ASSESSMENT OF THE CLINICAL TREATMENT OUTCOMES AND DIRECT MEDICAL COSTS AMONG TYPE 2 DIABETES MELLITUS OUTPATIENTS AT THE HOSPITAL UNIVERSITI SAINS MALAYSIA

by

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DEDICATION

This thesis is dedicated…….

The greatest person and greatest teacher in my life ……..

Prophet Mohammad

I would like to dedicate this work with lots of love and respect to my family

My father Selim Ibrahim Abougalambou, for giving me strength and support.

To my beloved mother Etidal Taha Ahamed, for her prayers, doa a, unflagging love, tremendous sacrifices, sufferings and pains. She was a constant source of inspiration to my life. Your supports have pulled me throughout my difficult times….

……to my best friends …..

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ACEI	Angiotensin Converting Enzyme Inhibitor
ADA	American Diabetes Association.
AGI	Alpha-Glucosidase Inhibitors
ALLHAT	The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALT	Alanine Aminotransferase Test
ANCOVA	Analysis of Covariance
AP	Asian- Pacific
ARBs	Angiotensin II Receptor Blockers
AST	Asparate Aminotransferase
ATP III	Adult Treatment Panel III
α-B	Alfa Blockers
β-B	Beta Blockers
BP	Blood Pressure
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCB	Calcium Channel Blockers
CDA	Canadian Diabetic Association
CHD	Coronary Heart Disease
CI	Confidence Interval
CPG	Clinical Practice Guideline
CrCl	Creatinine Clearance
CV	Cardiovascular

CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCCT	Diabetic Control and Complication trial
DECODE study	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe study
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
DN	Diabetic Nephropathy
ECG	Electrocardiography
ESRD	End Stage Renal Failure
ETDA	Ethylene Diamine Tetrachloroacetic
FDA	Food and Drug Administration
FFA	Free Fatty Acids
FLP	Fasting Lipid Profile
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GFR	Glomerular Filtration Rate
HbA1c	Glycosylated Hemoglobin
HDL-C	High Density Lipoprotein- Cholesterol
HMG-CoA	3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase
HMO	Health Maintenance Organization
HOPE study	Heart Outcomes Prevention Evaluation Study
HOT study	Hypertension Optimal Treatment Study
HPT	Hypertension
HUSM	Hospital Universiti Sains Malaysia

ID	Identification Number
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IHD	Ischemic Heart Disease
IQR	Inter - Quartile Range
JNC VII	Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure VII
KPP	Klinik Pakar Perubatan
LC-Co A	Long-Chain Coenzyme A
LDL-C	Low-Density Lipoprotein Cholesterol
LFT	Liver Function Test
MCPG	Malaysian Clinical Practice Guidelines
MCV	Macrovascular
MICRO-HOPE	Microalbuminuria, Cardiovascular and Renal Outcomes-HOPE.
MOH	Ministry of Health
MP	Malaysian Plan
NCEP	National Cholesterol Education Program
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Panel III
NDIC	National Diabetes Information Clearinghouse
NEFA	Non- Esterified Free Fatty Acids
NGSP	The National Glycohemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey
NHMS	The National Health Morbidity Survey
NIDDK	National Institute of Diabetes, Digestive and Kidney Diseases

NPH	Neutral Protamine Hagedorn
OADs	Oral Antidiabetics Drugs
OHA	Oral Hypoglycaemic Agent
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PPAR	Peroxisome Proliferator-Activated Receptor
PPG	Post Prandial Plasma Glucose
PR	Pulse Rate
Pre-HT	Prehypertension
PS software	Power and Sample Size Software
RFT	Renal Function Test
RM	Ringgit Malaysia
RM ANCOVA	Repeated Measure Analysis of Covariance
ROC	Receiver Operating Characteristic
ROS	Reactive Oxygen Species
SBGM	Self Blood Glucose Monitoring
SBP	Systolic Blood Pressure Level
SCR	Serum Creatinine
SD	Standard Deviation
SPSS	Statistical Package of Social Science
4S-STUDY	Scandinavian Simvastatin Survival Study (4S)
SU	Sulfonylurea
T2DM	Type 2 Diabetes Mellitus
TCH	Total Cholesterol
TG	Triglycerides.

TZDs	Thiazolidinediones
USM	Universiti Sains Malaysia
UKPDS	United Kingdom Prospective Diabetes Study
WC	Waist Circumference
WHO	World Health Organization

PENILAIAN KEBERKESANAN RAWATAN KLINIKAL DAN KOS PERBUATAN LANGSUNG DIKALANGAN PESAKIT-PESAKIT LUAR YANG MENGHIDAP PENYAKIT DIABETES MELLITUS JENIS 2 DI HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRAK

Diabetes mellitus kian menjadi masalah yang besar dalam kesihatan awam, terutamanya pada masa ini apabila sebahagian besar daripada perbelanjaan penjagaan kesihatan dilbelanjakan ka atas rawatan penyakit ini dan komplikasinya. kajian ini merupakan satu kajian cerapan bersifat prospektif terhadap pesakit diabetes jenis 2 yang betujuan untuk menilai modaliti rawatan ,kawalan glisemik, dan faktor-faktor yang berkaitan dengan perkembangan komplikasi makrovaskcular dan mikrovaskular penyakit tersbut, dan menilai kos perubatan langsung bagi merawat pesakit diabetes jenis 2 di Hospital Universiti Sains Malaysia (HUSM). Semua pesakit diabetes jenis 2 yang dating ke klinik diabetes HUSM dan mereka yang seterusnya diberi rawatan susulan di klinik tersebut dimasukkan dalam kajian ini.

Sejumalah 1077 orang pesakit yang menghidap diabete jenis 2 telah dimasukkan ke dalam kajian ini, dengan julat umur mereka antara 18 hingga 88 tahun, dan umur median 58 tahun. Majoriti pesakit terdiri daripada wanita, dan kurang daripada separuh pesakit-pesakit itu mempunyai sijil tinggi persekolahan. Tempoh min diabetes ialah 11.2 tahun, min HbA1c ialah 8.7%, manakala min tahap glukosa darah berpuasa ialah 7.8 mmol/L, dan glukosa plasma pascaprandial ialah10.0 mmol/L.

Kajian in telah mendapati bahawa 26.3% daripada pesakit – pesakit mempunyai kawalan optimum (HbA1c$\leq$ 7.0%) dan 73.7% mempunyai kawalan yang tidak mencukupi (HbA1c > 7%). Pada keseluruhannya, 747 pesakit (69.4%) diberikan rawatan ubat antidiabetik bersama makanan, manakala 30.6% diberikan suntikan insulin semata-mata, atau suntikan bersama agen hipoglisemia. Kajian juga mendapati faktor-faktor yang mempengaruhi tahap HbA1c terdiri daripada umur, bangsa dan rawatan antidiabetes. Bagaimanapun, faktor-faktor yang mempengaruhi glukosa plasma berpuasa adalah umur dan merokok, manakala faktor-faktor yang mempengaruhi glukosa plasma pascaprandial adalah gender dan tempoh menghidap

diabetes. Tambahan lagi, kajian ini telah mendapati bahawa faktor-faktor berubah yang mempengaruhi perkembangan komplikasi makrovaskular terdiri daripada umur, tahap pendidikan, indeks jisim badan (BMI), lilitan pinggang, rawatan antidiabetes, tekanan darah diastolik, dan kolesterol. Bagaimanapun, komplikasi mikrovaskular dipengaruhi oleh umur, trigliserid dan klearans kreatinin.

Retinopati berlaku pada kadar 39% dalam kalangan pesakit-pesakit yang dikaji, dan mereka yang dipengaruhi oleh tempoh penyakit tersebut, neutropati, trigliserid, dan klearans kreatinin. Kejadian neuropati adalah 54.7%, dan faktor risiko utama mereka ialah tempoh menghidap diabetes, dan wujudnya retinopati, bertambahnya HbA1c dan klearans kreatinin. Nefropati telah dikesan delam 90.7% daripada pesakit- pesakit, dipengaruhi terutamanya oleh gender, trigliserid dan klearans kreatinin.

Hasil kajian ini juga menunjukkan bahawa hipertensi berlaku dalam 92.7% daripada pesakit yang dikaji, dan hanya 47.2 % daripada mereka mencapai sasaran tekanan darah yang optimum. Daripada sejumlah itu, 104 (22.1 %) mendapat rawatan ACEI, 76 (16.1 %) mendapat rawatan ARB dan CCB, 72 (15.3 %) mendapat rawatan gabungan ACEI dan CCB.

Daripada keputusan awal, dapatlah disimpulkan bahawa banyak protokol pengurusan telah gagal untuk mencapai dan mengekalkan tahap glisemik yang optimum. Terapi antidiabetis boleh memperbaiki glisemia, tetapi perbezaan dalam kalangan rawatan antidiabetes yang berlainan didapati tidak signifikan. Intervensi secara betul diperlukan untuk mengubah rawatan dan mencapai kawalan glisemik yang lebih baik. Untuk mengurangkan atau menangguhkan perkembangan komplikasi vaskular, strategi yang betul diperlukan bagi pengesanan awal, dan rawatan yang agresif terhadap faktor-faktor risiko boleh diubah suai termasuk menggunakan rawatan-rawatan antidiabetes, antihipertensi, antidislipedemia, dan antiplatelet. Bagi retinopati,neuropati, dan nefropati strategi kesihatan awam diperlukan untuk mengurangkan kesan faktor risiko, dan mengurangkan komplikasi-komplikasi tersebut. Kadar prevalens hipertensi adalah sangat tinggi, dan tekanan darah lebih daripada separuh pesakit-pesakit itu adalah di luar kawalan.

Hasil kajian ini menunjukkan bahawa kos tahunan purata rawatan pesakit luar adalah RM 1730.7 bagi seorang pesakit, dengan kos minimum sebanyak RM 546 bagi seorang pesakit, dan maksimumnya RM 5432.8. Daripada jumlah keseluruhan kos rawatan, 59.2 % (RM 1023.9) meliputi kos ubat-ubatan, 31.1% (RM 537.41) dibelanjakan ke atas kos penyelidikan makmal, 7.1 % (RM 124.28) meliputi kos tahunan lawatan ke klinik, dan 2.6% (RM 45.15) meliputi kos personel perubatan. Tahap glukosa darah yang terkawal baik akan dapat mengurangkan kos rawatan jagaan diabetes, justeru, dapat mengurangkan kos rawatan pesakit luar. Banyak perhatian dan usaha seharusnya ditujukan kepada mendapatkan pengetahuan tentang beban ekonomi diabetes di HUSM dan di hospital-hospital lain.

Kata kunci: Diabetes mellitus jenis2, Kos perubatan langsung, Hipertensi, Retinopati, Nefropati, komplikasi makrovaskular.

ASSESSMENT OF THE CLINICAL TREATMENT OUTCOMES AND DIRECT MEDICAL COSTS AMONG TYPE 2 DIABETES MELLITUS OUTPATIENTS AT THE HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRACT

Diabetes mellitus (DM) is becoming a major public health problem, especially now that a large proportion of health care expenditure is being spent on the treatment of this disease and its complications. This was a prospective observational study of diabetes type 2 patients with the objectives of assessing the treatment modalities, glycaemic control and the factors associated with the development of macro and microvascular complications, and evaluating the direct medical costs of treating diabetic type 2 patients at the Hospital Universiti Sains Malaysia (HUSM). All of the type 2 diabetes patients who attended and were followed-up at the HUSM diabetes clinic were included in this study.

A total of 1077 patients with type 2 diabetes were recruited for this study, with ages ranging from 18 to 88, and a median age of 58 years. The majority of the patients were female, and less than half of the patients had more than high school certificates. The mean duration of diabetes was 11.2 ($\pm$6.81) years, the mean glycosylated haemoglobin (HbA1c) was 8.7% ($\pm$2.34), the mean fasting blood glucose level was 7.8 mmol/l ($\pm$3.72), and the mean postprandial plasma glucose level was 10.0 mmol/l ($\pm$4.38).

It was found that 26.3% of the patients had optimal control (HbA1c $\leq$7%) and that 73.7% had inadequate control (HbA1c >7%). Overall, 747 patients (69.4%) were on oral antidiabetes medications, whereas 30.6% were on insulin injections, alone or with oral hypoglycaemic agents. The factors that influenced HbA1c levels were found to be age, race and antidiabetic medication. However, the factors that influenced fasting plasma glucose were age and smoking while the factors that influence postprandial plasma glucose were gender and duration of diabetes. Furthermore, it was found that the variable factors influencing the development of macrovascular complications were age, education level, body mass index (BMI), waist circumference, antidiabetic medication, diastolic blood pressure (BP), and

cholesterol level. However, microvascular complications were influenced by age, triglycerides, and creatinine clearance rate.

Retinopathies appeared at the rate of 39% among the study patients, and these were influenced by duration of the disease, neuropathies, triglycerides and creatinine clearance rate. The prevalence of neuropathies was 54.7%, and their main risk factors were duration of diabetes, the presence of retinopathies, and increased levels of HbA1c and creatinine clearance rate. Nephropathies were detected in 90.7% of the patients and were mainly affected by gender and creatinine clearance rate.

The present findings also show that hypertension was prevalent in 92.7% of the study patients, and only 471 (47.2%) of them achieved the optimal blood pressure targets. Of those, 104 (22.1%) were on angiotensin converting enzyme inhibitors (ACEI), 76 (16.1%) were on angiotensin receptor blockers (ARB) and calcium channel blockers CCB, and 72 (15.3%) were on combinations of ACEI and CCB.

From the initial results it was concluded that numerous management protocols have failed to achieve and maintain proper glycaemic levels. Antidiabetic therapy can improve glycaemia, but the differences between the different antidiabetic medications were not significant. Intended medication interventions are required to alter treatments and achieve better glycaemic control. In order to reduce or delay the development of vascular complications, proper strategies are required for early detection and aggressive treatment of the modifiable risk factors, including the appropriate use of antidiabetes, antihypertension, antidyslipidaemia, and antiplatelet treatments. For retinopathies, neuropathies, and nephropathies, public health strategies are required in order to reduce the risk factor effects, and reduce their prevalence. Early detection and appropriate management can reduce the burden of these complications. The prevalence rate of hypertension was very high, and the BP of more than half (527) of the patients was out of control.

The current findings revealed that the average annual direct medical cost of outpatient treatment was RM 1730.7 per patient, with a minimum cost of RM 546 per patient, and a maximum of RM 5432.8. Of the total treatment cost, 59.2% (RM 1023.9) covered the cost of the medications, 31.1% (RM 537.41) the cost of laboratory investigations, 7.1% (RM 124.28) covered the cost of annual visits to the

clinic, and 2.6% (RM 45.15) covered the cost of medical personnel. Good control of blood glucose levels leads to decreased treatment costs in diabetes care, and hence a decrease in outpatient treatment costs. More attention and efforts should be directed towards gaining knowledge of the economic burden of diabetes in HUSM and elsewhere.

Key words: Type 2 Diabetes mellitus, Direct Medical Cost, Hypertension, Retinopathy, Nephropathy, Macrovascular Complications.

CHAPTER ONE

INTRODUCTION

1.0 Introduction

1.1 Background

Diabetes mellitus is a disease affecting nearly 10% of the global population above 20 years of age. Type 2 diabetes mellitus (type 2 DM) is the most prevalent form of diabetes. It accounts for about 90% to 95% of all Diabetes Mellitus (DM) cases and particularly affects overweight individuals usually over 40 years of age (Canadian Diabetic Association, 2005). Although a disease of adults, type 2 DM is now being diagnosed more frequently in children and adolescents (Canadian Diabetic Association, 2005). Type 2 DM is often part of a metabolic syndrome that includes obesity, elevated blood pressure and high levels of blood lipids.

Type 2 DM is a chronic, progressive disease characterized by insulin resistance and pancreatic β-islet cell failure. Three specific abnormalities contribute to hyperglycemia in type 2 DM: impaired insulin secretion, increased hepatic glucose production, and decreased insulin-stimulated uptake of glucose in peripheral tissues. In type 2 DM, the early phase of insulin secretion is lost, mainly resulting in the characteristically increased postprandial glucose. Increased insulin resistance also frequently occurs in people who are obese, and is associated with the metabolic syndrome (Evans and krenz, 2001).

The progressive aging of the world's population, resulting from better control of communicable diseases and improved nutrition and hygiene, has also played an important role in the marked increase in non-communicable diseases such as type 2 DM. The increase of prevalence and incidence of diabetes are attributable to several factors including the aging population, urbanization, sedentary lifestyles increased survival rates, and continued and increasing rates of obesity (Motala et al., 2003).

Type 2 DM is a major and growing health problem in most countries (Harris et al., 1998) that causes considerable loss due to disability, premature mortality and loss of productivities. Diabetes is in fact a serious vascular disease with poor prognosis, and that it is not only a disease characterized by elevated blood glucose (Marja-Ritta et al., 2002). Type 2 DM is already the leading cause of blindness among working-age adults, of end-stage renal disease and of non-traumatic loss of limb (Ulbrecht et al., 2004; Williamson et al., 2004). The American Diabetes Association (2008) reports that this disease is the fifth leading cause of death by disease in the United States. The consequences of persistant hyperglycemia can cause serious damage in nerves and blood vessels, the latter leading to macro- and microcomplications. Ragucci et al. (2003) reported that patients with diabetes mellitus carry an increased risk of two to four times greater for heart attack, stroke and other complications related to poor circulation. These complications can be reduced by normalisation of glucose levels (The diabetes control & complication trial research group, 1993; United Kingdom Prospective Study Group, 1998) this normalisation being the ultimate focus of all diabetes treatments. The overall treatment of type 2 DM is to prevent acute and chronic complications while maintaining a high quality of life.

As the disease progresses, many patients with type 2 DM will eventually be unable to adequately achieve or maintain glycaemic control, even through monotherapy or combination of oral therapies are employed. The reason for diminishing antihyperglycaemic effects with oral agents over time is multifactorial and includes progressive loss of β-cell function (Turner et al., 1999; Wright et al., 2002), comorbidities, lifestyle factors, and possibly glucotoxicity (Kuritzky, 2006). In most cases, patients on oral antidiabetic therapy will require not only an increase

in dosage but also the addition of a second or third oral agent (Banerjee and Singh, 2002). As the number and dosage of oral antidiabetic medications increases, the side effect profile, regimen complexity, and expenses rise commensurately.

1.2 Prevalence of diabetes in the world

Type 2 DM is rapidly rising as a global health care problem that threatens to reach pandemic levels by 2030. In 2003, an estimated 194 million (5.1%) adults had diabetes worldwide and 314 million (8.2%) people had impaired glucose tolerance (Sicree et al., 2003). This prevalence increased to 6.0 % and 7.5 % in 2007 and is predicted to increase to 7.3 % and 8.0 % by 2025 (Sicree et al., 2006). 380 million people are expected to have diabetes in 2025 (Sicree et al., 2006).

The prevalence of diabetes is higher in developed countries than in developing countries, but the developing world may be hit hard by the escalating diabetes epidemic in the future. Increased urbanisation and economic development in developing countries have already contributed to a substantial rise in diabetes (WHO, 2003). This is likely to continue and will be a significant factor in the forthcoming global epidemic of diabetes. While diabetes is most common among the elderly in many populations, prevalence rates are rising at an alarming rate among comparatively young and productive populations in the developing world (International Diabetes Federation, 2005).

1.3 Prevalence of diabetes in Asia

Asia is the major site of a rapidly emerging diabetes epidemic (Wild et al., 2004; Sicree et al., 2006). Roughly 80% of people with diabetes are in developing countries, of which India and China share the largest contribution (Ramachandran et

al., 2009). Traditional estimates based on population growth and ageing and rate of urbanisation in Asia show that India and China will remain the two countries with the highest numbers of people with diabetes 79.4 million and 42.3 million, respectively by 2030 (Wild et al., 2004). The further rapidly developing Asian nations like Singapore, Malaysia, Thailand and those making up Indochina will experience the surge (Zaini, 2000).

1.4 Diabetes in Malaysia

In Malaysia, the Third National Health and Morbidity Survey (NHMS III, 2006) showed that prevalence of type 2 DM for adults aged 30 years old and above was found to be 14.9 % in 2006, upped by almost 79.5% in the space of 10 years from 1996 to 2006.

In Malaysia, there is a growing public concern due to the escalation with number of people with diabetes while complication rates and associated diseases amongst diabetics are high. In addition, high prevalence of complications such as blindness, end stage renal disease, lower extremity amputations as well as premature cardiovascular disease, stroke and premature mortality related to poor control of blood glucose (Mafauzy, 2005).

Malaysia has a multiethnic population is expected to reach around 33.7 million by the 2020. The three main racial components of this region are Malays, Chinese and Indians are well represented in this country. If China and India are balanced to exceed the world's prevalence rate of type 2 DM, their respective counterparts in Malaysia may be much worse. The evidences so far indicate that the migrant status as well as socioeconomic and lifestyle changes are strong indicators to diabetes (National Health and Morbidity Survey, 1996).

1.5 Effectiveness of treatment in diabetes

Improved glucose control can improve long-term outcomes. Within the last decade, new treatments and glycaemic goals have created an opportunity to better manage this prevalent chronic disease.

For the purpose of evaluating the treatment outcomes and complications, several studies have evaluated percentage of diabetic control with each regimen drugs. The United Kingdom prospective diabetes study 33 (1998) demonstrated that each percentage point reduction in HbA1c was associated with a 35% reduction in microvascular complications, a 25% reduction in diabetes-related deaths and a 7% reduction in all cause mortality. The evaluation should review the previous treatments, and the past and present degrees of glycaemic control. Laboratory tests suitable to the evaluation of each patient's medical condition should be performed (American Diabetes Association, 2006 and 2007). Vivian and Ali (2000) suggested that combination treatment with once daily metformin, rosiglitazone improves glycaemic control, insulin sensitivity, and β-cell function more effectively than treatment with metformin alone. Acarbose was shown to be an effective addition therapy in combination with insulin. After 24 weeks of treatment, HbA1c was reduced by 0.40%, and insulin requirements were considerably lowered in patients in whom acarbose was added to their insulin regimen versus those remaining on insulin monotherapy (Coniff et al., 1995).

1.6 Economic burden of type 2 diabetes mellitus

1.6.1Economic cost of type 2 diabetic mellitus

The exact costs of diabetes are not easy to pin down but estimations can be obtained according to 3 levels which include:

1. Cost directly linked to the diagnosis and management of diabetes without complications.
2. Costs generated by complications of diabetes. These are difficult to quantify because diabetes is linked to micro and macro vascular diseases such as heart disease, kidney failure, eye disease and amputation. Moreover, diabetes may add a cost of care by complicating other unrelated medical situations like infections, accidents and surgery.
3. Indirect costs correlated with the quality of life and the economic productivity which can be somehow estimated by the degree of disability.

The direct healthcare costs of diabetes are high and are continuing to rise. They are rising because the prevalence of diabetes is increasing, and treatment is becoming more sophisticated and polypharmacy is becoming more common. It is suspected that direct healthcare costs for the diabetic disease already dominate healthcare budgets, particularly in developed countries and increasingly in developing countries (Williams, 2005). It is now well recognized that preventing or delaying the onset of type 2 DM results in considerable cost reduction.

There are many reasons for studying the economic burden of diabetes. Firstly, diabetes is costly especially in direct medical costs. Secondly, resources that can be devoted to prevention and control of diabetes are limited because of the "opportunity cost" of doing so. Thirdly, the need for resources will continue to increase because of the increasing prevalence of diabetes and thus, demand for comprehensive care and new treatments. These estimates do not include the cost of undiagnosed diabetes. Neither do they include the size of immeasurable costs, such as human pain and suffering (American Diabetes Association, 2003).

Research from Costa Rica by Morice et al. (1999) showed that people with diabetes made 1.55 times more medical visits than people without diabetes. Wong et al. (2002) showed that the treatment costs can be brought to a minimum without affecting effective diabetes care with good control of blood glucose level which leads to a sharp decrease in consultation and treatment procedures, hence, reducing the outpatient treatment.

Type 2 DM is a serious and expensive disease and one key issue in reducing costs is most certainly to address the associated late complications at an early stage. Comprehensive diabetes disease management program should improve patient outcomes, decrease costs, and ensure member and provider satisfactions. Although medication treatment costs are increased by combination therapy, this cost is expected to be partially balanced by a reduction in the costs of treating long-term diabetes complications (Ward et al., 2004).

1.6.2 Cost management of type 2 diabetes mellitus

Diabetes mellitus is a chronic disease that has been recognized by the Malaysian government as a major public health problem with far reaching consequences not just for its adverse impact on the health of Malaysians, but also for the economic burden it places on the health care system. Diabetes mellitus presents a high burden for individuals and society. This burden is not only related to health care costs, but also to indirect costs caused by loss of productivity from disability and premature mortality. Medical expenditures for people with diabetes are 2–3 times higher than that for those not affected by diabetes (Rubin et al., 1994).

Effective disease management programmes that aim to prevent complications could potentially lead to cost savings in managed care settings (Selby et al., 1997).

Hayward et al. (1997) found that patients taking insulin had 2.4 more diabetic outpatient visits, used 300 more glucose test strips, and had slightly higher laboratory costs per year than patients receiving sulphonylureas.

Johnson et al. (2006) found that metformin, alone or in combination, was the most frequently dispensed oral antidiabetic medication. A longer duration of diabetes was associated with increased use of oral medications and insulin therapy. Insulin was used in approximately 12% of patients with type 2 DM and was associated with approximately three times higher expenditure on diabetes testing supplies compared with patients on oral antidiabetic medications (Johnson et al., 2006).

1.7 Research questions:

The questions to be examined in this study are as follows:

- What is the most regimen of antidiabetic medication that achieved target glycaemic control?
- What are the factors affecting the glycaemic control?
- What are the factors that play a role in macrovascular complications development?
- What are the factors that enhance the microvascular complications?
- What are the factors that enhance the retinopathy, neuropathy and nephropathy complications?
- What are the prevalence and control levels of hypertension in diabetic patients?
- What are the antihypertensive drug regimens which lead to achievement of the targets of treatment among diabetic patients?
- What are the annual direct medical costs of type 2 diabetic treatment?

1.8 Rationale of the study

As highlighted earlier, the management of type 2 DM is always challenging for both patients and clinicians. Therefore, it is imperative to document the effectiveness of the treatment modalities available for controlling diabetes mellitus in Malaysia. This study was rationalized by some emerging facts about type 2 DM in Malaysia. The high prevalence of diabetes is associated with poor glycaemic control and a high rate of complications. This study will provide good baseline data about the current status of diabetic patients at the Hospital Universiti Sains Malaysia (HUSM) concerning the degree to which they control their glucose level. Knowledge of patients glucose status included {glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) & postprandial plasma glucose (PPG)}, body mass index (BMI), lipid profile [triglycerides (TG), low density lipoproteins (LDL), total cholesterol, high density lipoproteins (HDL)}, and blood pressure will help decision makers in evaluating the current epidemic level of diabetes at the HUSM.

Understanding the effectiveness of antidiabetes medications along with the factors of glycaemic control on the development of complications may allow planners to draw up proper plans for the overall improvement of this disease.

1.9 Significance of the study

This study followed and evaluated the outcomes of diabetic patients on antidiabetic medications over a period of one year. The effectiveness of antidiabetic medications and the annual direct medical costs in one year were also evaluated. Therefore, this study may also help in the assessment of the economic burden of type 2 DM in the HUSM in general. Previous studies have reported on the factors influencing glycaemic control and microvascular and macrovascular complications,

but these studies were limited, only mentioned a few factors, and did not follow-up the patients. Hence, a large scale multifactorial study was needed. To the best of our knowledge, there are no reports on the Asian population which extensively studied the factors influencing glycaemic control and micro and macrovascular complications. Furthermore, the current study also took into account clinical outcomes from an economic perspective, which gives this study an important edge as it could be used to draw a road map for the clinical treatment and costs of treatment for type 2 DM. It estimated the annual budgetary impact on treating type 2 DM. The main aims of this study were to obtain a profile of type 2 DM patients in the HUSM in order to assist in type 2 DM management programmes and to provide data for an economic evaluation. Accordingly, this study will provide a rough estimate of the direct medical costs incurred in the treatment of type 2 DM from the perspective of the HUSM management. This study also provides data about the prevalence and prescribing patterns of drugs used in treating this disease and it was also designed to help predict future consumption patterns.

1.10 Study objectives

1.10.1 General Objectives

To evaluate clinical treatment outcomes of type 2 diabetic patients and estimate the annual direct medical costs of type 2 diabetic outpatients at Hospital Universiti Sains Malaysia (HUSM) in year 2008.

1.10.2 Specific objectives

1. To evaluate the following parameters: glycaemic control (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), body mass index (BMI), waist circumference (WC), low density lipoprotein (LDL-C), high-density lipoprotein, (HDL-C), total cholesterol, triglyceride and blood pressure in diabetic patients attending outpatient clinics in HUSM.

2. To compare the effectiveness of various antidiabetic regimens with regards to achievement of treatment targets (through glycaemic control).

3. To evaluate the factors influencing glycaemic control which include personal characteristics and health characteristics. Personal characteristics include age, gender, race, smoking history, alcohol consumption history, physical activity, education level and family history and health characteristics include BMI, WC, duration of diabetes, patterns of diabetic medications which affect glycaemic control (HbA1c, FPG & PPG).

4. To evaluate the factors that lead to the enhanced development of macrovascular complications, such as personal characteristics, health characteristics and clinical

variables (HbA1c, FPG, PPG, BMI, WC, LDL-C, HDL-C, total cholesterol, triglycerides, blood pressure, and creatinine clearance rate.

5. To evaluate the factors that lead to the development of microvascular complications, such as personal characteristics, health characteristics and clinical variables (HbA1c, FPG, PPG, BMI, WC, LDL-C, HDL-C, total cholesterol, triglycerides, blood pressure, and creatinine clearance rate.

6. To evaluate the factors that lead to the enhanced development of retinopathy, neuropathy and nephropathy complications, such as personal characteristics, health characteristics and clinical variables (HbA1c, FPG, PPG, BMI, WC, LDL-C, HDL-C, total cholesterol, triglycerides, blood pressure, and creatinine clearance rate.

7. To determine prevalence and control of hypertension among diabetic patients attending the outpatients clinics at HUSM.

8. To calculate the annual direct medical costs among type 2 diabetes mellitus patients at Hospital Universiti Sains Malaysia.

CHAPTER TWO

PART ONE: ASSESSMENT OF THE CLINICAL TREATMENT OUTCOMES OF TYPE 2 DIABETES MELLITUS OUTPATIENTS AT THE UNIVERSITI SAINS MALAYSIA

2.1 Background

The main focus of this literature review is on type 2 DM outpatients. The purpose of the review will be to focus on research been done in the following areas:

1) The background about type 2 diabetes disease.
2) Clinical variable characteristics of type 2 diabetes patients.
3) The factors that exert effects on glycaemic control.
4) Effectiveness of antidiabetic medications.
5) The factors related to macrovascular complications.
6) The factors related to microvascular complications.
7) The factors related to retinopathy, neuropathy& nephropathy.
8) Hypertension in patients with type 2 DM.

Diabetes is one of the most growing public health problems which cause major morbidity and mortility cases all over the world. Centre for Disease Control and Prevention (2006) described diabetes as an 'epidemic of our time that threatens to spiral out of control unless early, focused preventative actions are taken'. The challenge for health professionals and governments encompasses economic, social, and health planning in developed nations as well as in newly developed or developing countries, irrespective of culture or location.

2.2 Definition of type 2 diabetes mellitus

Type 2 diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia caused by defects in insulin production, action or both (National Diabetes Information Clearinghouse, 2008). Symptoms of diabetes mellitus include frequent urination (polyuria), excessive thirst (polydipsia), extreme hunger

(polyphagia), unusual weight loss, increased fatigue, irritability and/or blurry vision (American Diabetic Association, 2003).

2.3 Diagnosis and classification of diabetes mellitus

Diagnoses of diabetes according to the American Diabetic Association (2007) criteria for the diagnosis of diabetes mellitus are as follows;

1. FPG ≥126 mg/dl (7.0 mmol/l).
2. Symptoms of hyperglycemia and casual plasma glucose ≥ 200 mg/dl (11.1mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
3. Two hours plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

2.4 Epidemiology of type 2 diabetes mellitus

Type 2 DM is usually preceded by a long period of asymptomatic hyperglycemia that may last for years. In this prediabetic state, postprandial levels are mildly elevated whereas fasting blood glucose can usually be maintained within the near-normal range. The elevation of postprandial levels is used for the definition of impaired glucose tolerance (IGT), a nonspecific reversible stage. About 30% of these subjects progress to overt diabetes within 10 years (Unwin et al., 2002). Elevation of fasting glucose is used for the definition of impaired fasting glucose (IFG). In some individuals β-cells compensate for insulin resistance by increased insulin secretion, and type 2 DM does not develop. However, in a large number of

prediabetic individuals, multiple defects in insulin action and /or insulin secretion gradually lead to sustained hyperglycemia. As a consequence of insulin resistance, the β-cell produce increased amounts of insulin, and compensatory hyperinsulinemia maintains normoglycemia. When β-cell compensation to insulin resistance fails, decompensated hyperglycaemic state develops. Thus, type 2 diabetic subjects have relative insulin deficiency. Usually such individuals do not need insulin treatment to survive.

Epidemiological studies had already identified "diabetes epidemic" in 1970s. Bennett et al. (1971) was reported that the extremely high prevalence of type 2 DM in Pima Indians and also in the Micronesian Nauruans in the Pacific (Zimmet et al., 1977), and subsequently in other Pacific and Asian island populations (Zimmet, 1992). These studies showed that transition from traditional lifestyle to western way of life resulted in obesity, lack of exercise, changes in the diet, and finally to type 2 DM. Several studies have shown that type 2 DM has reached epidemic proportions in several developing countries as well as in Australian Aboriginals (O'Dea et al., 1991), African Americans, and Mexican Americans (Burke et al., 2001). Large variations in the prevalence of type 2 DM in different populations can be attributed to environmental as well as genetic determinants.

Lately, type 2 DM was regarded as a disease of the middle-aged and the elderly. However, evidence is accumulating that onset in subjects aged under 30 years is increasing. Even children and adolescents are diagnosed to have type 2 DM (Alberti et al., 2004) for example, among the children in Japan type 2 DM is already more common than type 1 and accounts for 80% of childhood diabetes (Kitagawa et al., 1998). In the United States between 8% and 45% of newly presenting children and adolescents have type 2 DM (Laakso, 2008).

An epidemic of type 2 DM is determined not only by an increase in the incidence but also by mortality rates. Although cardiovascular complications in nondiabetic subjects have significantly reduced in the United States during the last decades this is not the case in diabetic patients, particularly among women, (Gu et al., 1999).

2.5 Risk factors for type 2 diabetes mellitus

The identification of risk factors is essential for the successful implementation of primary prevention programs. Risk factors for type 2 DM can be classified as modifiable and nonmodifiable (Table 2.1). Subjects who subsequently develop diabetes have multiple adverse changes in risk factor levels.

Table 2.1.Risk factors for type 2 DM

Modifiable	Non modifiable
Obesity	Ethnicity
Central obesity	Age
Lack of physical activity	Sex
Smoking	Genetic factors
Alcohol abstinence	Family history of type 2 DM
Low fiber in the diet	Prior gestational diabetes
High saturated fat in the diet	Prior glucose intolerance
	History of cardiovascular disease
	History of hypertension
	History of dyslipidaemia
	Low birth weight

Source: Laakso (2008) page 7.

2.5.1 Modifiable risk factors

Visceral adiposity leads to the development of type 2 DM. The obesity is risk factor for developing type 2 DM. Boyko et al. (2000) in their study of Japanese Americans patients showed that intra-abdominal fat area remained a significant predictor of diabetes incidence even after adjustment for body mass index, total body fat area, and subcutaneous fat area and other risk factors for diabetes. Interestingly, high insulin resistance and low insulin secretion predicted diabetes independently of directly measured visceral adiposity suggesting that visceral adiposity could contribute to the development of diabetes through actions independent of its effect on insulin sensitivity. Van Dam et al. (2001) reported that in Dutch patients the association between abdominal obesity and hyperglycemia was stronger in the presence of a parental history of diabetes.

In study by Knowler et al. (2002) mentioned that a minimum of 7% weight loss or weight maintenance in combination with a minimum of 150 minutes weekly physical activity resulted in 58% reduction in the incidence of diabetes. Physical inactivity is considered the most important risk factor for the development of type 2 DM. Physical activity reduces insulin resistance and total and visceral fat mass (Kay and fiatarone, 2006).

A combination of several lifestyle factors, including low body mass index (< 25 kg/m^2), a diet high in cereal fiber, polysaturated fat and low in saturated fat and trans fats and glycaemic load, regular exercise, abstinence from smoking and moderate alcohol intake, were associated with a reduction of type 2 DM incidence.

2.5.2 Non modifiable risk factors

The prevalence and incidence of type 2 DM are strongly related to age. The age is a risk factor for developing type 2 DM. In fact, about 50% of type 2 diabetic patients are over 60 years old (Laakso, 2008). Ethnicity is a strong determinant of diabetes occurrence. In Chinese, the prevalence of type 2 DM is 1% whereas in Pima Indians it is > 50% in the adult population, possibly due to genetic influences or due to interaction between genes and environment. No systematic effects of gender on the prevalence and incidence of type 2 DM observed. Previous abnormality of glucose tolerance, a history of gestational diabetes and a family history are all strong predictors of type 2 DM. Interestingly, the presence of other disease states or conditions, for example, hypertension and dyslipidemia increase the risk of type 2 DM (Laakso, 2008). Associations between low birth weight and increased risk of type 2 diabetes in adult life have been reported in various populations (Barker, 2004).

2.6 Pathogenesis of type 2 diabetes mellitus

2.6.1 Pathophysiology of hyperglycemia

Insulin is the hormone for regulating blood glucose. In general, normoglycaemia is sustained by the balanced interplay between insulin secretion and the efficacy of insulin actions. In the fasting state, the major part of glucose is created by the liver, and roughly half of it is used for brain glucose metabolism. The residue is taken up by various tissues, mainly muscle and for a minor part adipose tissue. In this situation insulin levels are low and have no substantial effect on muscle glucose uptake. The normal liver is capable of rising glucose production four fold or more, and the main effect of the relatively low insulin levels is to control liver glucose production (Stumvoll et al., 2008). After a meal, insulin is secreted in bigger

amounts, which reducing liver glucose production level further, and will lead to an enhancement of muscle glucose uptake (Stumvoll et al., 2008). The normal pancreatic cell is capable of adjusting to changes in insulin action, that is, a decrease in insulin action is accompanied by upregulation of insulin secretion. When the adaptation of the β-cell is not enough, the subjects will develop impaired glucose tolerance (IGT) or type 2 DM. Weyer et al. (1999) have shown that β-cell dysfunction is critical in the pathogenesis of type 2 DM. It is of note that even small increases in fasting and postprandial glucose occur in people with insulin resistance, which should stimulate insulin release. Thus, when insulin action decreases the system normally compensates by increasing β-cell function, in the face of higher glucose (Stumvoll et al., 2003).

2.6.2 Insulin resistance

Insulin resistance is present when the natural effects of insulin are subnormal for both glucose disposals in skeletal muscle and suppression of endogenous glucose production primarily in the liver (Dinneen et al., 1992). In the fasting state, however, muscle accounts for only a small amount of glucose disposal while endogenous glucose production is responsible for all of the glucose appearing in plasma. In type 2 diabetic patients and in patients with impaired fasting glucose (IFG) endogenous glucose production is accelerated (Weyer et al., 1999).

Insulin resistance is strongly associated with obesity. A number of hormones, cytokines and metabolic fuels, such as nonesterified free fatty acids (NEFA) originate in the adipocyte and reduce insulin action. In obese subjects, adipocytes are large, which provide them resistance to the ability of insulin to suppress lipolysis, especially in deep subcutaneous fat. In addition, elevated release and circulating

levels of NEFA and glycerol, both of which aggravate insulin resistance in skeletal muscle and liver (Boden, 1997).

2.6.3 Insulin secretion in type 2 diabetes mellitus

In type 2 diabetic patients, plasma glucose levels are raised; and accordingly, fasting plasma insulin was elevated. While the insulin levels sometimes increase slightly after a meal in type 2 diabetic patients this is considerably less than normal. In a study by Gerich (1998) reported that in which glucose levels have been raised by glucose infusions (hyperglycaemic clamps) to comparable levels in diabetic subjects and controls, it has become clear that second-phase insulin secretion is roughly 25% (IGT) to 50% decreased in type 2 DM. First-phase secretion is generally completely lost. In normoglycaemic first-degree relatives insulin secretion is also diminished but to a lower extent, presumably on a genetic basis (Pimenta et al., 1995). It is suspected that upon acquisition of insulin resistance (obesity, physical inactivity) the pancreas that has already lower secretory capabilities can adapt less than normal, which might lead to decreased glucose tolerance or diabetes. It has been commonly suggested that various mechanisms might further aggravate β-cell insulin secretory dysfunction, among which glucose toxicity and lipotoxicity (Stumvoll et al., 2008)

2.6.4 Glucose toxicity

Over time, insulin secretion appears to decrease in most diabetic patients, it has been proposed that glucose itself is toxic to β-cells. In pancreas β-cells oxidative glucose metabolism will also lead to the formation of reactive oxygen species (ROS), which would damage β-cells. Indeed, β-cells have low amounts of catalase and

superoxide dismutase, enzymes which normally metabolise the ROS (Robertson et al., 2003).

2.6.5 Lipotoxicity

Free fatty acids (FFA) extremely increase insulin secretion and chronic FFA overload reduces β-cell function. Type 2 DM subjects have frequently increased FFA due to insulin resistance to lipolysis. It is currently obvious that high glucose inhibits β-cell fatty acid oxidation, which may lead to accumulation of long-chain coenzyme A (LC-CoA) (Robertson et al., 2004).

2.7 Heredity in type 2 diabetes mellitus

A positive family history confers a two to three fold increased risk for the disease with a 15% to 30% risk to develop type 2 DM or IGT in first degree relatives of type 2 DM subjects (Pierce et al., 1995). The risk is even higher (around 60% by the age of 60 years) if both parents have diabetes (Tattersal and Fajans, 1975).

2.8 Genetic factors in type 2 diabetes mellitus

The polygenic nature of diabetic disease has it difficult to dissect individual genes conferring increased risk for diabetes. Type 2 DM has a strong genetic component and most Asian diabetic patients have a first-degree relative with diabetes (Ng et al., 2001).

Ramachandran et al. (2009) noted that most of the loci originally associated with diabetes in European populations have been replicated in Asian populations. Most genetic variants related with type 2 DM seem to be related to insulin secretion rather than insulin resistance, and several of the risks are associated with reduced

islet-cell function (Frayling, 2007; Florez, 2008; Yasuda et al., 2008; Ramachandran et al., 2009).

2.9 Diabetic outpatients

Diabetic outpatient is defined as the patient who receives services in the hospital for less than 24 hours, who is registered on the hospital records as an outpatient, and who receives outpatient hospital services, other than supplies or prescription drugs alone, from the hospital. Outpatient clinics are an important part of every hospital because of following check-up. Outpatient clinics are where the decision to admit a patient is taken. Reduction of inpatient length of stay creates more work for outpatient clinics. Through frequent visits, the work in these units becomes well-organised and coordinated with the work of doctors in the hospital.

Diabetes services are largely outpatient based. A complex local network of services is required to encompass the needs of all people with diabetes throughout their lifelong pathway of care. A center requirement for all patients is support for self-efficacy, which necessitates effective, continuing patient education programmes and compliance influences glycaemic control (Chen et al., 2004).

2.9.1 Compliance of type 2 diabetes mellitus

Therapeutic compliance is adherence of the patient to treatment indications prescribed by the physician. It is necessary to evaluate not only therapy compliance but also the non-medical indications. Kravitz et al. (1993) studied that the level of adherence to exercise, diet, and the administration of medication in patients with chronic diseases such as diabetes mellitus. They found frequencies of noncompliance of 19%, 69%, and 91%, respectively. In diabetic outpatients the compliance is very

difficult to define. People with diabetes are poorly compliant with dietary and exercise recommendations and that primary non-compliance with medication is common (Cradock, 2004).

The diabetic outpatients services are different from diabetic inpatients in:

2.9.1 (a) Diet

Diet plays an essential role in the therapeutic strategy to keep patients with diabetes in good glycaemic control and prevent microvascular and macrovascular complications. The management of diabetes has been prescribing dietary recommendations for the treatment of diabetes since many years. Although the importance and the scientific basis of these recommendations are very well recognized, their conversion into daily routine is very difficult.

- In diabetic inpatients dietitians used more information from medical records to make clinical judgment than diabetic outpatients dietitians.
- In diabetic inpatients dietitians are more likely to identify nutrients related problems via information from medical records while outpatients dietitians more frequently identify specific behaviorals goals whearesa inpatients dietitians recommend general goals.

2.9.1(b) Exercise

The compliance of exercise is very important in diabetic patients because exercise is beneficial in diabetic patients for the following reasons:

1. Regular aerobic exercise decreases the dosage or need for insulin or oral antihyperglycaemic agents.
2. It reduces cardiovascular risk factors.