the lipid profile) of the type 2 diabetic patients?

iii. Is there any association between the diabetes duration and each of the following: pharmacological treatment regimen, number of complications, and co-morbidities?

iv. Is there any difference in the glycaemic control achieved by patients on different doses of anti-diabetic agents?

1.4 Rationale of the Study

Given that each anti-diabetic agent can lower HbA1c levels to some extent, we must determine the best way to utilise these drugs to optimise their effects in treating diabetes. Three years after the diagnosis of diabetes, 50% of diabetic patients need more than one therapeutic agent to achieve sufficient glycaemic control. By nine years after diagnosis, 75% of diabetic patients will require multiple therapies to properly control their glucose levels (Turner *et al.*, 1999). Since patients on both SU and metformin monotherapy experience a deterioration of glycaemic control over time, β-cell failure may be a fundamental characteristic of type 2 diabetes and not the result of a specific therapy failure (Kimmel and Inzucchi, 2005). This statement may only be valid if the patient is compliant to the drug therapy.

ADA recommends metformin as the first-line treatment for type 2 diabetes (American Diabetes Association, 2008c). Also it recommends the use of additional agents including insulin, if the target glycaemic control is not achieved with metformin therapy. Early initiation of insulin therapy is recommended for patients who are losing weight or have severe hyperglycaemic signs (American Diabetes Association, 2008c). The consensus algorithm for the medical management of type 2 diabetes regarding the second medication added to metformin was to choose either insulin or SU. The HbA1c level will help to determine which agent is selected next (American Diabetes Association, 2008c; Nathan *et al.*, 2009). Also, the ADA cautioned against the use of thiazolidinediones (TZD), and did not include other medications (pramlintide, exantide, α-glucosidase inhibitors, glinides and dipeptidyl peptidase IV inhibitors) in its consensus algorithm due to their relatively lower efficacy (American Diabetes Association, 2008c). The AACE gave examples of treatment regimens for type 2 diabetes, and SU were their first choice in combination with metformin when HbA1c levels are 6%-7% (Rodbard *et al.*, 2007). Optimal second- and third-line therapies, as well as the best combinations of oral anti-diabetic agents (both with or without insulin therapy) must be identified in order to attain the desired glycaemic control in diabetic patients. To our knowledge, studies that investigated anti-diabetic therapies and glycaemic control among type 2 diabetes mellitus patients in Malaysia are very limited. This study aimed to evaluate the use of anti-diabetic therapies and to determine the level of glycaemic control in Malaysian type 2 diabetes mellitus patients.

1.5 Objectives of the Study

The main objective of this study was to evaluate the anti-diabetic medication regimens (including OHAs monotherapy, multiple OHAs, OHAs with insulin and insulin monotherapy) used at Penang General Hospital in relation to the clinical outcomes. The clinical parameters focused on include fasting plasma glucose (FPG), HbA1c, systolic BP, diastolic BP, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (TG) and total cholesterol.

Other specific objectives of the study are:

i. To evaluate the patient- and disease-related characteristics in relation to the glycaemic control.

ii. To determine the proportion of diabetic patients who achieved the target glycaemic control.

iii. To investigate the association between diabetes duration and each of the following: treatment strategies, number of complications and co-morbidities.

iv. To evaluate the incidence of diabetes related complications, diabetes co-morbidities, and changes in lipid profile and BP.

v. To determine the relationship between the changes of dose regimen of the anti-diabetic medications and the glycaemic control.

1.6 Significance of the Study

i. This study has an important implication for the Malaysian population not just with regard to the high prevalence of type 2 diabetes mellitus, but also with regard to the large number of patients with uncontrolled diabetes. These conditions will require the Ministry of Health in Malaysia to create many

programmes to guide diabetic patients to improve the management of the disease and quality of life.

ii. Physicians need to optimize drug therapy earlier in order to improve glycaemic control and delay the onset of diabetic complications.

iii. Uncontrolled diabetes may not necessarily be attributed to the progression of the disease or the failure of the treatment strategy; rather it may be due to the patients' non-compliance to drug therapy.

1.7 The Scope of the Study

This study focused on evaluation of type 2 diabetic patients who attended an out-patients clinic at Penang General Hospital, Malaysia.

CHAPTER 2

LITERATURE REVIEW

This chapter aims to review the relevant literature related to the types of diabetes mellitus, its signs and symptoms, diagnostic investigations, screening tests, diabetes prevalence and economic burden, and the strategies used in the management of the disease.

2.1 Background

Diabetes is a group of metabolic disorders characterized by an elevation in the blood glucose level that results from a deficiency in insulin production, insulin action, or both (Wild *et al.*, 2000; Centers for Disease Control and Prevention, 2007). Diabetes mellitus is considered a growing health problem, with patients experiencing a high incidence of morbidity, premature mortality, and disability. Furthermore, complications of the disease lead to a considerable amount of lost productivity, as well as an increased demand on the health care system (Ooyub *et al.*, 2004; Yun *et al.*, 2007). Although Type 2 diabetes likely results from an interaction between genetic predisposition, behavioural risk, and environmental risk (Qvist *et al.*, 2008; Brill, 2009).

Type 2 diabetes is one of the most common chronic diseases, and is associated with other health conditions, such as obesity, hypertension, cardiovascular disease (CVD), and hyperlipidaemia (American Diabetes Association, 2008a). The increase in the prevalence of type 2 diabetes is associated with the worsening obesity epidemic, as 90% of type 2 diabetic patients possess excess weight (Hossain *et al.*,

2007; American Diabetes Association, 2008a). Diabetes mellitus, which is accompanied by abnormalities in carbohydrate, fat, and protein metabolism, can cause acute health problems, such as hypoglycaemia and hyperglycaemia (American Diabetes Association, 2008a). Chronically, diabetes mellitus can cause both microvascular disease, including retinopathy, nephropathy, and neuropathy, as well as macrovascular diseases, such as ischemic heart disease, stroke, and peripheral vascular disease (American Diabetes Association, 2008a). All complications of diabetes lead to increased morbidity and premature mortality (Ministry of Health Malaysia *et al.*, 2004; Centers for Disease Control and Prevention, 2007).

2.2 Types of Diabetes

The ADA issued diagnostic and classification criteria in 1997, and modifications were made in 2003 regarding the diagnosis of impaired fasting glucose (IFG) (American Diabetes Association, 2008c). Diabetes mellitus includes four possible clinical classes as defined below.

2.2.1 Type 1 Diabetes

It was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. Type 1 diabetes is described by an absolute insulin deficiency due to the destruction of β-cells by the body's immune system. This type of diabetes usually strikes children and young adults, although onset of the disease can occur at any age. Diabetes mellitus type 1 in adults represents 5% to 10% of all diagnosed cases of diabetes (Centers for Disease Control and Prevention, 2007; American Diabetes Association, 2008c; American Diabetes Association, 2008a).

2.2.2 Type 2 Diabetes

It was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes. Type 2 diabetes is the result of improper insulin utilization by cells, either through a progressive insulin secretory defect or through the development of insulin resistance. Type 2 diabetes mellitus usually presents in older adults, although some children and adolescents have been diagnosed as well. Diabetes mellitus type 2 in adults represents 90% to 95% of the diagnosed cases of diabetes (Wild *et al.*, 2000; Centers for Disease Control and Prevention, 2007; American Diabetes Association, 2008a). As obesity contributes to the development of insulin resistance, most type 2 diabetic patients are obese (American Diabetes Association, 2008a).

2.2.3 Gestational Diabetes Mellitus (GDM)

A form of glucose intolerance that develops during pregnancy, GDM, requires treatment to normalize maternal blood glucose in order to avoid complications in the infant. After pregnancy, 5% to 10% of women with GDM are found to have diabetes mellitus, most likely type 2 diabetes. Women with a previous history of GDM have a 40% to 60% chance of developing diabetes in the next 5-10 years (Centers for Disease Control and Prevention, 2007; Rodbard *et al.*, 2007; American Diabetes Association, 2008a).

2.2.4 Other Specific Types

Other types of diabetes are due to genetic defects in β-cells function, genetic defects in the activity of insulin, diseases of the pancreas gland, and drugs or chemicals, including Human Immunodeficiency Virus (HIV) treatment or

immunosuppressants (Wild *et al.*, 2000; Triplitt *et al.*, 2005; American Diabetes Association, 2008c).

2.3 Pre-diabetes

Pre-diabetes refers to blood glucose levels that are higher than normal, but not elevated enough to be classified as diabetes. Patients with pre-diabetes have an increased risk of developing type 2 diabetes, heart disease, and stroke. Pre-diabetes is categorized as either IFG or impaired glucose tolerance (IGT), depending on the test used for identification: FPG test or the 75-g oral glucose tolerance test (OGTT) (World Health Organization Consultation, 1999; Zhang *et al.*, 2005; Grundy, 2006; Centers for Disease Control and Prevention, 2007; American Diabetes Association, 2008a).

2.4 Diagnosis, Screening, and Monitoring of Diabetes Mellitus

The ADA recommends using FPG test to diagnose diabetes in non-pregnant adults and children. Although the 75-g OGTT is more sensitive and specific than the FPG in diagnosing diabetes, it is also more difficult and cosier to use in practice (Gabir *et al.*, 2000; Rodbard *et al.*, 2007; American Diabetes Association, 2008c). However, the OGTT is used to screen pregnant women with a risk of developing diabetes (American Diabetes Association, 2008c; American Diabetes Association, 2008a). The HbA1c test is not recommended for the diagnosis of diabetes mellitus (American Diabetes Association, 2008a). However, this test reflects average blood sugar over several months and has a strong predictive value for future diabetic complications. Therefore, HbA1c should be used to monitor diabetic patients (Edelman *et al.*, 2004; American Diabetes Association, 2008c).

2.5 Testing for Pre-diabetes and Diabetes in Asymptomatic Adults

Type 2 diabetes has long presymptomatic phase until the patient is diagnosed. Testing is considered in patients with high risk including overweight (body mass index (BMI) 25-29.9 kg / m^2) and obesity (BMI ≥30 kg / m^2) (Colman *et al.*, 1999; American Diabetes Association, 2008a). Furthermore, patients who have the under-listed additional risk factors should also undergo screening for diabetes (Rodbard *et al.*, 2007; American Diabetes Association, 2008c; American Diabetes Association, 2008a):

- Irregular physical activity.
- A first or second degree relative with diabetes.
- High-risk ethnic groups such as non-Hispanic blacks, Hispanic / Latino Americans, Asian Americans, Pacific Islanders, American Indians and Alaska Natives.
- Women who had GDM or delivered a baby weighing > 9 lb.
- Patients with low HDL cholesterol or high TG.
- Clinical conditions associated with insulin resistance or signs of insulin resistance, example severe obesity, acanthosis nigricans, dyslipidaemia, hypertension, polycystic ovarian syndrome (PCOS).
- People with IFG or IGT in a previous test.
- History of CVD.
- Age ≥ 45 years.

Pre-diabetes detection is important and appropriate to prevent the progression of the pre-diabetes to diabetes and to decrease the risk of the disease complications (American Diabetes Association, 2008c).

2.6 Warning Signs and Symptoms of Diabetes

People with type 1 diabetes present with acute symptoms of diabetes and elevated blood glucose levels, so most cases are diagnosed directly after the onset of hyperglycaemia. On the other hand, type 2 diabetes is difficult to diagnose before the appearance of complications (American Diabetes Association, 2008a). Symptoms of extreme hyperglycaemia include: frequent urination; extreme hunger; unusual thirst; extreme fatigue; unusual weight loss; irritability; frequent infections; and blurred vision. Additionally, type 2 diabetic patients can experience: poor wound healing; tingling in the hands and feet; and repeated gum, skin, or bladder infections. Uncontrolled diabetes can cause acute life-threatening hyperglycaemia with ketoacidosis or non-ketotic hyperosmolar syndrome (World Health Organization Consultation, 1999; American Diabetes Association, 2008c; American Diabetes Association, 2008a).

2.7 Prevalence of Diabetes Mellitus

Diabetes mellitus is considered one of the most prevalent chronic diseases worldwide. The diabetes population is increasing steadily for numerous reasons, including population growth, aging, decreased physical activity, obesity, and urbanization (World Health Organization, 2000). Diabetes mellitus is recognized as one of the common non-communicable diseases worldwide, and is a major cause of mortality and morbidity (World Health Organization, 2000; Regional Committee, 2008). The incidence of type 2 diabetes is steadily increasing in Europe and the U.S., and has rapidly increased in Africa, Asia, and South America, making this disease an epidemic of public health significance (World Health Organization, 2000; Boyle *et al.*, 2001). Based on statistics from hospital data and routinely collected information;

Ministry of Health in Iraq show that non-communicable diseases represent the most leading cause of mortality (tenth leading cause) from five years old and over for the last past years (World Health Organization, 2006). They account for about 60% of deaths in Iraq (World Health Organization, 2006).

In 1995, the World Health Organization (WHO) estimated that 135 million individuals were diabetic. This number is projected to increase to 300 million people by 2025, with 42% of this increase occurring in developed countries (King *et al.*, 1998). In 1998, the WHO predicted a three-fold increase in the prevalence of diabetes mellitus in Asia by 2025. This dramatic increase will be felt not only in the larger nations, i.e., China and India, but also in rapidly developing Asian nations like Singapore and Malaysia (King *et al.*, 1998). The International Diabetes Federation (IDF) has estimated that the number of diabetic patients in 2003 and 2025 will be 194 million and 333 million, respectively (Zimmet *et al.*, 2003). Africans, Middle East populations, Asia, and Latin America had the highest rates of type 2 diabetes, with diabetics representing 98%, 97%, 91%, and 88%, respectively (Zimmet *et al.*, 2003).

According to the IDF report estimation in 2006 about 246 million people worldwide were diabetic, and that number was expected to increase to 380 million diabetic within the next 20 years, and more than 70% of this increase will be in the developing countries (International Diabetes Federation, 2006). Based on the 2006 IDF estimations, diabetes affected 67 million people in the Western Pacific, 53 million Europeans, 40.9 million people in India, and 39.8 million Chinese (International Diabetes Federation, 2006). High diabetes prevalence in 2007 were

reported in five countries which are Nauru (30.7%), United Arab Emirates (19.5%), Saudi Arabia (16.7%), Bahrain (15.2%), and Kuwait (14.4%) (International Diabetes Federation, 2006).

The prevalence of diabetes in the U.S. is increasing (5.6 million in 1980, to 6.6 million in 1990 and 8.1 million in 1994) (Centers for Disease Control and Prevention, 2008). In 2007, the total prevalence of diagnosed and undiagnosed diabetes in American adults and children was 23.6 million, or 7.8% of the population (Centers for Disease Control and Prevention, 2007). The prevalence of diabetes in patients ≥ 20 years was 23.5 million, equal to 10.7% of the total population. Fifty-seven million people were estimated to have pre-diabetes (Centers for Disease Control and Prevention, 2007).

The prevalence of diabetes mellitus in Malaysia has steadily increased over time. In 1960, 0.65% of Malaysians were estimated to have type 2 diabetes, but this number increased to 2% by 1982. According to the First National Health and Morbidity Survey (NHMS), the prevalence of diabetes mellitus in 1986 rose to 6.3% (Ministry of Health Malaysia, 1986). The Second NHMS, estimated that 8.3% of the Malaysian population had diabetes (Bakri, 2007). In 1993, another estimation for the diabetes prevalence in Malaysia showed that diabetes among adults was 8.2% in the urban areas and 6.7 % in the rural areas (World Health Organization, 2000). Furthermore, the Third NHMS, conducted between April and July 2006, estimated that 14.9% of the Malaysian population older than 30 years had diabetes. This shows that the diabetes prevalence in Malaysia has been increased much more than

expected by the IDF estimation which was 12.4% diabetes prevalence in 2025 (International Diabetes Federation, 2003; Zanariah *et al.*, 2008).

The prevalence of diabetic complications remain high, 10% of diabetic patients had kidney disease, and 50% developed nerve damage after having diabetes for over 25 years (Bakri, 2007). Diabetic patients are 2-4 times more likely to develop heart disease and about 27.7 times more likely to require leg amputation due to diabetic neuropathy (Bakri, 2007). In many Asian countries, stroke and renal disease are the most common causes of death among diabetic patients (World Health Organization, 2000). About 15,000-39,000 diabetic patients loss their sight over the course of their lifetimes. Hospital data confirm the complication rates in many of the diabetic patients (Bakri, 2007). Ten to 20 percent of diabetic patients have hypertension, while 29% have hypercholesterolemia. The prevalence of undiagnosed diabetes in Malaysia is estimated to be around 2.5% (NHMS II) (Bakri, 2007).

Diabetes mellitus is the 5th leading cause of death in most developed countries and the 7th leading cause of death in the U.S. (Centers for Disease Control and Prevention, 2007). However, lower mortality rates were reported in the poorest countries: Mongolia, Chile, Paraguay, Iceland, and highest in North America, the Eastern Mediterranean and Middle East, Mauritius and in the small Western Pacific island countries (International Diabetes Federation, 2006). In Malaysia, the mortality rate of diabetes increased by 50% from 1991 to 2001 (Ooyub *et al.*, 2004). Diabetes is considered the 6th most common cause of death in Singapore (Lee, 2000).

2.8 Economic Burden of Diabetes Mellitus

Because of the severity and chronic nature of its complications, diabetes mellitus is a costly disease for both the diabetic patient and the healthcare sector. The costs of diabetes include: direct cost to the patients and their families, direct cost to the healthcare sector, indirect cost to society (productivity cost), and psychosocial cost (Zhang *et al.*, 2003; Ooyub *et al.*, 2004).

In 2007, the estimated cost of caring for diabetic patients in the U.S. was 174 billion dollars (American Diabetes Association, 2008b). Direct and indirect medical costs in the U.S. attributable to diabetes in 2002 were 132 billion dollar (Hogan *et al.*, 2003). In 2003, the total cost of screening 54.4 million Americans for diabetes was 3.03 - 5.3 billion dollars, with the direct medical costs totalling 2.16 - 3.76 billion dollars. Pre-diabetes or undiagnosed diabetes cost 247 - 332 dollars per patient. While most screening strategies cost less than $200 per person, the best screening strategy, HbA1c, is also the most expensive (Zhang *et al.*, 2003).

In Australia, at least $720 million US were spent on diabetes healthcare in 1995 (World Health Organization, 2000). In 2005 WHO used econometric models to estimate diabetes, heart disease, and stroke which together cost 557.7 billion dollar in lost national income in China between 2005 and 2015, 303.2 billion dollar in India, 49.2 billion dollar; these are very large losses (International Diabetes Federation, 2006).

A Malaysian study in 2002 showed that the annual provider cost per diabetic patient was RM 185.97. However, the direct cost of each visit for one diabetic patient was RM 53.03 (Ooyub *et al.*, 2004). The cost of providing annual care to a diabetic

patient was 2.4 times greater than that provided to a non–diabetic patient of the same age, gender, and geographical location (Selby *et al.*, 1997). The primary care interventions for the chronic disease by public health policy are more costly than secondary and tertiary care interventions (Ramli and Taher, 2008).

2.9 Management of Diabetes Mellitus According to the American Guidelines

The appropriate components of care for diabetic patients include nutritional therapy, physical activity, weight management, pharmacological treatment, and self-management education. The target laboratory values signifying sufficient glycaemic control are: HbA1c $\leq$ 6.5%; FPG < 110 mg/dl (or < 6.1 mmol/l); and a 2-hour postprandial glucose concentration < 140 mg/dl (or < 7.7 mmol/l) (Rodbard *et al.*, 2007).

When a patient's HbA1c is between 6-7%, the physician should prescribe single OHAs. Additional medication is considered if monotherapy does not achieve sufficient glycaemic control within 2 - 3 months (Rodbard *et al.*, 2007). For an initial HbA1c between 7% - 8%, the patient should receive two anti-diabetic medications. If glycaemic control is not achieved within 2 - 3 months, the doses of the current medications can be increased, or additional medications can be added (Rodbard *et al.*, 2007). Metformin is recommended by the ADA as a first line oral anti-diabetic medication (American Diabetes Association, 2008c). Insulin therapy, either as a monotherapy or in combination with oral anti-diabetic agents, is considered when the patient's HbA1c levels are between 8% - 10%. At HbA1c levels greater than 10%, intense insulin therapy is strongly recommended (Rodbard *et al.*, 2007).

2.10 Management of Diabetes Mellitus According to the Malaysian Clinical Practice Guidelines

Diabetes management includes non-pharmacological and pharmacological therapies. Sufficient glycaemic control is considered achieved when the FPG level is between 4.4 – 6.1 mmol/l, and/or random plasma glucose is between 4.4 – 8 mmol/l, and/or the HbA1c level is less than 6.5% (Ministry of Health Malaysia *et al.*, 2004).

2.10.1 Non-pharmacologic Management

Non pharmacological management of diabetes mellitus include diabetes education and lifestyle modifications. The latter includes:

- **Diet Therapy:**

  Dietary management is an essential part of any diabetes management strategy. Even with medication, effective management of diabetes cannot be achieved without the proper diet (Franz, 1997; Ministry of Health Malaysia *et al.*, 2004).

- **Physical Activity:**

  Any increase in physical activity benefits diabetes management (Franz, 1997; Ministry of Health Malaysia *et al.*, 2004). Physical activity prevents and helps in the treatment of many established atherosclerotic risk factors, like high BP, insulin resistance and glucose intolerance, high TG levels, low HDL cholesterol and obesity. Exercise in addition to the weight loss can decrease LDL cholesterol and limit the reduction in HDL cholesterol (Stefanick *et al.*, 1998).

2.10.2 Pharmacologic Therapy

2.10.2(a) Oral Agent Monotherapy

If a newly diagnosed diabetic patient does not achieve sufficient glycaemic control within 1 – 3 months of the lifestyle modification, oral anti-diabetic agents (see section 2.11) should be started. Alternatively, oral anti-diabetic agents can be started in addition to lifestyle modifications in the type 2 diabetic patients, especially in those who present with complications (Ministry of Health Malaysia *et al.*, 2004).

2.10.2(b) Combinations of Oral Agents

Furthermore, if the patient does not reach the target glycaemic control within 3 months of a single medication, or if the HbA1c is greater than 10% upon diagnosis, multiple OHAs should be prescribed (Ministry of Health Malaysia *et al.*, 2004).

2.10.2(c) Combinations of OHAs and Insulin

If optimal doses of the maximal combination therapy do not achieve glycaemic control within 3 months, adding intermediate- or long - acting insulin is recommended. The combination of insulin and oral anti-diabetic agents has been shown to dramatically improve glycaemic control (Ministry of Health Malaysia *et al.*, 2004). Insulin can be combined with the following OHAs for patients with uncontrolled or severe type 2 diabetes:

- Biguanides (metformin).
- Insulin secretagogues: SU.
- Insulin sensitizers or TZD (the combination of a TZD and insulin is not an approved indication).

- α-glucosidase inhibitor, e.g., acarbose.

Insulin dose can be increased until the target FPG level is achieved (Ministry of Health Malaysia *et al.*, 2004).

2.10.2(d) Insulin Therapy

Insulin is a 51-amino acid peptide hormone first identified in 1921; it is synthesized and secreted by pancreatic beta cells (Wilcox, 2005). The first artificial insulin preparations come from cows and then from pigs; later in the early 1980s the human insulin produced using the Recombinant DNA technology (Vajo *et al.*, 2001). The use of insulin as anti-diabetic medication as reported in a study had no association with the mortality adjusted hazard ratio in comparing with other anti diabetic medications (Masoudi *et al.*, 2005). while another study suggested an increase in the mortality rate with insulin treatment (Murcia *et al.*, 2004).

- **Rapid Acting Insulin**

  Insulin lispro and insulin aspart, both of which are rapidly absorbed, are suitable at mealtime (Dewitt and Hirsch, 2003).

- **Short Acting Insulin**

  Regular insulin has a delayed onset of action of 30–60 min, and is therefore given 20-30 minutes prior to meals (Dewitt and Hirsch, 2003).

- **Intermediate Acting Insulin**

  Neutral protamine hagedorn (NPH) is an isophene insulin, and thus is absorbed slowly (Dewitt and Hirsch, 2003).

- **Long Acting Insulin**

  Ultralente insulin, which is a zinc-extended insulin, is released slowly, peaking at 20 to 24 hours (Dewitt and Hirsch, 2003).

2.10.2(d).1. Short-Term Use

Emergencies, stress, surgery, pregnancy, breast-feeding, acute illnesses, or any situation causing marked hyperglycaemia and severe metabolic decompensation (i.e., hyperosmolar non-ketotic coma, lactic acidosis, diabetic ketoacidosis, severe hypertriglyceridaemia) can necessitate the use of insulin as an initial therapy in type 2 diabetic patients (Ministry of Health Malaysia *et al.*, 2004).

2.10.2(d).2. Long-Term Use

If a patient receiving an optimal dose of combination therapy or insulin does not achieve sufficient glycaemic control, changing to a multi-dose insulin regimen can be considered. In this case, the patient would stop insulin secretagogues, but could continue taking insulin sensitizers like metformin and TZD (Ministry of Health Malaysia *et al.*, 2004).

2.11 Oral Anti-Diabetic Agents

There are five classes of oral anti-diabetic agents (Kimmel and Inzucchi, 2005; Joshi and Joshi, 2009). The first four classes are mentioned previously in (section 2.10.2.C.) and fifth class is insulin secretagogues – non-sulphonylureas (e.g., repaglinide, nateglinide). Recently, dipeptidyl peptidase-4 inhibitors (DPP–IV) and glucagon-like peptide-1 (GLP1) agents were registered for use in the U.S. and Europe (Joshi and Joshi, 2009).

2.11.1 Biguanides (Metformin)

Metformin is widely accepted as the first-line drug when instituting monotherapy. It is effective, safe, cheap, and is the only anti–diabetic drug to promote weight loss (Heine *et al.*, 2006; Joshi and Joshi, 2009). In trials versus a placebo, metformin was shown to reduce HbA1c by 1-2% and LDL cholesterol and TG by 0.12 - 0.26 mmol/L. Metformin had little effect on HDL cholesterol levels. UKPDS and other more recent trials demonstrated that metformin reduces diabetes-related death and diabetes related clinical end-points in diabetic patients more than patients receiving insulin and/or sulfonylurea (Uk Prospective Diabetes Study (Ukpds) Group, 1998a; Holman *et al.*, 2008). A Japanese study indicated that metformin had a potent anti–atherogenic effect in patients with type 2 diabetes (Katakami *et al.*, 2004). The prevalence of heart failure in patients using metformin is unknown, although published data suggest an incidence between 10 - 25% of patients receiving metformin (Kimmel and Inzucchi, 2005; Eurich *et al.*, 2007). Metformin is also associated with a lower rate of hospital admission compared to other anti-diabetic drugs. Metformin is approved as a monotherapy and can be used in combination with other oral anti-diabetic agents and/or insulin (Eurich *et al.*, 2007). The Diabetes Prevention Program data showed that in patients with IGT, use of metformin reduced the risk of diabetes progression over patients who made only lifestyle changes (31% versus 58%, respectively) (Diabetes Prevention Program Research, 2002).

2.11.2 Insulin Secretagogues – Sulfonylurea

SU are classified as either first or second generation, depending on their duration of action. Examples of the second generation SU group are glibenclamide,

gliclazide, and glipizide. Most of the clinical trials reported that SUs reduce HbA1c by 1.5 – 2% when used as monotherapy (Joshi and Joshi, 2009). Like metformin, these drugs are effective both as monotherapy and in combination with other anti-diabetic agents. There are no new data from prospective clinical trials on its vascular endpoints. Some retrospective analyses have even reported worse cardiovascular outcomes in patients taking SU agents compared to those taking metformin or TZD (Uk Prospective Diabetes Study (Ukpds) Group, 1998b; Johnson *et al.*, 2002). However, a recent meta-analysis indicated that SU are not associated with cardiovascular events (Heine *et al.*, 2006). Further complicating the issue, one study found that SU as monotherapy was associated with a worse outcome (all-cause mortality and all-cause hospitalization) (Eurich *et al.*, 2005), although another study refuted this association (Masoudi *et al.*, 2005). A Japanese study found that gliclazide, but not glibenclamide, had a potent anti-atherogenic effect in type 2 diabetic patients (Katakami *et al.*, 2004).

2.11.3 Insulin Secretagogues – Non-Sulfonylureas

Also known as glinides, non-sulfonylureas have different efficacies. This class of drugs includes repaglinide and nateglanide. Both drugs are approved as monotherapy and in combination with most other oral agents. Unlike SUs, these drugs can be used in patients with sulpha allergies. Unfortunately, these drugs have shorter half–lives and are more expensive than SU (Joshi and Joshi, 2009). Long-term outcomes data are unavailable; however, their effect on long term complication rates is likely to be similar to SU (Kimmel and Inzucchi, 2005).