

**EVALUATION OF DIABETIC MANAGEMENT
OUTCOME AND PHARMACIST INTERVENTION
IN PULAU PINANG, MALAYSIA**

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**EVALUATION OF DIABETIC MANAGEMENT
OUTCOME AND PHARMACIST INTERVENTION IN
PULAU PINANG, MALAYSIA**

By:

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**Thesis submitted in fulfillment of the requirement for the degree of
Doctor of Philosophy**

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DEDICATION

I dedicated this thesis to my Father (Syed Zamir Hussain), Mother (Khalida Syeda), Brother (Syed Muddassir Gillani), Sister in Law (Mariyam), Sister (Saima Syed) and my lovely nieces (Ayesha, Horiya and Fatimah) in the hope that they appreciate the commitment, courage, patience and perseverance involved in completion of this thesis and embrace these indispensable qualities in their own pursuit of knowledge.

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LIST OF ABBREVIATIONS

WHO	World Health Organization
DM	Diabetes Mellitus
NIDDM	Non-insulin dependent diabetes mellitus
HRQOL	Health-related Quality of life
DCCT	Diabetes control and complication trial
UKPDS	United Kingdom prospective diabetes study
ACR	Urine Albumin creatinine ratio
HbA1c	Glycosylated haemoglobin
HOPE	Heart outcomes Prevention Evaluation
FPG	Fasting Plasma glucose
SMBG	Self monitoring blood glucose
PHCP	Patient In-Home Care Program
OAM	Oral anti-hyperglycemic medication
PS	Patient Satisfaction
PC	Pharmaceutical Care
CMs	Complementary medicines
HCPs	Health Care Professionals
OPD	Out-Patient Department
PSS	Perceived Stress Scale
CRC	Clinical Research Committee
KKM	Ministry of Health Malaysia
DKA	Diabetes Ketoacidosis

BMI	Body Mass Index
IQR	Interquartile range
EI:BMR	Ratio of reported energy intake to basal metabolic rate
AGFI	Adjusted goodness of fit index
RMSEA	Root mean square error of approximation

**PENILAIAN HASIL PENGURUSAN DIABETES DAN INTERVENSI OLEH
AHLI FARMASI DI PULAU PINANG, MALAYSIA.**

ABSTRAK

Objektif kajian ini adalah untuk menilai dapatan pengurusan penyakit secara klinikal dan tanggapan pesakit terhadap keberkesanan rawatan. Kajian primer diklasifikasikan sebagai metodologi bercampur dengan kajian intervensi secara rintang, yang merangkumi empat fasa dengan metodologi yang berbeza. Fasa I (penilaian retrospektif), Fasa II (aplikasi penjagaan farmaseutikal secara prospektif), Fasa III (penilaian kajian kes secara prospektif) dan fasa IV (kajian psikometrik berasaskan populasi).

Terdapat 2174 pesakit diabetes yang menerima rawatan sepanjang tempoh Januari 2008 ke Disember 2010, dimana 2174 (100%) carta pesakit telah di teliti. Terdapat 1063 (48.9%) pesakit lelaki dan selebihnya 1111 (51.1%) wanita. Mean dan distribusi piawai bagi wanita lebih rendah (35.2 ± 4.187 tahun) berbanding dengan lelaki (37.9 ± 5.724 tahun). Sejumlah 798 (36.7%) pesakit mempunyai risiko infeksi sebelum atau semasa rawatan di hospital dan signifikan secara statistik seperti dapati berkaitan dengan diabetes ketoacidosis (DKA) dan pendedahan terhadap jangkitan. Sebanyak 384 (48.1%) kes jangkitan merupakan kes berulang dalam masa 3 bulan. Terdapat 176 kes andaian jangkitan viral (18.2%), dan 679 kes jangkitan bakteria (70.2%). Dari kes jangkitan bakteria itu, 453 kes merupakan jangkitan secara minor (66.7%), dan 226 jangkitan major (33.3%).

Dalam kajian penjagaan farmaseutikal secara prospektif seramai 253 pesakit telah di ambil dari Klinik Pesakit Luar Hospital Pulau Pinang, yang terdiri dari pada 127 kes kajian dan 126 kes kawalan. Tiada perbezaan signifikan antara kedua-duanya terhadap

sebarang variable demografik yang direkodkan. Kebanyakan pesakit yang tua mengalami DM jenis 2. Intervensi tidak dilakukan dalam kumpulan kawalan memandangkan penyelidik tidak menilai rawatan yang dilakukan. Untuk program pesakit di rumah, daripada 109 subjek yang memenuhi criteria kajian, 3 subjek menolak untuk menyertai program ini disebabkan oleh kekurangan waktu dan minat. Keputusan utama kajian ini adalah berdasarkan data daripada 93 subjek yang menamatkan selama 24 minggu (6 bulan) penyelidikan (intervensi=47, Kawalan=46). *Principal component factor analysis* telah dilakukan untuk menganalisa 10 item PSS terhadap 1924 sampel pesakit diabetes. Dari jumlah tersebut, seramai 992 pesakit adalah wanita dan 932 adalah lelaki. Keputusan Ujian Barlett's adalah 1603.417 ($p < 0.001$) dan pengukuran Kaiser-Meyer-Olkin adalah 0.83, yang menyokong penggunaan data ini untuk analisa faktor. Analisa awal menghasilkan dua komponen dengan nilai Eigen melebihi 1, dengan sejumlah 59.16 peratus untuk varians. *Scree-plot inspection* menjelaskan dua perkara. Rotasi Varimax digunakan dengan menggunakan kedua-dua faktor tersebut. Faktor A mengintegrasikan item item 1, 2, 3, 6, 9 and 10, dan dilabelkan sebagai "*Perceived Avoidance*" sementara faktor B terdiri dari item 4,5,7,8 dilabelkan sebagai "*Perceived controllable*" dalam Penggunaan antibiotik yang meningkat dan berulang dalam kalangan Melayu yang juga menunjukkan pengawalan glisemik yang kurang baik jika dibandingkan dengan bangsa lain. Jangkitan bakteria yang berpotensi sebagai sangat serius berlaku dalam kalangan sepertiga pesakit (33.3%).

Umur didapati mempunyai kesan signifikan terhadap kadar dan jangkaan untuk mendapat jangkitan. Leukocytosis sering ditemui tetapi ianya lebih menunjukkan tahap keterukan ketoasidosis dan bukannya berlaku kehadiran jangkitan. Kajian PC (Pharmaceutical Care)

ini menjelaskan nilai khidmat seorang ahli farmasi sebagai pakar dalam menyumbangkan maklumat untuk pesakit diabetes. Ini dipanjangkan kepada CM (Complementary Medicines) dimana kemungkinan berlaku potensi interaksi yang tidak diteliti dengan sempurna. Data terkini menyarankan penilaian yang lebih besar terhadap PC untuk diabetes pusat penjagaan kesihatan primer.

Skala *Psychometric validation of perceived stress* versi Bahasa Melayu menunjukkan PSS-10 merupakan alat yang boleh dipercayai untuk penilaian tekanan dalam kalangan pesakit diabetes dalam masyarakat. Paras tekanan yang tinggi dikenalpasti dalam kalangan pesakit diabetes wanita berbanding lelaki. Program penjagaan pesakit di rumah (PHCP) telah menunjukkan keberkesanan program pembelajaran yang merangkumi sains tingkahlaku terutama yang berkaitan dengan efikasi sendiri adalah sangat berkesan dalam peningkatan pengetahuan, praktis sendiri dan pengawalan glisemik dalam kalangan kumpulan kawalan. Penambahbaikan praktis sendiri yang memerlukan perubahan gaya hidup seperti perubahan pada diet dan senaman masih lagi bermasalah.

EVALUATION OF DIABETIC MANAGEMENT OUTCOME AND PHARMACIST INTERVENTION IN PULAU PINANG, MALAYSIA

ABSTRACT

The objectives of the study were to evaluate clinical disease management outcome and patient responsiveness to treatment. The primary current study is classified as 'mixed-methodology' cross sectional interventional study, which includes four phases of evaluation with different methodologies. Phase I (retrospective evaluation), Phase II (prospective pharmaceutical care application), Phase III (prospective case-control cohort evaluation) and Phase IV (Psychometric population based survey).

During the time period of January 2008 through December 2010, a total of 2174 diabetes patients were admitted; 2174 (100%) patients' medical profiles were reviewed. This comprised of 1063 (48.9%) males and rest 1111 (51.1%) females. Mean and Standard Distribution (SD) should females have less mean age distribution (35.2 ± 4.187 years) as compared to males (37.9 ± 5.724 years). A total of 798 (36.7%) had infection exposure before and/or during hospital admission, statistical significance ($p < 0.001$) found in association of diabetes ketoacidosis (DKA) and infection exposure. Majority 384 (48.1%) infection type was relapsed cases within 3 months. There were 176 with presumed viral infection (18.2%), and 679 with bacterial infection (70.2%). Of those with bacterial infection, 453 had minor infection (66.7%), and 226 had major infection (33.3%). In prospective pharmaceutical care study, two hundred and fifty three patients from the Diabetes Outpatient clinic Hospital Pulau Pinang were recruited, comprising 127 cases and 126 controls. There were no significant differences between cases and controls for any of the demographic variables that were documented. The sample was predominantly

elderly type 2 DM patients. No interventions were made in the control group as there was no medication review in this group by the investigator. For patient home-care program, Of the 109 subject who met the study-entry criteria, 3 subjects declined to participate due to lack of time and interest. The primary result of this study as based on data from the 93 subject who completed the 24-weeks (6 months) follow-up (intervention=47, control=46). Principal component factor analysis was done for the analysis of 10 item PSS dimensionality with a sample of 1924 diabetic patients. A total of 1924 diabetic patients with age ≥ 18 (mean age = 39.51) were approached, 992 of them were female and 932 of them were male. Barlett's test of sphericity was 1603.417 ($p < 0.001$) and Kaiser-Meyer-Olkin measure of the sampling adequacy was 0.83, which supported the use of these data in a factor analysis for further investigation. Initial analysis yielded two components with Eigen values exceeding 1, accumulating the total of 59.16 per cent of the variance. Scree-plot inspection indicated two factors. Varimax rotation was conducted with these two identified factors. Factor A integrated items 1, 2, 3, 6, 9 and 10, labeled as 'Perceived Avoidance' while Factor B containing items 4, 5, 7, 8 and labeled as 'Perceived Controllable'. Increased and recurrent use of antibiotic was found among Malays. Malays predominantly experienced poor glycaemic control as compared to other races.

Major bacterial infections with potential serious sequel are particularly common (33.3%), as every third patient being presumed to have serious consequences. Age has a significant effect on the rate and prediction of infection. Leukocytosis is commonly found but more likely reflects the severity of ketoacidosis rather than the presence of infection. The PC study highlights the value of the pharmacist as an information resource for patients with

diabetes. This extends to CMs where potential interactions with conventional therapy may be neither suspected nor recognized. The present data may suggest that a larger evaluation of a PC program for diabetes in the primary care setting may be valuable.

Psychometric validation of perceived stress scale in Malay version shows that the PSS-10 is a reliable tool for assessing the stress measures among diabetic living of the society.

Female diabetic patients were identified to experience high stress level as compared to male patients. Patient home-care program (PHCP) has shown a brief structured education program that incorporated behavior science specifically self-efficacy was effective in enhancing knowledge, some of the self-care practices (SMBG and medication adherence) and improving glycaemic control in the intervention group. Improvement of self-care practices that require lifestyle changes such as diet and increased in physical activities are problematic.

CHAPTER 1

INTRODUCTION

The prevalence of diabetes is on the increase and an estimated 239 million people worldwide are expected to have the condition by the year 2020 (Patel A, 1999). Diabetes mellitus (DM) represents a serious health care challenge. It is a heterogeneous disorder characterized by varying degrees of insulin resistance and insulin deficiency, which leads to disturbances in glucose homeostasis. It is commonly associated with prolonged ill health and premature death (Douglas *et al.*, 1998). The mortality rate in patients with DM may be up to eleven times higher than in persons without the disease (Florence & Yeager, 1999; UKPDS, 1998). DM is the leading cause of blindness, renal failure and foot and leg amputations in adults in developed countries (Patel A, 1999).

The World Health Organization (WHO) classification system of DM recognized two major forms of diabetes (King H *et al.*, 1993);

1. Type 1 diabetes mellitus (DM), formerly known as insulin dependent diabetes mellitus (IDDM; patient is dependent on exogenous insulin for survival)
2. Type 2 DM, formerly known as non-insulin dependent diabetes mellitus (NIDDM; patient is not necessary dependent on exogenous insulin for survival).

Teamwork and collaboration are essential components of successful DM management, both to prevent complications and maintain the patients' health-related quality of life (HRQOL) over a lifetime of coping with the disease (Patel A, 1999).

Type 1 DM is characterized by insulin deficiency resulting from immune-mediated pancreatic beta-cell destruction. The most serious acute consequence of this is ketoacidosis. Pancreatic beta-cell destruction eventually results in absolute insulin deficiency (Patel A, 1999). Type 1 DM accounts for approximately ten percent of all DM cases in the world population. Type 2 DM is generally characterized by peripheral insulin resistance with relative insulin deficiency to predominant insulin secretory defect with insulin resistance (Patel A, 1999). Type 2 DM accounts for approximately ninety percent of all DM cases.

The major risk factors in the development of type 2 DM are (Florence & Yeager, 1999);

1. Family history
2. Obesity
3. Race/raceity
4. Increasing age (especially greater than forty five years)
5. Previous identified impaired fasting glucose or impaired glucose tolerance
6. Hypertension
7. Hyperlipidemia
8. History of gestational DM

There is evidence that good glycaemic control can slow or prevent the development of diabetes complications (Miller M, 1996; Keen H, 1998; UKPDS, 1998; Turner *et al.*, 1998; Stratton *et al.*, 2000). The Diabetes Control and Complication Trial (DCCT) demonstrated the association between the degree of glycaemic control and the development of microvascular complications in type 1 DM patients (DCCT, 1993; DCCT, 1996). The DCCT determined that there was an

approximately 50% reductions in microvascular complications in the intensive treatment group and a non-significant tendency to fewer major cardiovascular events. Intensive control was accompanied by a significantly between the groups. The DCCT investigators did advice caution in extending the findings to patients with type 2 DM regardless to age and coexisting diseases.

The DCCT was an important study, due to the relatively large number of patients included and the long followed-up period. The entire cohort of 1441 patients was followed for a mean of six and half years. Primary and secondary prevention cohorts were included. The care in the intensive group was carried out by an expert team of diabetologists, nurses, dieticians and behavioral specialists, and the time, effort and cost involved was considerable. It is important to note that the resources used in the intensive group are not widely available and the DCCT investigators suggested that new strategies were needed to adapt methods of intensive treatment for use in the general community in an efficient and cost effective way.

The United Kingdom Prospective Diabetes Study (UKPDS) was the largest scale long-term intervention study in newly diagnosed type 2 DM patients and involved over 5000 patients. The UKPDS used an intensive blood glucose control policy, which achieved a medium HbA1c of 7% compared with 7.9% in those randomized to conventional treatment over a median 10 years follow-up (Stratton *et al.*, 2000). The UKPDS confirmed the benefit of intense glycaemic control on microvascular disease in type 2 DM patients(UKPDS 17, 1996; UKPDS 23,1998; UKPDS33, 1998; UKPDS 34, 1998; UKPDS 37, 1998, UKPDS 39, 1999). The complications of type 2 DM and the treatment with preventions of these complications, especially with respect to pharmacotherapy, are discussed in following section.

1.1 COMPLICATIONS & TREATMENT OF TYPE 2 DIABETES MELLITUS

1.1.1 Microvascular complications

Complications such as retinopathy, nephropathy and peripheral neuropathy can lead to blindness, renal failure and limb amputations respectively (Patel A, 1999). The DCCT (DCCT, 1993; DCCT 1996) and the UKPDS (UKPDS 34, 1998; UKPDS 37, 1998, UKPDS 39, 1999) have demonstrated an association between microvascular complications and glycaemic control in both type 1 and type 2 DM patients.

1.1.1.1 Nephropathy

Nephropathy develops in approximately twenty percent of persons with type 2 DM. Its earliest manifestations in microalbuminuria (urine albumin creatinine ratio (ACR) $\geq 3\text{mg}/\text{mmol}$). Within 10 years of diagnosis of type 2 DM, one third of patients will have macroproteinuria and 0.6% will have features of renal failure (Miller M, 1996; Bloongarden ZT, 1999). In patients with type 2 DM, microalbuminuria is also associated with an increase in cardiovascular mortality (Spelstra-de Man *et al.*, 2000; Valmarid *et al.*, 2000; Capes SE *et al.*, 2000).

Gaede, 1999 found that intensive intervention in type 2 DM patients can reduce the progression of nephropathy. The study was a randomized, open, parallel trial (n=149) conducted to determine whether intensive multifactorial, intervention that included changes in behavior and pharmacological management, slowed the initiation and progression of microvascular complications in patients who have microalbuminuria and type 2 DM. The HbA1c level at baseline for the standard treatment group was $8.8 \pm 1.7\%$ and for the intervention group $8.4 \pm 1.6\%$ after the four year period the results were $8.6 \pm 1.9\%$ and $7.6 \pm 1.6\%$ respectively ($p < 0.05$, across

time and between groups). Physician, nurse and dietician provided the intensive intervention for the cases. Some of the treatment goals are provided in Table 1.1.

Table 1.1: Multifactorial intervention in patients with type 2 DM; treatment goals in standard and intensive group – (Gaede, 1999).

Intervention	Standard group n=76	Intensive group n= 73
Systolic blood pressure (SBP) mm Hg	<160	<140
Diastolic blood pressure (DBP) mm Hg	<95	<85
Glycosylated haemoglobin (HbA1c) %	<7.5	<6.5
Angiotension converting enzyme (ACE) inhibitor	No	Yes
Irrespective of blood pressure (BP)		
Aspirin to patients with ischaemic heart disease (IHD)	Yes	Yes
Aspirin in patients with peripheral vascular disease	No	Yes
Triglycerides (mmol/L)	<2.2	<1.7
Total cholesterol (mmol/L)	<6.5	<5.0
High density lipoproteins (HDL)-Cholesterol (mmol/L)	>0.9	>1.1

This study was collectively on small sample size and demonstrated that intensive multifactorial intervention in patients with type 2 DM and microalbuminuria slowed the progression of nephropathy, as well as progression of retinopathy and autonomic neuropathy. This study was not designed to assess which aspect of the multifactorial intervention resulted in the results seen, but highlighted the need for intensive intervention in type 2 DM patients to see clinically relevant improvement in diabetes control.

Various treatments have been investigated to determine whether pharmacological intervention can slow the progression of nephropathy, in particular ACE inhibitor (Taguma *et al.*, 1985; Bauer *et al.*, 1986; Kefleher C, 1990; Mathiesen *et al.*, 1991; Sano *et al.*, 1994; Alimad *et al.*, 1997; Adler A *et al.*, 2000). Some of these studies concluded that the reduction in microalbuminuria seen with ACE inhibitors could not be simply attributed to good BP control (Cahn J *et al.*, 1992; Goa K, Haiia M, Wilde M, 1997), while others, including the findings of the UKPDS-39 concluded that the suggestion to ACE inhibitors have a specific renal protective effect in the treatment of type 2 DM is not supported. There was some controversy over the role of ACE inhibitors in slowing the progression of nephropathy until 2000, when the Heart outcomes Prevention Evaluation (HOPE) study found that the ACE inhibitor ramipril provided nephroprotection (HOPE, 2000; Sleight P, 2000). This benefit was independent of ramipril's effect on BP and was determine in over 3000 people. The HOPE study was a landmark study and solved the controversy surrounding ACE inhibition and DM. The use of ACE inhibitors in DM patients is now considered standard therapy (Pahor M *et al.*, 2000; Lovell H, 2003). The HOPE 2000 study concluded that, the treatment represents a vasculoprotective and renoprotective effect for people with diabetes. Angiotension receptor II (ARII) blockers have also been shown to slow the progression of nephropathy in patients with type 2 DM (Lewis EJ *et al.*, 2001; Parving H *et al.*, 2001). Like ACE inhibitors, the renoprotective effect appears independent of the drugs ability to lower BP.

Management of patients with microalbuminuria and/or nephropathy must also focus on good glycaemic control, good BP control, lowering of cholesterol levels where necessary and cessation of smoking (Patel A, 1999; Nathan DM, 1998).

1.1.1.2 Neuropathy

The manifestations of neuropathy in DM are extensive (Patel A, 1999). Abnormalities can be detected in most patients who have had DM for five to ten years. Peripheral neuropathy can cause sensory loss in the feet and legs resulting in the loss of protective sensation in the feet (Patel A, 1999). Other symptoms include impotence, gastrointestinal dysfunction, lack of sweating in the feet, resting tachycardia and a fall in SBP on standing. Good glycaemic control to slow the progression of neuropathy is paramount (UKPDS 33, 1998).

1.1.1.3 Retinopathy

Globally retinopathy is seen in about 15% of patients who have had DM for more than 15 years. In the Australia and the United States of America (USA), DM is the leading cause of blindness (Patel A, 1999). Microangiopathy affecting the retina develops over a number of years. Vision is not affected by all retinopathies, but regular review is important for controlling the condition and maintaining vision. All patients with diabetes should receive ophthalmologic examinations at least annually (Patel A, 1999). Good glycaemic control is the key to slowing the progression of retinopathy (Stratton *et al.*, 2000).

1.1.2 Macrovascular complications

Type 2 DM usually presents as part of a syndrome of metabolic abnormalities, which include hyperglycemia, central obesity, dyslipidemia, hypercoagulation, hypertension and insulin resistance (Patel A, 1999). Type 2 DM is associated with a two to three fold increased risk of cardiovascular morbidity and mortality and an increased risk of developing congestive heart failure (Miller M, 1996; Fagan & Sowers, 1999). The relative risk of stroke in patients with

diabetes is also increased 2 to 3 fold. Aggressive antihypertensive therapy and routine anticoagulation therapy for atrial fibrillation may reduce the risk of stroke (Davis *et al.*, 1999). In addition to stroke, treating hypertension in persons with DM reduces other cardiovascular endpoints (Adler A *et al.*, 2000).

Several potentially modifiable risk factors for coronary heart disease (CHD) in type 2 DM patients have been identified (UKPDS 33, 1998). The risk factors include hyperglycemia, hypertension, dyslipidemia and smoking.

1.1.2.1 Hyperglycemia

Dietary and lifestyle modification are the first line intervention in all type 2 DM patients unless the patient is acutely unwell. It is usual to institute dietary management for the first three months following diagnosis and then reassess blood glucose level (Patel A, 1999). The nutritional goals for people with DM are similar to those for a healthy diet in the non-diabetic population with the aim of attaining and maintaining good control of blood glucose, lipid and BP. The dietary modifications in type 2 DM patients must involve weight reduction in those patients who are overweight or obese. Type 2 DM patients should be encouraged to reduce the intake of refined carbohydrate (sugar) and fats in favor of unrefined carbohydrates, so that the latter makes up at least half of the patient's total energy intake (Patel A, 1999). A wide variety of foods should be included in the diet, with particular emphasis on food containing a high proportion of dietary fibers. As well as being generally beneficial, dietary fiber may retard the absorption rate of sugars in the diet, and aid in glycaemic control (Brown A, 1998). When dietary management succeeds, the benefits are undisputed. Blood pressure, lipids and BP falls and life expectancy may be

prolonged by three to four months for each kilogram lost during the first year of treatment (Williams O, 1994). However, dietary compliance over long periods tends to be poor (Wing & Anglin, 1996; Foreyt & Poston, 1999).

Lifestyle changes must include appropriate levels of exercise (minimum of 30 minutes three times a week; ideally 30 minutes daily), minimization of alcohol intake and cessation of smoking (Ponte C, 1996). Most patients with type 2 DM have a reduced functional capacity for exercise and a thorough physical assessment (with special reference to CHD) is recommended before the patient begins any exercise program. The exercise program should normally begin slowly and the need for persistence should be emphasized (Ponte C, 1996). However, permanent lifestyle changes are difficult to achieve (Wing & Anglin, 1996; Foreyt & Poston, 1999).

The American Diabetes Association (ADA) recommends that action should be taken in the type 2 DM patient whose fasting plasma glucose (FPG) concentration exceeds 7.8mmol/L and the HbA1c value is more than 8% (Mensing C *et al.*, 2000). The target should be FPG <6.7 mmol/L and HbA1c < 7% (Bailey & Turner, 1996). These targets may be achievable in the early stages of the disease but become more difficult to achieve as the disease progresses. Drugs available to maintain glycaemic control include metformin, sulphonylurea, Acarbose, insulin, meglitinides and the thiazolidinediones. No study to date has determined the drug regimen of choice for type 2 DM (UKPDS 33, 1998; UKPDS 34, 1998; Turner *et al.*, 1999; Stratton *et al.*, 2000). The main translatable finding of the UKPDS is that intensive therapy for type 2 DM is beneficial (Nathan DM, 1998). It is also estimated that a two percent reduction to HbA1c over a four-year period

would be associated with significant decrease in proliferative retinopathy and sensory neuropathy in patients with type 2 DM ((Miller M, 1996).

1.1.2.1.1 Metformin

1.1.2.1.1.1 Mechanism

Metformin is a biguanide that may reduce glucose absorption from the intestine, increase uptake of glucose into the tissues from the blood, reduce liver production of glucose and reduce insulin requirements for disposal of glucose. It has no effect on insulin resistance (Baily CJ, 1992; Baliga & Fonseca, 1997). Metformin can be used either in initial therapy, as add-on therapy when sulphonylurea alone has failed and diet and exercise are no longer maintaining appropriate blood glucose levels, or in combination with insulin therapy (Bailey & Turner, 1996). Metformin and sulphonylurea cause similar reduction in FPG concentrations in patients with type 2 DM (Mensing C *et al.*, 2000).

1.1.2.1.1.2 Features of metformin and place in therapy

Metformin decreases appetite, can promote weight loss and has a beneficial effect on serum lipids. Reductions in triglyceridaemic individuals with type 2 DM can be up to fifty percent (Bailey CJ, 1992). Metformin does not usually induce hypoglycemia because metformin has an antihyperglyceamic action rather than the hypoglycaemic actions typical of sulphonylureas and insulin. Metformin is often be preferred as initial therapy in the obese patient because it promotes weight loss (UKPDS-34, 1998). The features of metformin and its place in therapy is presented in Table 1.2 (Moses *et al.*,1999; stang M, Wysowski DK, dutler-Jones, 1999; Anonymous, 2003)

Table 1.2 Metformin: features and place in therapy

Variable	Comment
Type of therapy	Monotherapy; combination therapy with a sulphonylurea or a meglitinide, combination with insulin, combination with a thiazolidinedione
Indications	After failure of diet and exercise in type 2 DM, especially in overweight patients. After failure with sulphonylureas, combination therapy with insulin, combination with a thiazolidinedione
Tablet sizes	500mg, 850mg and 1gm
Dose range	250mg – 3gm in daily divided doses (maximal effect is seen at doses of 2 gm daily)
Treatment schedule	Taken with meals, increase dose slowly, maximum dose 3 gm daily
Contraindication	Moderate to severe renal or hepatic disease, cardiac or respiratory insufficiency, any hypoxic conditions, severe infections, alcohol abuse, history of lactic acidosis, pregnancy
Side Effects	Gastrointestinal symptoms and metallic taste, may impair absorption of vitamin B12 and folic acid (rarely causes deficiencies), Hypothetical risk of lactic acidosis with listed contraindications
Bioavailability	50-60%
Blood concentration	Maximal 1-2 hours after oral dose, negligible binding to blood proteins
Blood half-life	1.5-4.9 hours
Metabolism	Not measurably metabolized
Elimination	Ninety percent eliminated in the urine in twelve hours.

Metformin has been shown to lower both FPG levels and HbA1c in moderately obese patients with type 2 DM who were inadequately controlled by diet (DeFronzo RA, 1999). The primary

failure rate for metformin is reported to be 5-20% but this includes who discontinue the drug because of initial gastrointestinal side effects. Secondary failures are reported to be five to ten percent per year which is similar to sulphonylurea (Bailey C & Turner R, 1996). The data from UKPDS indicate that metformin is as effective as insulin or sulphonylurea therapy in decreasing both FPG levels and HbA1c, without causing weight gain, hypoglycemia or hyperinsulinaemia (Turner, Cull & Holman, 1996). The UKPDS-34, 1998 showed that among overweight patients allocated intensive blood glucose control, metformin showed a greater effect than sulphonylureas or insulin for any DM related endpoint, all-cause mortality and stroke. Early addition of metformin in sulphonylureas treated patients was associated with an increased risk for diabetes-related deaths and all-cause mortality in over-weight patients (both subsets of patients were reviewed separately and together). The reason for this increased risk is currently unknown and requires further study to clarify the place of metformin and sulphonylureas in the treatment of type 2 DM. Overall, metformin does seem to be advantageous as a first-line pharmacological therapy in diet-treated over-weight patients with type 2 DM. It can also be used first-line in normal weight type 2 DM patients (UKPDS 34, 1998, UKPDS 39, 1999).

1.1.2.1.1.3 Side effects

Metformin has a tenfold lower risk of lactic acidosis than its predecessor phenformin (Arc, Korhonen T, Halinen, 1978). Metformin should be used with caution in patients with any risk factors that may precipitate lactic acidosis, such as moderate to severe renal failure, although evidence for this is mainly from case reports. Diarrhoea is a common side effect of metformin and may limit its use (Bailey & Turner, 1996). This side effect can be minimized by starting at a low dose (250 mg to 500mg daily) and slowly titrating upwards according to FPG results.

Long-term therapy with metformin is associated with decreased intestinal absorption of cyanocobalamin and folate, but anaemia has developed in few patients (Bailey & Turner, 1996).

1.1.2.1.4 Potentially significant drug interactions

Renal clearance of metformin may be reduced by concurrent administration of cimetidine (Somogyl A *et al.*, 1987). The proposed mechanism is competition between cimetidine and metformin for proximal tubular secretion. If cimetidine is introduced to a patient on a stable dose of metformin, the patient should monitor the blood glucose closely.

1.1.2.1.2 Sulphonylureas

1.1.2.1.2.1 Mechanism

The mechanism of action is currently thought to be beta cell receptor specific stimulation of insulin release from the pancreas, thereby increasing circulating levels of insulin (Lubbo, Miller & Rose, 1995). There is evidence that insulin levels fall over the ensuing months or years after commencing therapy, although the drugs often retain their effectiveness as hypoglycemics. Sulphonylureas may also have effects on reducing glucose production in the liver and increasing glucose uptake by skeletal muscle cells (Brown A, 1998), although these effects are relatively minor.

1.1.2.1.2.2 Place in therapy

The UKPDS, 1998 showed that intensive blood-glucose control by either sulphonylureas or insulin substantially decreased the risk of microvascular complications, but not macrovascular diseases. An intensive blood-glucose control policy was associated with an average HbA1c of 7.0% over the duration of the study compared with 7.9% in conventionally managed patients.

Sulphonylureas are generally used in type 2 DM patients who do not respond to diet alone, do not require insulin and are not obese (Florence & Yeager, 1999). Sulphonylureas are contraindicated

in severe insulin deficiency, pregnancy, in intercurrent illness, and in perioperative patients (because of their prolonged hypoglycemia). How long sulphonylureas remain effective cannot be predicted, and patients must be reviewed regularly (Williams O, 1994). Approximately two third of patients who begin therapy with a sulphonylureas respond, although depending on glycaemic targets, twenty percent or more eventually require additional therapy (Ponte C, 1996). There are several identified causes of secondary failure in patients receiving sulphonylureas. These include addition of drugs causing hyperglycemia, non-adherence to dietary requirements or drug therapy, stressors (CHD, infection, surgery, thyrotoxicosis, trauma) and/or weight gain (Ponte C, 1996). A list of common used sulphonylureas is listed in Table 1.3 (Baliga & Fonseca, 1997; Anonyous, 2003; Yeap BB, 2001).

Table 1.3 Characteristics of sulphonylureas

Agent	Daily dose	Tablet strength	Duration of effect	Half life
Gibenclamide	5mg(elderly 2.5mg); max 15 mg	2.5mg and 5 mg	20-29 hours	10 hrs (longer in impaired renal function)
Gliclazide	40-80mg; max 320mg (divided doses) 30-90mg (single dose)	80 mg	10-15 hrs	6-15 hours
		30mg MR*	24 hrs	
Glipizide	205-5mg; max 40mg (divided dose)	5 mg	14-16 hrs	1-5 hours
Glimepiride	1-8mg daily (single dose)	1,2,3 and 4 mg	24 hrs	5 hours

*MR= Modified release

1.1.2.1.2.3 Pharmacokinetics

Sulphonylureas are almost completely absorbed following oral administration. The rates of absorption, biotransformation and duration of action differ for each compound. They are metabolized by the liver and excreted predominantly in the urine. Glibenclamide is a typical long

acting agent, which is excreted as metabolites in the bile and urine (Riddle M, 2000). Due to an enhanced risk of accumulation, this drug should be avoided in patients with moderate to severe renal disease in favor of an agent that is solely hepatically metabolized, such as gliclazide.

1.1.2.1.2.4 Significant drug and food interaction

Many drugs interact with sulphonylureas and may interfere with diabetes control (William O, 1994). Important interactions include aspirin and sulphonamides. A study in which high dose aspirin was introduced to glibenclamide therapy resulted in an increase in the free fraction of glibenclamide and potential hypoglycemia (Kubacka *et al.*, 1996). Patients on low dose aspirin did not experience this effect. Patients on stable sulphonylurea therapy should be counseled to take paracetamol for pain, rather than aspirin as high dose aspirin may cause hypoglycemia. The literature has varying reports concerning non-steroidal anti-inflammatory drugs (NSAID) and sulphonylureas; the interaction is probably not of clinical significance at standard doses (Lubbos, Miller & Rose, 1995). Introduction to sulphonamides to stable sulphonylurea therapy can cause severe hypoglycemia. This interaction is more significant with the longer acting sulphonylureas (Wing & Miners, 1985; Hansen & Kristensen, 1991).

Alcohol blocks gluconeogenesis and the surge in hepatic glucose output, that is crucial for recovery from hypoglycemia and may subsequently cause hypoglycemia, in patients on sulphonylureas. Average amount of alcohol (< 2 standard drinks per day for a male) should not cause a problem, but consumption of large amounts of alcohol or binge drinking may precipitate hypoglycemia (Riddle M, 2000). There are case reports of patients developing hypoglycemia with concurrent administration of glibenclamide and ACE inhibitors (Arauz *el al.*,1990). The

proposed mechanism of action is increased insulin mediated removal of glucose in skeletal muscle and tissues via a vasodilatory action of ACE inhibitors. When patients on stable sulphonylureas therapy are commenced on an ACE inhibitor they should be informed that sudden hypoglycemia has been reported and that they should monitor their blood glucose levels.

Concurrent administration of some antacids containing magnesium hydroxide may increase the rate of absorption of some sulphonylureas (Kivisto & Neuvonen, 1991; Self T, Tsiu, Fowler, 1992). Patients should be counseled to separate administration of antacids and sulphonylureas by two hours to avoid potential hypoglycemia.

Rifampicin induces hepatic metabolizing enzymes and longer doses of some sulphonylureas may be required to control blood glucose levels during concomitant therapy (Self T, Tsiu S, Fowler S, 1992). When the rifampicin is ceased the doses must be reduced to prevent hypoglycemia. There are many other reported interactions in the literature between sulphonylureas and other drugs but most have unproved clinical relevance. Introduction of a new drug to a patient on stabilized sulphonylurea therapy warrants an increase in frequency of blood glucose monitoring and appropriate counseling of the patient.

1.1.2.1.2.5 Side effects

The main side effects of sulphonylureas are nausea, epigastric fullness, heartburn, hypoglycemia, hyperinsulinemia, weight gain and liver enzyme elevations. Sulphonylureas act via endogeneous insulin and their main side effects of hypoglycemia and weight gain are generally predictable and dose related. Hypoglycemia, although relatively uncommon, may be severe and difficult to reverse (Ponte C, 1996). Certain risk factors may dispose a patient to hypoglycemia

episodes and these include increased age, renal dysfunction and decreased energy intake (Den-Ami *et al.*,1999). Enhanced therapeutics monitoring may be warrant in patients with the above risk factors.

Skin rashes can occur with sulphonylureas. Sulphonylureases are chemically related to sulphonamides but do not share the same pharmacological adverse effect profile. Severe hypersensitivity reactions (e.g, blood dyscrasias and Stevens Johnson syndrome) are rare (Brown A, 1998).

1.1.2.1.3 Acarbose

Acarbose is an alpha-glucosidase enzyme inhibitor and can diminish postprandial blood glucose by delaying carbohydrate absorption from the small intestine (UKPDS 44, 1999). It is a useful addition to other oral treatments for lowering blood glucose, especially if insulin may not be desired or is inappropriate. Careful titration of the dose of acarbose is necessary to minimize side effects. The starting dose should be 25 mg taken at the beginning of each meal. The dose can be increased every four to eight weeks, depending on response. Doses greater than 300 mg should not be required (Patel A, 1999).

There are significant compliance problems with acarbose due to high incidence of flatulence and diarrhea and the necessity to take acarbose three times a day for maximum benefit. A randomized double blind trial showed that acarbose significantly improved glycaemic control over three years in patients with type 2 DM, irrespective of concomitant therapy (UKPDS 44, 1999). In patients who continued to take acarbose for the full three years a reduction in HbA1c of

0.5% was seen. This may be a clinically relevant reduction in HbA1c, as acarbose is used in combination with other agents and may be added to avoid progression to insulin therapy.

Acarbose alone does not cause hypoglycemia but, when used in combination with a sulphonylurea, hypoglycemia may result. The hypoglycemia caused by this combination cannot be treated with oral carbohydrates because acarbose delays its absorption. Patients on acarbose should use glucose tablets, glucose liquid or glucagon injections for the treatment of hypoglycemia (Bohannon N, 1996). Acarbose is used for type 2 DM patients whose blood glucose concentrations are inadequately controlled despite diet, exercise and maximal tolerated doses of other oral anti-diabetic agents, and where insulin therapy is inappropriate (Anonymous, 2003).

1.1.2.1.4 Thiazolidinediones

These drugs have been described as insulin sensitizers because they have been shown to enhance glycaemic control, lower insulin levels and promote glucose utilization in the tissues. They do not cause hypoglycemia, weight gain or lactic acidosis (Anonymous, 1998). The currently available thiazolidinediones or glitazones are pioglitazone and rosiglitazone, and these drugs have been recently listed to use in treatment therapy (Anonymous, 2003).

About 40 cases of serious hepatic dysfunction were reported with the use of troglitazone, including rarely, severe hepatocellular damage, hepatic necrosis and hepatic failure (Plosker & Faulds, 1999). Among troglitazone patients who started treatment in 1998, the estimated risk of liver-related death was approximately 1 in 100,000 (Juhi *et al.*, 2000). Troglitazone has subsequently been withdrawn from the market. The level of liver dysfunction seen with troglitazone has not been demonstrated with the newer glitazones, but vigilance is required.

Liver function tests should be performed regularly and the thiazolidinedione should be discontinued in the presence of unexplained deterioration of liver function (Plosker & Faulds, 1999).

1.1.2.1.5 Meglitinides

Meglitinides, such as repaglinide act as prandial glucose regulator (Juhi *et al.*,2000). Repaglinide is short acting with a rapid onset of effect and should be taken shortly before a meal. It should not be taken if the meal is missed. Long-term glycaemic control is similar to that seen with sulphonylureas and the tolerability profile is also similar (Anonymous, 1998). Repaglinide is not listed to used in Australia and UK for the therapeutic treatment and rarely use in clinical practices (Anonymous, 2003).

1.1.2.1.6 Insulin

Over the long natural history of type 2 DM, up to 30% of patients eventually fail to respond to oral agents and require insulin (Turner *et al.*,1999; Yeap BB, 2001). The decision to start insulin is dependent on many factors including age, complication, symptoms, concomitant diseases and overall life expectancy. Increased hepatic output of glucose, especially at night, is the main determinant of fasting hyperglycemia in patients with type 2 DM (Baliga & Fonseca 1997). The bedtime administration of an intermediate acting insulin can be very beneficial as this may improve glycaemic control through only one injection a day. In some cases, patients who are falling oral therapy are switched to a multiple-insulin injection regimen similar to that given to type 1 DM patients (Ragucci, zonsein & Frishkan, 2003). Commonly, type 2 DM patients may be given twice daily subcutaneous injections of premixed short and intermediate insulins (Yeap BB, 2001). There is no standard dose of insulin and requirements depend on many factors such as diet, weight, exercise levels, stress and illness (Bryant, Knights, Salerno, 2003). Each patient's

needs must be determined individually and may change on a day-to-day basis and over the course of the disease. A typical daily dose might be in the order of 0.5-0.7 units/kg/day split into 1-4 injections and possibly 2 or 3 different types of insulin. Treatment schedules need to be reviewed regularly and adjusted as necessary (Bryant, Knights, Salerno, 2003). The UKPDS 1998 showed that intensive blood glucose control whether by insulin or oral therapy substantially decreased the risk of microvascular complications. Exogenous insulin has been suggested as a potentially harmful treatment because *in-vitro* studies with raised insulin concentration induced atheroma. The UKPDS 1998 did not find any evidence of this, while intensive blood glucose control does have some disadvantages in that risk of hypoglycemia and weight gain is higher. A simple treatment algorithm for the management of type 2 DM is presented in Figure 1.1.

1.1.2.2 Dyslipidemia

Aggressive treatment of dyslipidemia in DM is essential (Golomb & Criqui, 1999; Herman *et al.*, 1999). Plasma cholesterol is an independent risk factor for CHD and the risk is higher in people with DM than in the non-diabetic population (Patel A, 1999). Determination of the lipid profile (total cholesterol, triglycerides, low density lipoproteins (LDL) and HDL-cholesterol) should form a part of the annual assessment of the diabetic patient. Targets of patient with diabetes should include reaching a total cholesterol of < 4.0 mmol/L, LDL-cholesterol of <2.5 mmol/L, HDL-cholesterol of > 1.0mmol/L and triglycerides of < 2.0 mmol/L (Guidelines, 2003).

Emphasis needs to be placed on weight reduction, exercise and restriction of saturated fat, cholesterol, sugar, sodium chloride and alcohol. The efficacy and tolerability of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins, puts them as first-line therapy for hypercholesterolaemia (Montori *et al.*, 2000). Simvastatin, pravastatin, fluvastatin

and atorvastatin are currently available worldwide for treatment (Anonymous, 2003). For patients who cannot tolerate statins or need combination therapy fibrates are a useful alternative (Guideline, 2003). Of the fibrates, gemfibrozil and fenofibrate are listed options. Fenofibrate is only available via clinical trials. A recent quantitative systemic review has also confirmed that fish oil supplement (containing omega-3 fatty acids) in type 2 DM lowers triglycerides (Montori *et al.*, 2000). The review did emphasize that further research was needed into the use of fish oil in type 2 DM, however they may provide a useful alternative or addition to DM patients with raised triglycerides.

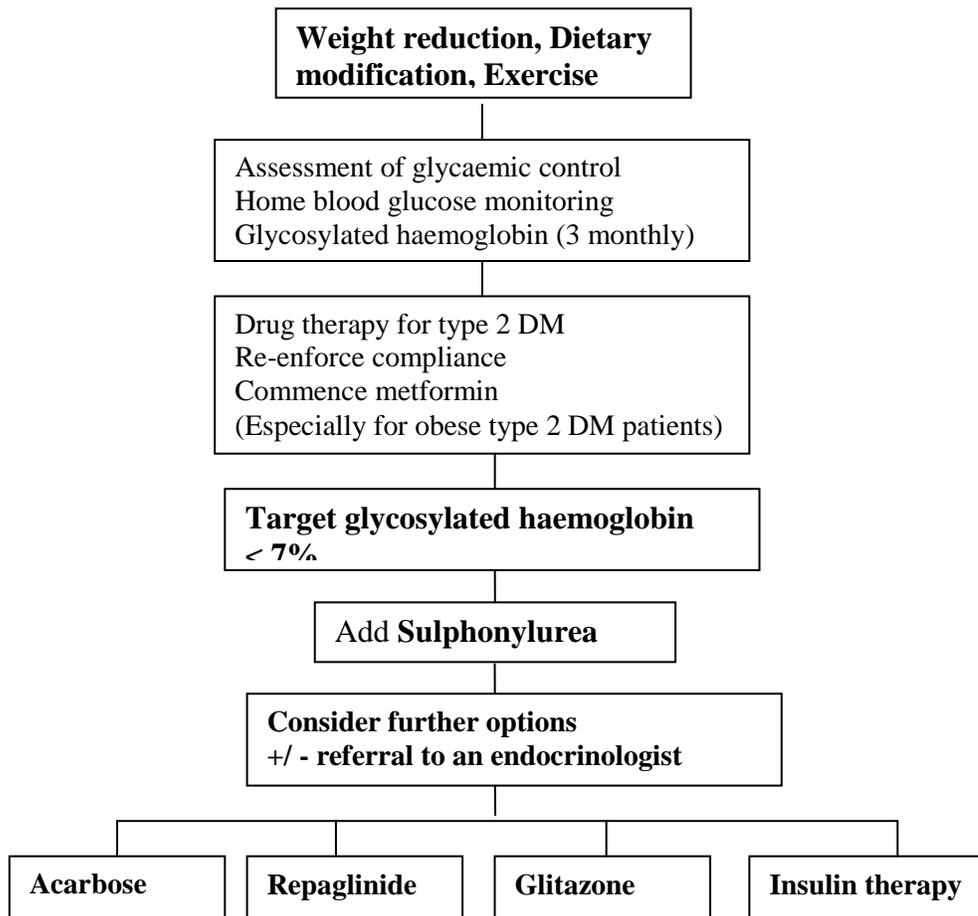


Figure 1.1 Management of type 2 DM in Malaysia (Montori *et al.*, 2000)

1.1.2.3 Hypertension

The development of stroke and microvascular disease in patients with DM is related to hypertension. Tight control of BP in hypertensive patients with type 2 DM substantially reduced the cost of complications, increased the interval without complications, increased survival, and had a cost effectiveness ratio that compared favorably with accepted healthcare programs (Mogensen CE, 1998; UKPDS, 1998). Hypertension in DM also responds well to weight loss and exercise (Chobanian *et al.*, 2003).

The UKPDS-38, 1998 found that tight control of BP reduced death caused by DM by 32%. The hypertension in diabetes study was a multicentre, controlled trial embedded within the UKPDS that was designed to determine whether tight BP control (less than 150/85 mmHg), reduced morbidity and mortality in hypertensive patients with type 2 DM, compared to less tight control. Of the 4297 patients recruited to UKPDS, 1544 (38%) had hypertension (defined as a BP > 160/90 mmHg or antihypertensive therapy) and, of these, 1148 were eligible for the hypertension in Diabetes study. Recruitment ran over a four-year period. Patients visited study clinics every three to four months and BP was measured and adjustments to medications were made where necessary and appropriate. The median follow up to the end of the trial was 8.4 years. Patients allocated to tight BP control compared with less tight control had a 24% reduction in risk of developing any end point related to diabetes ($p = 0.005$). Tight BP control also resulted in a reduction of 44% for stroke, 56% for heart failure and 37% for microvascular disease. UKPDS suggested the goal with BP reduction could be as low as SBP < 135 mmHg and DBP <

85mmHg. The UKPDS achieved a mean BP of 144/82 mmHg in the tight control group. The UKPDS-38, 1998 concluded that

“Tight control of BP achieves a clinically important reduction in the risks of deaths related to DM, complications related to DM, progression of diabetes retinopathy, and deterioration in visual acuity”.

While it is clear that lowering BP is important with diabetes, optimal treatment of hypertension in DM continues to be controversial. The currently recommended goal in clinical management is a BP of 135/85 mmHg or lower (Mogensen CE, 1998; Nosadini R *et al.*, 1998). Recently, the results of the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) (ALLHAT, 2002) concluded that thiazide diuretics were the preferred first-line treatment, in non-diabetic patient. Subgroup analyses of comparative trials, including the ALLHAT trial, have demonstrated no advantage of ACE inhibitors over thiazides in people with DM and no renal disease (Anonymous, 2003). The results of the Second National Blood Pressure Study (Wing, Reid & Ryan, 2003) contradicted the results of ALLHAT and concluded that treatment with ACE inhibitors leads to better outcomes than treatment with diuretics.

The controversies will continue to persist but it would appear that the data is leaning towards the use of ACE inhibitors in DM patients, as first line anti-hypertensive therapy, especially in light of their other proven benefits in DM patients (HOPE, 2000; Mann J, 2000; Hoogwerf & Young, 2000).

1.1.2.4 Summary

Addressing the complication of DM with appropriate lifestyle modification and pharmacotherapy are essential components in reducing the morbidity and mortality associated with type 2 DM.

optimal pharmacotherapy will continue to be reviewed and modified according to the ongoing results of large-scale trials. It is also clear that multifactorial interventions targeting lifestyle modification and appropriate pharmacotherapy are necessary in DM. Different race group have differences in rates of complications and response to pharmacotherapy (Gulliford & Mejia, 1999; UKPDS 55, 2001).