EVALUATION OF COMBINED METFORMIN-LOVASTATIN THERAPY IN THE TREATMENT OF DIABETIC TYPE 2 PATIENTS WITH DYSLIPIDEMIA IN HOSPITAL PULAU PINANG

By

NADA FAISAL ZAKI GHAITH

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Dedication…

My beloved husband and my two little angels....

Nawfal... I am so glad it was you; I chose to walk my life with. Thank you for your care and support and for sharing my dreams and fears. You light up my world.

Ahmed and Yara... You are the sunshine of my life. You mean everything to me. I did this for you, and I hope that you always be proud of your mother.

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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
BNF	British National Formulary
B.P.	Blood Pressure
CVD	Cardiovascular disease
DIA B.P.	Diastolic Blood Pressure
DM	Diabetes Mellitus
FDA	Food and Drug Administration
FFA	Free Fatty Acid
FPG	Fasting Plasma Glucose
HbA_{1c}	Glycosylated Haemoglobin A_{1c}
HDL	High Density Lipoprotein
HMGCoA	Hydroxy Methyl Glutaryl Co Enzyme A
HPS	Heart Protection Study
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
LDL	Low Density Lipoprotein
MOH	Ministry Of Health
NCEP ATP III	National Cholesterol Education Panel Adult Panel III

NDDG	National Diabetes Data Group
NHS	National Health Survey
NIDDM	Non Insulin Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
PH	Penang Hospital
RPG	Random Plasma Glucose
SPSS	Statistical Package of Social Sciences
SYS B.P.	Systolic Blood Pressure
TC	Total Cholesterol
TG	Triglyceride
UKPDS	United Kingdom Prospective Diabetes Study
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

PENILAIAN TERHADAP PENGGUNAAN GABUNGAN METFORMIN-LOVASTATIN DALAM RAWATAN PESAKIT DIABETES JENIS 2 DENGAN DISLIPIDEMIA DI HOSPITAL PULAU PINANG

ABSTRAK

Diabetes jenis 2 dapat dicirikan melalui kehadiran rintangan insulin yang sering wujud bersama dengan pelbagai faktor risiko kardiovaskular. Dislipidemia merupakan faktor risiko yang telah dikenalpasti dan boleh diubah suai. Ianya perlu dirawat segera secara agresif untuk mengelak daripada berlakunya prognosis penyakit kardiovaskular. Kajian ini ber matlamat untuk menilai hasilan klinikal di sebalik penggunaan metformin dan lovastatin dalam rawatan pesakit diabetes jenis 2 dengan dislipidemia. Di samping itu, suatu penilaian tentang perbezaan dalam respons terapeutik turut dilakukan berdasarkan faktor bangsa dan gender. Suatu pemerhatian retrospektif dijalankan di klinik pesakit luar, Hospital Pulau Pinang, Malaysia. Data seperti demografi, profil perubatan, dan maklumat daripada ujian makmal telah dikumpulkan dan dianalisis dengan menggunakan program SPSS (Pakej Statistik daripada Sains Sosial) versi 15. Daripada 873 rekod perubatan yang terkumpul, hanya 501 pesakit memenuhi kriteria kajian ini. Responden wanita terdiri dari 55.9%, sementara 44.1% adalah responden lelaki. Berdasarkan taburan bangsa, responden Cina adalah 41.7%, diikuti 34.3% Melayu dan 24% India. Secara signifikan, responden Cina menunjukkan peratusan tahap HDL terkawal tertinggi iaitu 97.5%. Berbeza dengan lelaki, secara signifikannya, responden wanita menunjukkan min TC (Total cholesterol) dan nilai HDL (High density lipoprotein) tertinggi (5.40

± 1.09 mmol/l dan 1.32 ± 0.29 mmol/l masing-masing). Profil lipid secara signifikannya dikurangkan ke tahap normal dalam tempoh kajian. Begitu juga dengan min FPG (Fasting plasma glucose) yang semakin berkurangan. Namun demikian, nilai-nilai tersebut didapati melebihi matlamat rawatan (8.22 ± 2.33 mmol/l). Kajian ini juga menunjukkan bahawa 93.5% daripada pesakit dengan LDL terkawal adalah secara signifikannya berada dalam rawatan dos terapeutik metformin. Sebaliknya, secara signifikan, status lipidemia terkawal didapati lebih tinggi (86.6%) dalam kalangan pesakit yang mendapat rawatan monoterapi lovastatin. Pesakit dengan tahap FPG yang tidak terkawal mempunyai korelasi dengan tahap TG (Triglyceride) tidak terkawal (81.7%). Berdasarkan gaya hidup pesakit, didapati diet yang tidak terkawal dihubungkaitkan dengan FPG yang tidak terkawal. Didapati, 78.7% daripada pesakit yang mengamalkan senaman mempunyai lipidemia yang terkawal. Walau bagaimanapun, 90.8% daripada pesakit yang mempunyai gaya hidup yang tidak terkawal, mengalami komplikasi. Sebagai kesimpulan, metformin dan lovastatin, sama ada sebagai monoterapi atau dalam gabungan dengan agen antidiabetes atau antihiperlipidemik lain adalah efektif dalam mengurangkan peningkatan glukosa dan profil lipid. Walau bagaimanapun, min FPG masih menunjukkan kawalan yang lemah. Kedua-dua drug menunjukkan toleransi yang baik dengan kesan mudarat yang minor. Kajian ini mencadangkan agar kawalan glukosa dan lipid yang ketat berserta dengan gaya hidup yang baik adalah perlu untuk mencapai hasil yang baik.

Kata kunci: diabetes jenis 2, dislipidemia diabetes, metformin, lovastatin, kawalan glisemik, kepatuhan kepada ADA dan garis panduan diabetes Malaysia.

EVALUATION OF COMBINED METFORMIN-LOVASTATIN THERAPY IN THE TREATMENT OF DIABETIC TYPE 2 PATIENTS WITH DYSLIPIDEMIA IN HOSPITAL PULAU PINANG

ABSTRACT

Diabetes type 2 is characterized by the presence of insulin resistance which frequently co-exists with multiple cardiovascular risk factors. Dyslipidemia is a well-recognized and modifiable risk factor that should be identified and treated aggressively to prevent the onset and prognosis of cardiovascular disease. This study aimed to assess the clinical outcomes behind the usage of metformin and lovastatin in the treatment of diabetes type 2 patients with dyslipidemia. Furthermore, an evaluation of difference in therapeutic response was done according to race and gender. A retrospective observational study was performed at the outpatient clinic of Hospital Pulau Pinang, Malaysia. Demographic, medication profile, and laboratory tests information were collected. Data were analyzed by using Statistical Package of Social Sciences (SPSS) program version 15. From 873 medical records, only 501 patients met the inclusion criteria of this study. Females constituted 55.9%, while 44.1% were males. Racial distribution showed that Chinese were 41.7%, Malay 34.3% and Indians 24%. Significantly, Chinese showed the highest percentage (97.5%) of controlled HDL levels. Unlike males, females demonstrated the highest mean TC and HDL values (5.40 ± 1.09 mmol/l and 1.32 ± 0.29 mmol/l respectively) significantly. Lipid profile has

been reduced significantly to the normal levels within the study period. Similarly, mean FPG has been decreased. However, those values were observed to be above treatment goals (8.22 ± 2.33 mmol/l). This study also revealed that 93.5% of patients with controlled LDL were on therapeutic doses of metformin significantly. Controlled dyslipidemia status was attained to be more (86.6%) among patients on lovastatin monotherapy significantly. Patients with uncontrolled FPG levels were correlated with the uncontrolled TG levels (81.7%). Based on patients' lifestyle, it was observed that uncontrolled diet was associated significantly with the uncontrolled FPG. Noticeably, 78.7% of patients performed exercise had controlled dyslipidemia. However, 90.8% of patients with uncontrolled lifestyle suffered from complications. In conclusion, metformin and lovastatin either as monotherapy or in combination with other antidiabetic or antidyslipidemic agents were effective in reducing elevated glucose and lipid profile. However, mean FPG still indicating poor control. Both drugs were well tolerated with minor adverse effects reported. This study recommends strict glycemic and lipid control coupled with lifestyle modifications to achieve better outcomes.

Keywords: diabetes type 2, diabetic dyslipidemia, metformin, lovastatin, glycemic control, Malaysian clinical practice guidelines.

CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes mellitus is one of the most common, widely distributed metabolic disorders around the world (WHO, 1985). This disorder is characterised by hyperglycemia resulting from defects in insulin action or secretion or both (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; ADA, 2004; Lin and Sun, 2009). Such defects may be accompanied by changes in fat, carbohydrate and protein metabolism (Levene, 2003).

The term Diabetes mellitus is an ancient Greek and Roman term that means "passing through of sugar". It refers to one of the diabetes major symptoms (excessive production of sweet and smelly urine or polyuria). This term is used also to describe other features of diabetes such as thirst (polydypsia) and weight loss despite increasing appetite, or polyphagia (Leahy, 2000). These clinical features were depicted by the ancient Egyptians 3000 years ago, and later in 1675, sweetness of patient blood and urine were noticed by the ancient Indians. Only in 1776 Dobson confirmed that the presence of excess sugar in the blood and urine was the cause of sweetness (Ahmed, 2002).

Diabetes is a chronic non-curable complex disease that affects most body organs resulting in severe complications such as cardiovascular disease, peripheral vascular disease, stroke, renal failure, blindness, amputation and premature death (Engelgau and Geiss, 2000; Harvey *et al.*, 2006).

Diabetes mellitus is classified into two major types, which are, insulin-dependent diabetes mellitus (IDDM) or type 1 (known as juvenal-onset), and non-insulin

dependent diabetes mellitus (NIDDM) or type 2 (known as adult-onset). Other classes include impaired glucose tolerance (IGT) and the gestational diabetes mellitus (WHO, 1999).

Diabetes type 1 results from the autoimmune destruction of β-cells that are responsible for producing insulin in the pancreas leading to absolute deficiency of insulin (ADA, 2004). This type occurs at any age but mostly begins in childhood or young adulthood. It is treated by insulin, diet and exercise. Type 1 accounts only 5-10% of patients with diabetes (WHO, 1999).

Diabetes mellitus Type 2 accounts for 90-95% of diabetes cases. It occurs due to insufficient production of insulin by the body or inadequate response to insulin by the body tissues (insulin resistance) or both (Engelgau and Geiss, 2000). This type is a serious condition that must be managed to avoid the onset and development of macrovascular and microvascular complications. It is treated by oral antidiabetic agents, insulin in some cases, changing lifestyles, diet and exercise (Koda-Kimble *et al*., 2005).

Diabetes mellitus is associated with an increase in the risk of developing cardiovascular disease (CVD), which is the primary cause of death in individuals with both types of diabetes (Kannel and Mcgee, 1979; Morrish *et al.*, 2001; Kalofoutis *et al.*, 2007; Paterson *et al.*, 2007). Diabetes type 2 is characterised by the presence of insulin resistance that frequently co-exists with multiple cardiovascular risk factors such as obesity, hypertension and dyslipidemia (Laaksonen *et al.*, 2002; Kendall *et al.*, 2003; Farmer, 2008). Glycemia may be associated with CVD (Hsueh *et al*., 2004), but it co-exists more with microvascular complications, while lipid abnormalities that occur in diabetic type 2 subjects are more associated with macrovascular complications (Haffner, 1999).

Diabetes causes disorders in all metabolic functions of the body; lipid disorder is one of such abnormalities, and it is known as the diabetic dyslipidemia (Knopp *et al.*, 2003).

1.2 Diabetic Dyslipidemia

Diabetic dyslipidemia is referred to the lipid abnormalities associated with diabetes mellitus (Solano and Goldberg, 2006). It is common in the diabetic population and is a serious risk factor for coronary heart disease (Syvanne and Taskinen, 1997). Diabetic dyslipidemia is characterised by an increase in triglyceride cholesterol levels (TG), low levels of high-density lipoproteins (HDL), small, dense low-density lipoprotein particles (LDL) with slight increase or normal total cholesterol (TC) levels (Wilson *et al.*, 1985; Haffner, 1998; Brunzell and Ayyobi, 2003). The levels of LDL in diabetic type 2 patients are generally comparable to those found in the non-diabetic subjects. However, those small and dense LDL particles are highly atherogenic due to their increased susceptibility to oxidation and uptake by the arterial wall (Demacker *et al*., 2000).

Lipid abnormalities will lead to the development of atherosclerosis (Farmer, 2008), the central pathological mechanism that causes the macrovascular complications in type 2 diabetes (Fowler, 2008). This will result in 2-4 folds increase in the probability of developing vascular complications in diabetes (Stamler *et al.*, 1998). Approximately, 75% of all atherosclerotic-related events are mostly due to coronary artery disease, while 25% of such events are peripheral or cerebrovascular disease (Haffner *et al.*, 1998; Farmer, 2008). Dyslipidemia is a modifiable well-recognised risk factor that if identified and treated early may lead to the reduction of both incidence and development of CVD (Solano and Goldberg, 2006).

1.3 Prevalence of Diabetes Mellitus Type 2 and CVD

The number of diabetic subjects is becoming larger worldwide. Factors such as age, population growth, urbanization and increased prevalence of obesity and physical inactivity resulting from an unhealthy diet and sedentary lifestyle contribute to this increase (Zimmet *et al.*, 2001; Wild *et al.*, 2004).

According to the WHO, prevalence of diabetes worldwide in the year of 2000 was approximately 171 million in adults 20 years old and above and will be 366 million in the year of 2030 (WHO, 2008).

The International Diabetes Federation (IDF) estimated that over 150 million people in the year 2000 were diabetics, this number increased to 194 million people in 2003. In the year of 2007 the number was 246 million and expected to reach 380 million in the year 2025 (IDF, 2008). This difference in the statistics between WHO and IDF is due to the difference in the methodologies and the inclusion criteria used by the IDF and that of WHO to estimate diabetes prevalence for subjects 20-79 years old (Wild *et al.*, 2004).

In the United States of America 23.5 million (10.7%) of people 20 years or older have type 2 diabetes, 12 million (11.2%) are males and 11.5 million (10.2%) are females, while 12.2 million (23.1%) are 60 years or older (ADA, 2007b). North American region has the highest prevalence rate of diabetes which is 9.2%, followed by the European region with a prevalence of 8.4%. The highest number of people with diabetes are found in the Western Pacific region (67 million) followed by the European region (53 million) people (IDF, 2008).

Some ethnic groups appear to be more susceptible for developing diabetes, such as Amerindians, African-Americans, Australian aborigines, Hispanics, Pacific Island people and South Asians (IDF, 2001). In Malaysia, the National Health and

Morbidity Survey I, estimated that the prevalence of diabetes in the year 1960 was 0.65%, which later increased to 6.3% in 1985, while in the second survey conducted in 1996 the prevalence was 8.3%. Studies conducted in the country in 1998 showed that between 600,000 and 700,000 people of 30 years and above were diabetics (Lim *et al.*, 2000; Omar *et al.*, 2002).

According to WHO, Malaysia had 942,000 people with diabetes in the year of 2000. This number is expected to reach 2,479,000 in 2030 (WHO, 2007). In 2005, an estimated 1.1 million people died from diabetes worldwide, approximately 80% of them were from the low and middle–income countries, half of the death cases occurred among people under the age of 70 and 55% of the cases were women (WHO, 2006a).

In Malaysia, according to the Ministry of Health records, admission to Governmental hospitals due to diabetes mellitus increased from 19,629 cases in 1991 to 30,661 cases in 2001. An increase of 50% in death cases due to diabetes mellitus was recorded between the years 1991-2001(Ooyub *et al*., 2004).

Ninety-seven percent of adults with diabetes have one or more lipid abnormalities (diabetic dyslipidemia). Dyslipidemia is associated with cardiovascular and coronary artery diseases that are the primary cause of death among diabetes type 2 patients (Fagot-Campagna *et al.*, 2000; Henry, 2001).

In Malaysia, the prevalence of dyslipidemia among diabetes type 2 subjects is 63-76% (Mustaffa, 2004).

1.4 Diagnosis and Screening of DM Type 2 and Diabetic Dyslipidemia

Screening of DM aims to identify people who are asymptomatic and likely to have diabetes; this is done either by detecting all diabetic people in a population or detects diabetes among people most likely to have it (WHO, 2002). According to Leahy (2000) and Misbin (1999) the following are people who may develop diabetes:

a) Those who have typical diabetes symptoms.
b) Have family history.
c) High risk ethnic group.
d) Obese or overweight.
e) Hypertensive people.
f) Have high TG and cholesterol levels.
g) Had gestational diabetes or delivered a baby weighing more than 4.5 kg.
h) Who had Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG).

Before 1997 there were no standard diagnostic criteria for the diagnosis of diabetes. In 1980 WHO, in association with the National Diabetes Data Group (NDDG) in the United States developed the criteria for the diagnosis of DM (Miller and Kraemer, 2000; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). These diagnostic criteria are:

a) Random plasma glucose (RPG): this test is done during the day regardless of the last meal taken. When typical symptoms of diabetes are present, which are polyuria, polydipsia and weight loss, RPG $\geq$ 11.1 mmol/l (200 mg/dl) confirms the diagnosis.

b) Fasting plasma glucose (FPG): this test is done after at least 8 hours of last meal taken and the value $\geq$ 7 mmol/l (126 mg/dl) confirms diabetes.

c) Oral glucose tolerance test (OGTT): this test is done 2 hours after ingestion of a glucose load of 75 g dissolved in water and a value of ≥ 11.1 mmol/l (200 mg/dl) confirms diabetes (ADA, 2004). OGTT test is not recommended for routine clinical use because it is more difficult and more expensive than the other tests (Leahy, 2000).

Measurements of HbA_{1c} are useful during therapeutic monitoring but not as a diagnostic test because of the poor standardisation among clinical labs (Miller and Kraemer, 2000). Diagnostic tests for diabetes are recommended to be done for all people 45 years old or above and repeated every 3 years. However, for those at high risk the tests must be done more frequently and at younger age (Leahy, 2000).

In asymptomatic people, diagnosis should not be made depending on one abnormal glucose level value but after repeated tests, unless the subject has obvious hyperglycemia along with its symptoms (WHO, 2006b).

For measuring lipid levels, TC and HDL can be measured in fasting and non-fasting conditions. For TG the measurements are done after 10-12 hours fasting. LDL values are measured using the FriedeWald equation: LDL (mmol/l) = TC-HDL-TG/2.2 (MOH-Malaysia, 2003). This equation is not valid if TG levels are above 4.5 mmol/l, because the ratio of VLDL to serum TG gradually changes with increased TG levels leading to a gradual increase in the error of estimated LDL (Nader *et al*., 1992).

Lipid targets recommended for diabetic patients are TG ≤ 1.7 mmol/l, HDL ≥ 1.1 mmol/l and LDL ≤ 2.6 mmol/l. Abnormal values are considered as diabetes dyslipidemia (MOH-Malaysia, 2004).

1.5 Pathogenesis of Type 2 DM and Diabetic Dyslipidemia

The specific etiology of type 2 diabetes is not known, but unlike type 1, there is no autoimmune destruction of β-cells (ADA, 2004).

Diabetes mellitus type 2 is characterised by impairment in the function of pancreatic β-cells which lead to impairment in insulin secretion, insulin resistance, decrease in insulin-mediated glucose transport in muscles and adipose tissue and increase in the production of glucose by the liver (Olefsky, 1989; Reaven, 1995; Mahler and Alder, 1999; Goldstein and Muller-Wieland, 2003).

The cause of diabetes type 2 may be due to genetic defects that run through patients with family history and to this date only little information is known about the genetic defects (Leahy, 2000; Cnop *et al.*, 2007).

Most of the patients in this type are obese, and obesity itself causes a degree of insulin resistance (ADA, 2004; Alan *et al.*, 2005). Environmental factors other than obesity such as aging, unhealthy diet, physical inactivity, hypertension, lipid abnormalities, steroids and pregnancy are all related to insulin resistance and may increase the incidence of type 2 diabetes in the third world population (Miller and Kraemer, 2000; Lorenzo *et al.*, 2003). Other factors including utilization of specific drugs, poor nutrition, hypokalemia and hypocalcemia are also associated with increased incidence of diabetes type 2 (Leahy, 2000).

After glucose ingestion, its homeostasis is maintained by 3 coordinated processes: insulin secretion, stimulation of glucose uptake by visceral and peripheral tissues in response to hyperinsulinemia and hyperglycemia and suppression of glucose production by the liver (Defronzo, 1999). In type 2 diabetes when there is a defect in β-cell function and insulin resistance, hepatic glucose production will increase and hyperglycemia will develop (Hother-Nielsen and Beck-Nielsen, 1991; Davidson and

Peters, 1997). Insulin resistance will lead to increased demands and exhaustion of β-cells, as a result of circulating insulin levels that will increase potential defects in the ability to regulate circulating glucose and lipoproteins (Defronzo *et al.*, 1992). Diabetic patients are more susceptible to coronary heart disease (CHD) at younger age than non-diabetic individuals, which is the reason of death among the diabetic population (Gotto, 2002). Hyperglycemia is known to be a risk factor for microvascular complications of the eyes, kidney and nerves, and it is shown to be a CVD risk factor (Laakso and Lehto, 1997; Betteridge, 2004).

According to the United Kingdom Prospective Diabetes Study (UKPDS 35) and other studies, the management of hyperglycemia was only associated with reduction in microvascular complications and only 16% reduction in the macrovascular complications. Macrovascular events were improved by controlling lipid and blood pressure abnormalities (Stratton *et al.*, 2000; Stettler *et al*., 2006; Kelly *et al*., 2009).

The mechanism underlying atherosclerosis in type 2 diabetes includes the association of several CVD risk factors other than hyperglycemia. These factors are dyslipidemia, hypertension, insulin resistance, hemostatic abnormalities, protein glycosylation and oxidative stress (Bierman and George, 1992; Betteridge, 2004).

Increase circulating free fatty acids (FFA) levels is a common abnormality seen in insulin resistance as a consequence of increased lipolysis in the adipocytes due to poor insulinization (Lewis *et al*., 1995; Goldberg., 2001). The circulating FFA will be taken up by the liver to provide the metabolic substrate for synthesizing the endogenous TG-rich VLDL (Grundy, 2006; Farmer, 2008). Insulin resistance will cause a reduction in lipoprotein lipase enzyme hydrolytic activity leading to increased hepatic production of VLDL with subsequent increase in TG levels (Betteridge, 2004). The impaired catabolism and clearance of VLDL are associated

with decrease in the transfer of cholesterol into HDL, subsequently a reduction in this cardioprotective lipoprotein will arise (Superko, 2000; Farmer, 2008). Low HDL and high TG levels are associated with abnormal small, dense LDL particles which are highly atherogenic (Papadakis *et al*., 2001; Fonseca, 2003).

The high atherogenicity of these LDL particles resulted from its increased susceptibility to oxidation, endothelial cytotoxicity and increased ability to cross the endothelial barrier (Farmer, 2008). Moreover, in diabetic subjects, LDL is less efficiently bound to its receptor due to an increase in the rate of glycation of apolipoprotein B, thus the clearance of LDL from plasma is delayed, as a result LDL uptake will increase by macrophages leading to the formation of a foam cell (Lyons, 1992).

High TG levels are associated with the accumulation of the atherogenic remnant particles and with the low HDL levels (Farmer, 2008). Thus the diabetic dyslipidemia is characterised by high TG levels, low HDL levels and small, dense LDL particles (Solano and Goldberg, 2006).

1.6 Management of DM Type 2 and Diabetic Dyslipidemia

The initial management for patients with type 2 diabetes requires a programme that combines diet, exercise, smoking cessation and the use of oral antidiabetic agents and/or insulin together with antidyslipidemic medication (Miller and Kraemer, 2000; Kalofoutis *et al*., 2007).

The treatment programme includes: education about diabetes, nutritional recommendations and planning, exercise, use of oral antidiabetic agents and/or insulin and managing the associated conditions and complications. These factors require the cooperation of a health team including the diabetologist, the nutritionist and the diabetes educator. If complications developed, it is important that sub-specialists, such as neurologist, nephrologist, cardiologist and ophthalmologist be involved (WHO, 2006b).

1.7 Diet Composition for Diabetic Dyslipidemic Patients

1.7.1 Carbohydrates

There is strong evidence that the total amount of carbohydrates consumed in a meal is more important than the source of it. Accordingly, sucrose and sucrose containing food does not need to be restricted for diabetic patients but substituted for other carbohydrates (WHO, 2006b). Diets containing carbohydrates from vegetables, fruits, legumes, grains and low-fat milk are good for health and encouraged to be consumed by diabetics (ADA, 2007a). There are evidences suggesting that consuming high–fiber diets (150 g/day) by the diabetic patients have a good effect on glycemia, hyperinsulinemia and lipidemia (WHO, 2006b).

1.7.2 Fat

The goal from reducing the intake of dietary fat by diabetic patients is to minimize the risk of developing CVD. Saturated and trans saturated fatty acids are the main source of LDL cholesterol, thus saturated fat must be limited to less than 7% of total calories. Trans fat intake must be minimized and dietary cholesterol be limited to 200 mg/day (Garg *et al.*, 1994; Wood *et al.*, 1998; ADA, 2007a). Diets low in saturated FA and high in carbohydrates or monounsaturated FA will decrease the LDL but may also decrease HDL levels; poly- and mono-unsaturated FA diet will reduce both total plasma cholesterol and LDL levels (WHO, 2006b). The consumption of 2g/day of plant sterol and stanol esters was shown to decrease total plasma TC and LDL levels as they block intestinal and dietary cholesterol absorption (ADA, 2007a).

1.7.3 Proteins

In diabetic subjects 10-20% of total energy intake may be provided from proteins and only few studies suggest the modification of this intake. Protein ingestion has no effect on increasing glucose levels, but it stimulates insulin secretion in patients with controlled DM. Only limited studies suggest that it may be good to limit protein daily intake to not more than 20% to avoid the development of nephropathy (Goldstein and Muller-Wieland, 2003; Franz *et al.*, 2004).

1.7.4 Vitamins and minerals

If diabetes is not controlled it may be associated mostly with deficiency in vitamins and minerals. Patients must be made to know the importance of getting adequate amount of these nutrients from healthy diet. However, routine supplement with antioxidants like vitamins E and C and carotene is not recommended, due to lack of evidence on their efficacy and long-term safety. Deficiency in chromium, magnesium, potassium and possibly zinc may aggravate carbohydrate intolerance, but they are not recommended supplementations since benefits from such supplementations have not been demonstrated (ADA, 2007a).

1.8 Exercise

Exercise is important to improve diabetic control and decrease the risk of CVD; it also has a good effect on dyslipidemia by raising HDL levels significantly and lowers cholesterol and TG levels. Exercise is good for weight control because it burns calories and helps in reducing tension and stress. Furthermore, regular exercise enhances body response to insulin and may make pharmacological therapy more effective. Thus, it is good for the diabetic patients to do sports, unless there are complications that prevent it. Physical examination should be conducted by a physician before starting on an exercise programme (ADA, 2001; WHO, 2006b).

1.9 Therapeutic Management of Type 2 DM and Dyslipidemia

If 3-6 months period of diet and exercise therapy failed to control glucose and lipid elevated levels, then pharmacological therapy should be started (Miller and Kraemer, 2000). According to the UKPDS, controlling glycemia will reduce the progression and onset of microvascular complications, while controlling blood pressure and abnormal lipid levels will reduce the development of macrovascular complications in type 2 diabetic patients (Koda-Kimble *et al.*, 2005). Thus, the use of lipid lowering medications particularly statins as a first-line therapy is recommended to prevent or decrease the incidence of CVD (National Cholesterol Education Program NCEP, 2002). Some oral antidiabetic agents have effects on lipid levels such as lowering TG and LDL levels with slight or no effect on rising HDL (Henry, 2001). Different classes of oral antidiabetic agents are available in addition to insulin for the treatment of diabetes type 2 patients (BNF, 2005).

1.9.1 Insulin

Insulin is used when treatment with oral antidiabetic agents alone failed to control glucose levels in some type 2 diabetic patients who had diabetes for many years. It is used either combined to oral antidiabetic agents or as monotherapy in cases where oral antidiabetics must be discontinued (Miller and Kraemer, 2000). Insulin in some studies showed some effect on reducing serum cholesterol and TG levels, but with no effect on HDL. However, other studies showed that there was an increase in HDL levels (Merrin and Elkeles, 1991).

1.9.2 Oral antidiabetic agents

1.9.2.1 *Sulfonylureas*

Two generations are available in this class; the first generation sulphonylureas include acetohexamide, chlorpropamide, tolazamide and tolbutamide, while those of the second generation include glibenclamide, glimepiride and glipizide.

Agents of this group act by stimulating the secretion of insulin from the pancreatic β-cells and enhancing its sensitivity to glucose (Miller and Kraemer, 2000). These agents are equally effective in their glucose lowering effect but differ in their pharmacokinetics and side effects properties (Zimmerman, 1997; Koda-Kimble *et al*., 2005). Sulfonylureas may have a slight role in correcting serum lipids. Some studies found that chlorpropamide caused a reduction in both TG and VLDL lipoprotein with a rise in HDL levels. Glipizide, in another study, was found to reduce TG levels with no effect on HDL (Merrin and Elkeles, 1991). Agents of this group are safe but may cause hypoglycemia and weight gain, and they are also effective when used as monotherapy or combined with other oral antidiabetics or insulin (Miller and Kraemer, 2000).

1.9.2.2 *α-Glucosidase inhibitors*

Acarbose and miglitol are the only two agents available in this class of oral antidiabetics. These agents slow the digestion of complex carbohydrates by reversibly inhibiting glucosidases enzymes in the small intestine, as a result glucose absorption will be delayed and postprandial glucose levels will decrease (Yee and Fong, 1996; Koda-Kimble *et al*., 2005). They are effective as monotherapy or when combined with other oral antidiabetics or insulin. These agents have no effect on serum lipids (Miller and Kraemer, 2000).

1.9.2.3 *Nonsulfonylurea insulin secretagogues*

Drugs in this class include repaglinide and nateglinide. Nonsulfonylureas acts by closing adenosine triphosphate (ATP) potassium channels in the β-cells. This blockade will cause depolarization of the membrane and opening of the calcium channels. The resulting increase in calcium influx will stimulate insulin secretion (Koda-Kimble *et al*., 2005). These agents are effective when used as monotherapy or in combination with metformin or thiazolidinediones. Since these agents have the same action as sulfonylureas hence no beneficial effect is added when they are used together (Miller and Kraemer, 2000).

1.9.2.4 *Thiazolidinediones*

Agents under this class are insulin sensitizers acting by reducing resistance to insulin in liver and muscles, thus stimulating glucose utilization and reducing its output by the liver (Mudaliar and Henry, 2001; Koda-Kimble *et al.*, 2005). Rosiglitazone and pioglitazone are the two agents available in this class, and they are effective as monotherapy or in combination with other oral antidiabetics or insulin (Miller and Kraemer, 2000). According to one study, these agents are shown to have beneficial effect on serum lipids by decreasing TG levels and increasing HDL by 19% (Henry, 2001).

1.9.2.5 *Biguanides*

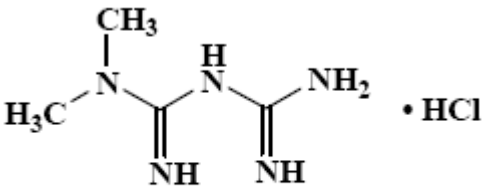
Metformin is the only member available in this class (BNF, 2005). It is of intrest in this research because of its wide usage in Hospital Pulau Pinang outpatient clinic and its effect on lipids in diabetic type 2 dyslipidemic patients.

1.9.2.5.1 History

The parent compound of this class is guanidine. It was derived from the plant French lilac *(Galega officinalis*) and has been used in eastern and southern Europe early in the 20th century. Guanidine was shown to have hypoglycemic properties, but it was very toxic to be given to humans. In the late of 1950s phenformin (phenethylbiguanide) and metformin (dimethylbiguanide) were developed (Miller and Kraemer, 2000).

Phenformin was the first biguanide available in the United States until 1977, when it was withdrawn from the market due to its high association with increasing incidence of fatal lactic acidosis. Metformin was available in the United States only in 1995, whereas the generic version came out in 2002 (Klepser and Kelly, 1997; Koda-Kimble *et al*., 2005).

Metformin is a crystalline compound, white in color, freely soluble in water and insoluble in chloroform, aceton and ether; its molecular formula is $C_4H_{11}N_5$.HCL with a molecular weight of 165.63. Metformin (*N, N*-dimethylimidodicarbonimidic diamide hydrochloride) has the following chemical structure shown in Figure 1 (Bristol-Myers Squibb, 2008):



Metformin Hydrochloride

Figure 1: Metformin hydrochloride chemical structure (Prescribing information leaflet for Glucophage®, Bristol-Myers Squibb Company, 2008).

1.9.2.5.2 Mechanism of action

Metformin HCL acts as an oral antidiabetic agent by:

a) Decreasing gluconeogenesis and hepatic glucose production (Hundal *et al.*, 2000).

b) Improving peripheral sensitivity to insulin by increasing utilization and uptake of glucose by the peripheral tissues (Kimmel and Inzucchi, 2005).

c) Reducing free fatty acid concentration and oxidation that may be related to its ability to decrease hepatic glucose production and increasing insulin-mediated glucose disposal in the muscle (Miller and Kraemer, 2000).

Metformin has a desirable effect on lipids by decreasing TC and TG with small or no change on HDL was observed (Kirpichnikov *et al*., 2002; Koda-Kimble *et al*., 2005).

Some studies showed that metformin could reduce blood pressure in case of hypertension. Furthermore, it may decrease atherosclerosis processes (Tandon, 2007).

1.9.2.5.3 Pharmacokinetics

When taken orally the bioavailability of metformin is 50-60%. The presence of food causes a slight delay in its absorption, which will reduce the bioavailability. It is not bounded to plasma proteins and its steady state concentration in plasma is reached within 24-48 hours (Bristol-Myers Squibb, 2008).

Metformin is excreted unchanged in urine and does not undergo hepatic metabolism or biliary excretion (Bailey and Turner, 1996). This clearance is 3-4 times greater than creatinine clearance, indicating that the drug is eliminated by renal tubular secretion, almost 90% of the drug is eliminated renally after absorption within 24 hours (Scheen, 1996; Miller and Kraemer, 2000). Metformin plasma half life is 6.2 hours, while its blood half life is 17.6 hours, which indicates its distribution into the red blood cells (Bristol-Myers Squibb, 2008).

1.9.2.5.4 Adverse effects

Gastrointestinal transient side effects may occur during metformin usage such as abdominal discomfort, diarrhea, nausea, vomiting, flatulence, metallic taste, and anorexia. These side effects can be overcome by taking the drug with meals or starting with a low dose and increasing it gradually. Headache, rash and skin reactions may develop in some cases. Occasionally, the concentration of vitamin B_{12} may decrease but developing anemia is rare (BNF, 2005).

Lactic acidosis is the most serious side effect that may develop during metformin usage and can lead to death, but it is very rare with an incidence of 0.03 cases/1000 patients-year. However, if developed it may be fatal in 50% of cases (Miller and Kraemer, 2000; Salpeter *et al.*, 2003). Lactic acidosis symptoms are weakness, abdominal distress, malaise, myalgia and heavy strained breathing. It is characterised

by elevated blood lactate levels > 5mmol/l, increased lactate/pyruvate ratio, decreased pH of the blood and electrolyte disturbance with an increased anion gap. Metformin plasma concentration is found to be > 5µg/ml (Bristol-Myers Squibb, 2008).

Metformin is rarely associated with lactic acidosis because it is not metabolised and does not inhibit glucose peripheral oxidation or enhance peripheral production of lactate. It may increase lactate production in the liver and gut as it may decrease the conversion of glucose lactate to glucose (Koda-Kimble *et al*., 2005). Metformin does not cause hypoglycemia and is associated with weight loss more than weight gain (Miller and Kraemer, 2000).

1.9.2.5.5 Precautions and contraindications

Metformin is contraindicated in cases of renal impairment or renal disease (when creatinine ≥ 1.5 mg/dl), liver disease, cardiac heart failure, shock, myocardial infarction or sepsis as these conditions may increase the risk of lactic acidosis (Koda-Kimble *et al.*, 2005). It is also contraindicated in acute or chronic metabolic acidosis such as diabetic ketoacidosis with or without coma or in case of hypersensitivity to metformin (Bristol-Myers Squibb, 2008).

Metformin should be used with caution in elderly patients because advanced age is associated with reduction in renal function. All elderly patients especially those above 80 years old should receive minimum effective doses with regular monitoring of renal function (Koda-Kimble *et al*., 2005). The drug must be temporarily discontinued in patients undergoing radiological procedures where intravenous iodinated contrast materials are used or surgery as these conditions may cause changes in renal status (Miller and Kraemer, 2000).

1.9.2.5.6 Metformin-drug interactions

Careful monitoring and dose adjustment is recommended on coadministration of metformin with furosemide as it will increase plasma and blood concentration of metformin but with no significant change in its renal clearance.

Nifedipine when used concomitantly with metformin will increase the plasma concentration and urinary excretion of metformin and also shown to enhance metformin absorption (Bristol-Myers Squibb, 2008).

Cimetidine when administered together with metformin will also increase plasma and blood concentration of metformin and competes with it for the renal tubular transport system. Such interactions are also seen when metformin is administered with cationic drugs like ranitidine, amiloride, digoxin, morphine, procainamide, quinidine, quinine, triamterene, trimethoprim or vancomycin (BNF, 2005).

Drugs like thiazides or other diuretics, corticosteroids, calcium channel blockers, phenytoin, oral contraceptives, estrogens, thyroid products, phenothiazines, nicotinic acid, isoniazid and sympathomimetics seem to cause hyperglymia and loss of glycemic control so patients must be monitored for loss of blood glucose control (Bristol-Myers Squibb, 2008).

Hypoglycemia is not developed during metformin monotherapy but may occur when it is used in combination with insulin or sulfonylurea (Miller and Kraemer, 2000).

Patients should be warned about excessive intake of alcohol as it may enhance the effect of metformin on lactate metabolism (Koda-Kimble *et al*., 2005).

Metformin usage is not recommended during pregnancy and for patients under 10 years old (Bristol-Myers Squibb, 2008).

1.9.2.5.7 Dosage and administration

The dose of metformin must be divided according to effectiveness and tolerance. The minimum effective dose is 500 mg to be taken 2-3 times in a day not exceeding the maximum daily dose which is 2250 mg or 850 mg once daily to be given with meals to decrease gastrointestinal adverse effects (BNF, 2005). Metformin should be started with a low dose, then increasing it gradually not only to overcome the gastrointestinal adverse effects, but also to help in identifying the minimum effective dose for adequate blood glucose control (Miller and Kraemer, 2000).

The therapeutic goal for the treatment with metformin is to reduce FPG and HbA_{1c} to normal or around normal values by using the lowest effective dose, thus the FPG should be monitored to identify this dose. HbA_{1c} monitoring is also required as three months' interval (Bristol-Myers Squibb, 2008).

1.9.3 Antidyslipidemic agents

Atherosclerosis is the main pathological process that leads to the development of macrovascular complications in diabetes type 2 patients (Boyle, 2007). Treating type 2 diabetes should focus on managing CVD risk factors including hypertension and dyslipidemia as well as controlling elevated glucose levels to reduce microvascular complications (Betteridge, 2004).

Diabetic dyslipidemia is a combined hyperlipidemia with high TG, low HDL and small, dense LDL particles which requires the combination of antidyslipidemic drugs together with oral antidiabetics to normalize glucose and lipid levels when the diet and exercise alone fail to control both (Knopp *et al*., 2003). Classes of antidyslipidemics are:

1.9.3.1 *Bile acid sequestrants*

Cholestyramine and colestipol are the two agents of this class. They act by binding bile acids and preventing their reabsorption which will enhance hepatic conversion of cholesterol to bile acids causing rise in LDL receptors and increase its clearance (Einarsson *et al.*, 1991; BNF, 2005).

These agents decrease LDL levels by 15-30% and increase HDL by 3-5% but may increase TG levels, thus they must be used with caution. They are usually used in combination with statins as a second–line therapy or sometimes as first-line in patients who cannot tolerate or allergic to statins (WHO, 2006b).

1.9.3.2 *Ezetimibe*

This agent inhibits cholesterol absorption from the intestine; it lowers LDL levels and is used in combination with statins (BNF, 2005). This agent has no effect on TG, but it decreases LDL levels by 15-20% and increase HDL levels by 3-4% (Bays *et al.*, 2001; WHO, 2006b).

1.9.3.3 *Nicotinic acid*

Its main action is to decrease hepatic production of VLDL by decreasing TG production (Kraemer and Miller, 2000). Nicotinic acid reduces LDL levels by 15-25% and decrease TG levels by 20-50% and increases HDL levels 15-35% (Grundy *et al.*, 1981; WHO, 2006b). It is used in combination with statins or alone in patients who have sensitivity to statins (BNF, 2005). Because of its mild action on raising blood glucose, nicotinic acid should be used with caution in diabetic patients and it is better to keep the dose below 2 g/day. It should be avoided in patients with poor glycemic control (Solano and Goldberg, 2006).

1.9.3.4 *Fibrates*

Bezafibrate, ciprofibrate, fenofibrate and gemfibrozil are agents of this class. They act by enhancing lipoprotein lipase activity leading to increase VLDL catabolism and subsequent reduction in VLDL and TG concentrations (Kraemer and Miller, 2000). The effect of fibrates on LDL is variable (BNF, 2005), in patients with elevated TG levels fibrates may increase LDL levels. When TG levels are normal these agents will reduce LDL levels by 5-20%, reduce TG levels by 20-50% and rise HDL levels by10-20% (WHO, 2006b). Fibrates may reduce the risk of CVD in patients with elevated TG levels either alone or in combination with statins. Combination with a statin will increase the risk of myopathy and in this case high statin doses must be avoided (Prueksaritanont *et al*., 2002; Solano and Goldberg, 2006).

1.9.3.5 *Statins or HMGCoA reductase inhibitors*

Atrovastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin are the agents of this class. They have the most potent efficacy in lowering cholesterol (BNF, 2005). These agents decrease LDL levels by 20-40% with initial doses and 35-60% with maximum doses; decrease TG levels by 15-45% and rises HDL levels by 5-8% (Jones *et al.*, 1998). All statins have the same mechanism of action which is the inhibition of the enzyme that is involved in cholesterol synthesis 3-hydroxy-3-methylglutaryl coenzyme A reductase, particularly in the liver (Mckenney, 2005). This research will focus on lovastatin because it is the drug most prescribed for patients with diabetic dyslipidemia in Hospital Pulau Pinang.

1.9.3.5.1 History of Lovastatin

During 1970s several metabolites were isolated from *Penicillium citrinum*. They could inhibit HMGCoA reductase enzyme which is the rate-limiting step in cholesterol synthesis. One of these metabolites was the compactin, but it was never released to the market for an unknown reason (Kraemer and Miller, 2000). Shortly after that a related compound was isolated from *Aspergillus terreus* and from the fungi *Pleurotus ostreatus,* which is mevinolin or lovastatin (Bobek *et al*., 1998). It was approved for sale in the United States in 1987 (Kraemer and Miller, 2000).

Lovastatin is a nonhygroscopic white crystalline powder, insoluble in water and sparingly soluble in methanol, ethanol and acetonitrile; its molecular formula is $C_{24}H_{36}O_5$ with a molecular weight of 404.55. Chemical structure of lovastatin is shown in Figure 2 (Merck and Co., 2008).

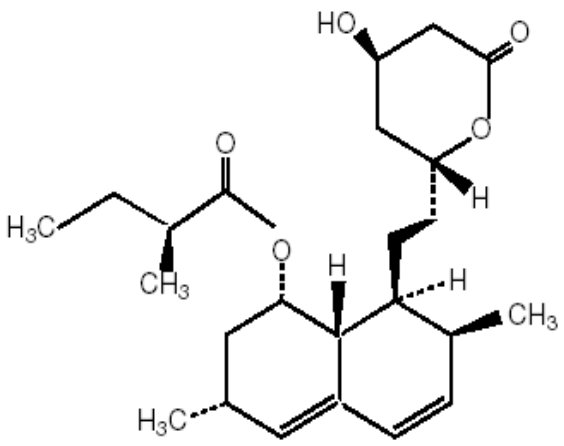


Figure 2: Lovastatin chemical structure (Prescribing information leaflet for Mevacor®, Merck and Co. Inc., 2008).