EVALUATION OF METFORMIN USAGE IN TREATMENT OF PATIENTS WITH TYPE-2 DIABETES MELLITUS IN PENANG GENERAL HOSPITAL

By

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Thesis submitted in fulfillment of the requirements for the Degree of Master of Science (Pharmacy)
Dedication…..

To the one whose feet Paradise rests on…..
My beloved mother, Madam Ma'eda Al-ka'bi…..for her prayers, unflagging love, and tremendous sacrifices which came with much difficulties and pains. She is always a constant source of inspiration and motivation in my life. I learned from her strength how to face life strappingly. Her support and love have pulled me throughout my difficult times.

In memory of the martyr hero…
My beloved father Mr. Suhail Najim Al-anbari…..who strived and sacrificed to give me and all people the best, prepared me to face challenges with faith in concepts, humility and morality. Although he is not here to give me the strength and support by his wonderful, encouraging smile, I always feel his presence, which motivates me to strive to achieve my goals in life. Thanks father for making me hold high your bright name and history. May Allah (SWT) forgive you and make Paradise your permanent residence.

To my beloved sisters…
Dr.Samera Suhail Al-anbari and Dr. Hind Suhail Al-anbari…
Thanks for your unconditional love that touches my heart…I thank God for such wonderful sisters…forever.

To my beloved brothers…
Dr.Mohamed Hassan Suhail Al-anbari and Dr. Najm Suhail Al-anbari…. You kept my spirits up when I found it difficult to endure the challenges….you kept me smiling and strong…Thanks for your love, passion, and tremendous concern that lifted me up when this thesis seemed undoable…I'm proud of you and will remain so, brothers…forever.
Thank you all for being my family…

Hafsa Suhail Najim Al-anbari
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TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEDICATION</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>iii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xv</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xvi</td>
</tr>
<tr>
<td>ABSTRAK</td>
<td>xix</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>xxii</td>
</tr>
</tbody>
</table>

CHAPTER 1 - INTRODUCTION

1.1 Background.................................................................1
1.2 Definitions.................................................................4  
   1.2.1 Type-2 diabetes......................................................4  
   1.2.2 Metformin..............................................................4  
1.3 Epidemiology and prevalence.........................4  
1.4 Pathophysiology of type-2.................................6  
1.5 Clinical presentations.................................9  
1.6 Diagnosis.............................................................10  
1.7 Treatment.............................................................11  
   1.7.1 Dietary therapy..................................................11
1.7.2 Exercise...........................................................................................................12
1.7.3 Pharmacologic therapy.....................................................................................13
  1.7.3.1 α-Glucosidase inhibitors..............................................................................13
  1.7.3.2 Nonsulfonylurea insulin secretagogues.......................................................14
  1.7.3.3 Sulfonylureas.................................................................................................14
  1.7.3.4 Thiazolidinediones (TZDs).............................................................................15
  1.7.3.5 Metformin.......................................................................................................15
  1.7.3.6 Insulin.............................................................................................................16
1.8 Complications of type-2 diabetes.....................................................................18
1.9 Prevention............................................................................................................20
1.10 Monitoring.........................................................................................................22
  1.10.1 Urine ketone test.............................................................................................23
  1.10.2 Plasma glucose.................................................................................................23
  1.10.3 Glycosylated hemoglobin (HbA1c)...................................................................24
  1.10.4 Glycated serum protein (GSP), glycated serum albumin.........................24
1.11 Guidelines..........................................................................................................25
  1.11.1 International guidelines..................................................................................25
  1.11.2 National guideline..........................................................................................26
1.12 Metformin Hydrochloride.................................................................................27
  1.12.1 Properties and chemical structure.................................................................28
  1.12.2 Dosage.............................................................................................................30
  1.12.3 Pharmacokinetics............................................................................................32
  1.12.4 Mechanism of action.....................................................................................34
CHAPTER 2 - LITERATURE REVIEW

2.1 The inappropriate prescribing of metformin with contraindications to its use
CHAPTER 3 - MATERIALS AND METHOD

3.1 Introduction.................................................................72
3.2 Literature search.........................................................72
3.3 Study design.............................................................73
  3.3.1 Intervention and tools.............................................74
  3.3.3 Pilot test.............................................................77
3.4 The study sample.........................................................78
  3.4.1 Sample size calculation.........................................78
  3.4.2 Samples Criteria..................................................79
    3.4.2.1 Inclusion criteria..........................................79
    3.4.2.2 Exclusion Criteria.........................................79
  3.4.3 Sampling technique..............................................79
3.5 Data analysis............................................................80
  3.5.1 Data entry.........................................................80
  3.5.2 Data classification...............................................81
  3.5.3 Statistical analysis..............................................81
3.6 Study approval..........................................................82

CHAPTER 4 - RESULTS

4.1 Introduction.............................................................83
4.2 Analysis and results..................................................83
  4.2.1 Demographic and lifestyle analysis..........................84
  4.2.2 Descriptive results of variables...............................87
4.2.3 Evaluation of Metformin usage..................................................105
   4.2.3.1 Descriptive analysis......................................................105
   4.2.3.2 Comparison of clinical findings between the appropriate and the inappropriate use of metformin ..............................112
       4.2.3.2.1 Comparing categorical variables........................112
       4.2.3.2.2 Comparing scaled data.................................123

CHAPTER 5-DISCUSSION AND CONCLUSION

CONCLUSION.............................................................................142
5.1 Conclusion.............................................................................160
5.2 Recommendations...............................................................164

REFERENCES..............................................................................166

APPENDICES

Appendix A Anti-diabetic drugs which are available in Malaysia
Appendix B Data collection form of metformin usage evaluation
Appendix C-1 School of Pharmaceutical Science request to start data collection of pilot test at USM health centre
Appendix C-2 USM health center approval letter
Appendix C-3 Penang General Hospital approval letter
Appendix C-4 Penang General Hospital, CRC approval letter to start data collection
Appendix D List of publications
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1</td>
<td>The most common adverse effects (&gt; 5%) in a placebo-controlled clinical study of Glucophage monotherapy.</td>
<td>36</td>
</tr>
<tr>
<td>Table 4.1</td>
<td>The crosstabulation between ethnic distribution and age group.</td>
<td>86</td>
</tr>
<tr>
<td>Table 4.2</td>
<td>The demographic and lifestyle variables</td>
<td>87</td>
</tr>
<tr>
<td>Table 4.3</td>
<td>The distribution of complications among races</td>
<td>88</td>
</tr>
<tr>
<td>Table 4.4</td>
<td>Metformin-drug interactions</td>
<td>89</td>
</tr>
<tr>
<td>Table 4.5</td>
<td>Common adverse effects among patients during study period</td>
<td>90</td>
</tr>
<tr>
<td>Table 4.6</td>
<td>Adverse effects- metformin prescription crosstabulation</td>
<td>90</td>
</tr>
<tr>
<td>Table 4.7</td>
<td>Presence of obesity among races</td>
<td>91</td>
</tr>
<tr>
<td>Table 4.8</td>
<td>Relationship between obesity and the presence of diabetic type 2 complications.</td>
<td>93</td>
</tr>
<tr>
<td>Table 4.9</td>
<td>Relationship between metformin dosing (overdose) and presence of diabetic complications</td>
<td>95</td>
</tr>
<tr>
<td>Table 4.10</td>
<td>Relationship between metformin dosing (overdose) and metformin regimen.</td>
<td>96</td>
</tr>
<tr>
<td>Table 4.11</td>
<td>The relationship between Metformin dosing and blood glucose level assessment.</td>
<td>97</td>
</tr>
<tr>
<td>Table 4.12</td>
<td>The relationship between Metformin dosing (subtherapeutic dose) and blood glucose level assessment.</td>
<td>98</td>
</tr>
</tbody>
</table>
Table 4.13  The relationship between blood glucose control and the presence of diabetic complications  

Table 4.14  The relationship between Blood glucose assessments and ethnicity  

Table 4.15  The relationship between blood glucose control and metformin regimen.  

Table 4.16  The relationship between presence of diabetic complications and metformin regimen  

Table 4.17  The relationship between the existence of adverse effects and metformin regimen  

Table 4.18  The association of metformin regimen and types of the common adverse effects among patients in study sample size.  

Table 4.19  Distribution of contraindications among 336 diabetic type 2 patients on metformin  

Table 4.20  The association of races with the use of metformin (AUM, IUM)  

Table 4.21  Types of contraindications associated with races contraindications and ethnic  

Table 4.22  Association of races with the number of contraindications  

Table 4.23  The relationship between clinical outcomes and metformin prescription.  

Table 4.24  The distribution of diabetic complications in among AUM and IUM groups.  

Table 4.25  The relationship between metformin prescription and metformin regimen as monotherapy and combination therapy  

Table 4.26  patients who had glucosuria at the endpoint among AUM and IUM groups
Table 4.27  Hyperkalemia among AUM and IUM groups at baseline and endpoint.

Table 4.28  Hyperuricemia among AUM and IUM groups at baseline and endpoint.

Table 4.29  Albuminuria among AUM and IUM groups at baseline and endpoint.

Table 4.30  The relationship between metformin prescription and body weight monitoring

Table 4.31  Metformin and high BMI crosstabulation

Table 4.32  The distribution of adverse effects among the metformin prescription groups.

Table 4.33  Comparison of means of age, metformin dose, weight, and BMI between metformin prescription groups

Table 4.34  The association between mean weight at baseline and at endpoint in within each group of metformin prescription.

Table 4.35  The association between mean BMI at baseline and at endpoint in within each group of metformin prescription.

Table 4.36  Comparison of means of systolic and diastolic blood pressure between metformin prescription groups.

Table 4.37  Relationship between mean systolic and diastolic blood pressure at baseline and at endpoint in within each group of metformin prescription.

Table 4.38  Relationship between mean diastolic blood pressure at baseline and at endpoint in within each group, AUM and IUM.
Table 4.39  Comparison of means of the highest and the lowest fasting glucose between the AMU and the IUM groups.

Table 4.40  Comparing mean of the highest FBG at baseline and at endpoint within each group, the AUM and the IUM group.

Table 4.41  Comparing mean of the lowest FBG at baseline and at endpoint in within each group, AUM and IUM.

Table 4.42  Glycocylated hemoglobin (HbA1c) initial and final means in AUM and IUM.

Table 4.43  Comparing mean Glycocylated hemoglobin (HbA1c) at baseline and at endpoint in within each group, AUM and IUM.

Table 4.44  Lipid profile at baseline and at endpoint among AUM and IUM groups.

Table 4.45  Comparison of mean of the total cholesterol at baseline and at endpoint in within each group, AUM and IUM.

Table 4.46  Comparison of of mean of the LDL at baseline and at endpoint in within each group, AUM and IUM.

Table 4.47  Comparison of of mean of the TG at baseline and at endpoint in within each group, AUM and IUM.

Table 4.48  Linear regression (listwise) of constants and the dependent HbA1c values at the endpoint (n=456).
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1.1</td>
<td>Metformin (N,N-dimethylimidodicarbonimidicdiamide) chemical structure (British Pharmacopeia, 2007).</td>
<td>29</td>
</tr>
<tr>
<td>Figure 1.2</td>
<td>Phenformin (Imidodicarbonimidic diamide, N-(2-phenylethyl)-) chemical structure (British Pharmacopeia, 2007).</td>
<td>29</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Age profile in diabetes mellitus type 2 patients (sample size) on metformin</td>
<td>84</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Ethnic distributions among sample size</td>
<td>85</td>
</tr>
<tr>
<td>Figure 4.3</td>
<td>Percentage of obesity in diabetic type-2 patients within ethnic groups</td>
<td>92</td>
</tr>
<tr>
<td>Figure 4.4</td>
<td>Frequency of metformin doses /day</td>
<td>94</td>
</tr>
<tr>
<td>Figure 4.5</td>
<td>The frequency of inappropriate use of metformin (with contraindications) among study population</td>
<td>105</td>
</tr>
<tr>
<td>Figure 4.6</td>
<td>Metformin use in percentage among ethnic groups</td>
<td>107</td>
</tr>
<tr>
<td>Figure 4.7</td>
<td>Comparing the percentages of complications among the AUM and IUM</td>
<td>113</td>
</tr>
<tr>
<td>Figure 4.8</td>
<td>Comparison between baseline and endpoint means of HbA$_{1c}$ in appropriate and inappropriate use groups of metformin</td>
<td>134</td>
</tr>
<tr>
<td>Figure 4.9</td>
<td>Mean total cholesterol at baseline and endpoint in AUM and IUM groups</td>
<td>136</td>
</tr>
<tr>
<td>Figure 4.10</td>
<td>Mean LDL at baseline and endpoint in AUM and IUM groups.</td>
<td>137</td>
</tr>
<tr>
<td>Figure 4.11</td>
<td>Mean TG at baseline and endpoint in AUM and IUM groups.</td>
<td>137</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

ACEI                Angiotensin-converting enzyme inhibitors
ADA                American Diabetes Association
AHFS              American Society of Health-System Pharmacists
ARBs               Angiotensin II-receptor blockers
AUC                Area under the curve
AUM               Appropriate use of metformin
BMI                 Body mass index
CAD                Coronary artery diseases
CDC                Center of Disease Control
CHF                Congestive Heart Failure
COPD              Chronic obstructive pulmonary diseases
CMS                Center of Medicare and Medicaid Services
CVA               Cerebrovascular Accident
CVD                Cardiovascular diseases
DECODE the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe
ED                Emergency Department
ESRD             End Stage Renal Disease
FDA                Food and Drug Association
FFA               Free fatty acid
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GSP</td>
<td>Glycated serum protein</td>
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<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic Heart Diseases</td>
</tr>
<tr>
<td>IUM</td>
<td>Inappropriate use of metformin</td>
</tr>
<tr>
<td>I.V</td>
<td>Intra Venous</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>MALA</td>
<td>Metformin-associated lactic acidosis</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MIEPA</td>
<td>the McKeever Institute of Economic Policy Analysis</td>
</tr>
<tr>
<td>NHMS</td>
<td>National Health Morbidity Survey</td>
</tr>
<tr>
<td>NDDG</td>
<td>National Diabetes Data Group</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
</tr>
<tr>
<td>NPH</td>
<td>Neutral Protamine Hagedorn</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>RAS</td>
<td>Renin-Angiotensin System</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>RPG</td>
<td>Random plasma glucose RPG</td>
</tr>
<tr>
<td>TZDs</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
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<td>-----------</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>USM</td>
<td>Universiti Sains Malaysia</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>UPMC</td>
<td>University of Pittsburgh Medical Center</td>
</tr>
<tr>
<td>USRDS</td>
<td>United States Renal Data System</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
PENILAIAN PENGGUNAAN METFORMIN DALAM RAWATAN PESAKIT DIABETES MELLITUS JENIS-2 DI PULAU PINANG GENERAL HOSPITAL

ABSTRAK

yang dikeluarkan oleh Kementerian Kesihatan di Malaysia. Daripada 1248 rekod pesakit, seramai 1001 orang pesakit diabetes jenis-2 menggunakan metformin iaitu 54.7% daripadanya golongan wanita dan 45.4% terdiri daripada golongan lelaki. Data juga menunjukkan pecahan berdasarkan kaum, iaitu, kaum Cina seramai 47.5%, diikuti oleh kaum Melayu seramai 28.4% dan kaum India 23.9%. Kajian turut mendapati penyakit kerosakan hati yang secara signifikan berlaku pada pesakit daripada kaum India. Selain itu, kajian juga mendapati bahawa penyakit kardiovaskular lebih banyak dihidapi oleh pesakit daripada kaum Cina berbanding kaum lain, manakala penyakit pernafasan yang kronik secara signifikan berlaku dalam kalangan pesakit kaum Melayu berbanding kaum lain. Masalah kegemukan pula didapati berlaku dalam 58.1% daripada populasi kajian. Daripada 1001 pesakit, sebanyak 33.6% mengalami sekurang-kurangnya satu kontraindikasi. Kontraindikasi yang paling ketara dalam kajian ini ialah kerosakan buah pinggang, kerosakan hati, penyakit kardiovaskular, dan penyakit pernafasan yang kronik. Selain itu, hasil kajian turut menunjukkan bahawa komplikasi seperti retinopati, neuropati, nefropati, hipertensi, dislipidemia, penyakit kardiovaskular dan komplikasi lain sering berlaku kepada pesakit yang menggunakan metformin dengan kontraindikasi (nilai \( P = 0.001 \)) iaitu sebanyak 96.1% (n=323/336). Sebagai kesimpulan didapati bahawa, kekerapan ketidaksesuaian penggunaan metformin adalah sebanyak 33.6%. Masalah ini berkaitan dengan adanya komplikasi dan kemungkinan akan bertambah pada masa hadapan. Semasa amalan terapeutik, kajian ini mencadangkan penilaian yang wajar sebelum memulakan terapi metformin, semasa terapi metformin dan pada setiap tahun.
Penyesuaian dos juga perlu dilakukan mengikut risiko penyakit yang ada. Kepatuhan pada garis panduan penggunaan juga perlu diberi perhatian.

**Kata kunci:** metformin, diabetes mellitus jenis-2, kontraindikasi, penggunaan yang kurang sesuai, Malaysia.
EVALUATION OF METFORMIN USAGE IN TREATMENT OF PATIENTS WITH TYPE-2 DIABETES MELLITUS IN PENANG GENERAL HOSPITAL

ABSTRACT

Metformin is common and effective in controlling blood glucose among type-2 diabetics when given alone or in combination with sulfonylurea or insulin. However, indiscriminate prescription of medications may lead to potentially avoidable complications and deteriorations of health status. This is usually observed in patients with major contraindications to metformin. In this study, the aim is to determine the prevalence of conditions regarded as contraindications to metformin usage and the adherence to the prescribing guidelines according to the manufacturer's recommendations and Ministry of Health guidelines in Malaysia. It went further to risk-benefit assessment of using metformin with contraindications throughout the therapeutic process. A retrospective-prospective observational study was carried out in Penang General Hospital outpatients' clinic, Malaysia. Demographic information and information about disease and medication profile were retrieved using the medical records. Data were analyzed by using Statistical Package of Social Sciences (SPSS) program version 15. The center of attention was on metformin usage. The identification of the appropriate and the inappropriate use of metformin were according to the manufacturer's recommendations and Ministry of Health guidelines in Malaysia. From 1248 patients' medical records, 1001 diabetic type 2 patients on metformin were included. There were 54.7% females group and 45.4% males in the study group.
Data also showed the race distribution that is 47.7% Chinese, followed by 28.4% Malays and 23.4% Indians. This study showed also that liver impairment was found to be significantly more among Indian patients than other races. Cardiovascular diseases were found to be significantly higher among Chinese patients than other races, while chronic respiratory diseases were found to be higher among Malay patients than other races. Obesity was found in 58.1% of study population. From 1001 diabetic type-2 patients on metformin, 33.6% had at least one contraindication. The most commonly present contraindications in this study were renal impairment, liver impairment, cardiovascular diseases, and chronic respiratory diseases. Besides, the results of the study showed that complications like retinopathy, neuropathy, nephropathy, hypertension, dyslipidemia, cardiovascular diseases and other complications found to be more frequent in 96.1% (n=323/336) of patients who used metformin with contraindications ($P$ value = 0.001). In conclusion, the inappropriate use of metformin is as frequent as 33.6% and disregarded. It is associated with presence of complications and has a possibility in growth in future. During therapeutic practice, this study recommends serious assessment before initiating and during metformin therapy and annually. Dose adjustment is also needed according to the presence of risk factors. More adherences to the guidelines should be taken in consideration.

**Key-words:** metformin, type-2 diabetes mellitus, contraindications, inappropriate use, Malaysia.
CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes mellitus is a syndrome that is caused by a relative or an absolute lack of insulin. It is a chronic disease characterized by symptomatic increase in blood glucose concentration (hyperglycemia) as well as lipid and protein metabolism alterations (Koda-Kimble et al. 2005). Chronically, these metabolic abnormalities, particularly hyperglycemia, contribute to complications development such as nephropathy, neuropathy, retinopathy and cardiovascular complications (Harvey et al. 2006). This syndrome was first recognized centuries ago by the initial observations of two Indian physicians - Chakrata and Susruta (600 B.C) - who differentiated two forms of the disease. During the last decade, research has led to the recognition that diabetes mellitus can be classified by different types with different etiologies, although their pathologic sequences may be similar after onset of disease (Koda-Kimble et al. 2005). Type-1 diabetes which results from the destruction of the auto immune pancreatic beta-cells and causes an absolute deficiency of insulin is also known as insulin-dependent diabetes. Type-1 diabetes is the type that most commonly afflict individuals around the time of puberty (Koda-Kimble et al. 2005). Type-1 diabetes is treated by insulin, diet and exercise (Franz et al. 2004). Diabetes type-2 is a non-insulin-dependant diabetes mellitus. It results when the pancreas retains some beta-cell function, but the variable insulin secretion is insufficient to maintain glucose homeostasis. Type-2
diabetes is also known as adult-onset diabetes (Howlett et al. 2003). Factors that influence the development of type 2 diabetes include genetic factors, environmental factors, obesity, physical activity, birth weight and diabetic pregnancy (Misbin, 1999).

Diabetes type-2 is treated by diet, exercise and oral anti-diabetic agents; insulin is used when the oral anti-diabetic agents fail to maintain glycemic control (Stenman et al. 1993). Oral anti-diabetic drugs that are used in type-2 diabetes include: Sulfonylurea; biguanides; α-glucosidase inhibitors; thiazolidandiones and non-sulfonylurea insulin secretagogues (Stenman et al. 1993). Metformin is the only currently available biguanide. Indeed, it is one of the most widely used oral anti-diabetic drugs, which is the first drug of choice in obese patients whose diet control fails to control diabetes. It’s also used in patients on sulfonylurea with inadequate control of diabetes (Kirpichnikov et al. 1993; United Kingdom Prospective Diabetes Study (UKPDS) 28, 1998).

Back to the folk cures, guanidine compounds in Galega officinalis (French lilac) were used in treating diabetes mellitus as early treatment for diabetes. Refined guanidine is the active agent in the Galega preparations which produced acceptable gastrointestinal toxicity. Consequently, derivative such as biguanides (a combination of two guanide molecules less ammonia radical) were synthesized and used in the early part of this century. These were rapidly displaced by insulin soon after its discovery, although they were used in clinical practice for years (Bailey et al. 1989). Metformin was marketed in Europe and Canada during the 1970s. Its approval in the United States was related primarily to inquiries regarding the potential risk of lactic acidosis.
Now, metformin is reviewed as an agent that improves the sensitivity of the liver and muscle to insulin, and it is demonstrated by the landmark United Kingdom Prospective Diabetes study (UKPDS). This group established that metformin has favorable effects on body weight, lipid profile and fibrinolysis (UKPDS 34, 1998). Lactic acidosis, the serious condition that prompted the removal of phenformin (the oldest member of biguanide) worldwide, has become a low incidence problem since metformin's introduction (Cusik & DeFronzo 1998).

Most cases of lactic acidosis associated with metformin have been reported in patients in whom metformin was contraindicated (Hulisz et al. 1998). Metformin is contraindicated in type-2 diabetics with conditions like renal and/or hepatic disease, cardiac or respiratory insufficiency, a history of alcohol abuse, severe infections, or pregnancy. It should be withheld in type-2 diabetes patient undergoing diagnosis requiring intravenous radiographic contrast agents (Koda- Kimble et al. 2005; Harvey et al. 2006). That is also in accordance with the Ministry of Health Guidelines in Malaysia (Ministry of Health, Persatuan Diabetes Malaysia (PMD), Academy of Medicine 2004). Studies assessing the appropriate use of metformin based on the recommendations of the manufacturer reveal the frequent inappropriate use of metformin. Metformin is frequently has been used with its contraindications (Koda- Kimble et al. 2005). As metformin is a very commonly used drug, we have to clarify the appropriate, inappropriate use of this drug and the clinical outcomes.
1.2 Definitions

1.2.1 Type-2 diabetes: a heterogeneous disorder that is characterized by pancreatic beta-cell dysfunction, resistance to insulin action, increased hepatic production of glucose and obesity. Its prevalence increased dramatically with age (Kenny et al. 1995). The majority of diabetics are with type-2 diabetes (Misbin, 1999).

1.2.2 Metformin: the only currently available form of biguanides group of oral antidiabetic agents. Generally, it has been available since 1995 in the United States (Klepser & Kelly 1997).

1.3 Epidemiology & prevalence

Diabetes mellitus has a high prevalence worldwide in both developed and developing countries (Wild et al. 2004). It affects all races, but some much more than others. Its prevalence and incidence has increased in many populations, especially those in the developing countries. According to the WHO (World Health Organization), the epidemiology of diabetes is extremely related to the lifestyle and economic changes (King & Rewer 1991). Type-2 diabetes has a distinctive epidemiology, with much of the variation in frequency accounted for by known risk factors, which are: Genetic factors, environmental factors, obesity, physical activity, diet, birth weight, and diabetic pregnancy (Misbin 1999).
Of the 100 million people affected by diabetes mellitus worldwide, 7 million are in Asia (Embong 2002). The worldwide prevalence of diabetes has grown to alarming levels and it is estimated that at least 170 million will be affected by diabetes by 2030; the increase is particularly evident in the developing countries (Bril & Ktorza 2006). It is possible that as many as half of the cases have not been diagnosed (Misbin 1999). Recent epidemiologic studies have shown an increased prevalence in diabetes in India, of 12.1% (Ramachandran et al. 2001), in Pakistan, of 11.1% (Shero et al. 1999), and in China, of 6.1% (Dong et al. 2005).

The increase in diabetes prevalence has also been noticed among Asian Americans. Among the contributing causes are population aging, urbanization, increasing obesity and physical inactivity (Marguerite et al. 2004). In Malaysia, prevalence of diabetes mellitus has gradually increased over the years from 0.65% in 1960 to 2% in 1982 (Embong 2002). The first National Health Morbidity Survey (NHMS) conducted in 1986 reported a prevalence of diabetes mellitus of 6.3%. In 1996 the prevalence had risen to 8.2% (National Health Morbidity Survey, 1997). According to the WHO statistics of Diabetes Program, the prevalence in Malaysia in 2000 numbered 942,000 and is estimated to rise to 2,479,000 by 2030 (UKPDS Group 37, 1999). A study in Kelantan reports the state’s prevalence to be at 10.5% (Mafauzy 2006).

The prevalence of type-1 diabetes constituted approximately 5%-10%. Type-2 prevalence constituted approximately 90% (King et al. 1998). Hospital-based data in Malaysia indicate complication rate to be as high as 50%, those associated with hypertension was seen in 10-20%, hyperlipidemia
in 29% of patients, and in one study, 38% of patients have multiple complications (Ooyub et al. 2004). Type 2 diabetes is the most common type and its prevalence varies enormously from population to population and throughout the world (King & Rewer 1991). WHO estimates that by 2025 about 200-300 million people worldwide will have developed type-2 diabetes and according to statistics from the Center of Disease Control (CDC). This means an increase of about 6 million patients every year (Center of Disease Control, 2002).

1.4 Pathophysiology of type-2 Diabetes Mellitus

Type-2 diabetes is the most common of the 2 types of diabetes mellitus. It affects the majority of people with diabetes and is a complex metabolic disease characterized by elevated plasma glucose levels (American Diabetes Association (ADA), 2004). Insulin is the major anabolic hormone and its action is essential for appropriate tissue development and growth. Homeostasis is the process of insulin secretion by the pancreatic β-cell in response to increased circulating levels of glucose and amino acids after meal (DeFrnozo 1988). Insulin regulates glucose blood level at several sites. It is reducing hepatic glucose production by decreased gluconeogenesis and glycogenolysis and increasing the rate of glucose uptake especially into skeletal muscle and adipose tissue (Shulman 2000). Insulin also affect lipid metabolism, increasing lipid synthesis in liver and fat cells, and decreasing fatty acid release from adipose tissue (Georgio Sesti 2006). Clinically, hyperglycemia during fasting is caused by unrestrained basal hepatic glucose output primarily a
consequence of liver resistance to insulin action. On the other hand, postprandial hyperglycemia is caused by the abnormal secretion of insulin from β-cell in the pancreas in response to meal, over production of glucose by liver, and effective glucose uptake by peripheral tissue, especially, skeletal muscles (Georgino 2005).

The secretion kinetic of the β-cell and tissue sensitivity to insulin is impaired by chronic hyperglycemia or phenomenon known as glucotoxicity (Dailey 2004). Thus, both insulin resistance (impaired insulin action) and insulin deficiency (dysfunctional insulin secretion) represent the pith in the pathogenesis of type-2 diabetes (Georgino 2005). Long studies of Pima Indians on type-2 diabetes; suggest that the development of Type-2 diabetes is preceded by a defect in insulin secretion and the disease become evident only in the progression of insulin secretory dysfunction (Weyer et al 1999). In Pima Indians (Bogardus 1993) and Mexican Americans (Gulli et al. 1992), insulin resistance is the first identifiable defect. In white populations, β-cell deficiency appears to be more marked at an early stage in the development of diabetes mellitus (Vaag et al. 1995). As stated in the American Diabetes Association (ADA) Clinical Practice Recommendations (Georgino 2005), although insulin resistance and insulin deficiency usually coexist in the same patient with type-2 diabetes, phenotypic characterization studies make it easy to detect patients with either/or:

1- Predominant insulin resistance with relative insulin secretion impairment.

2- Predominant insulin secretion defect with various degree of insulin resistance.
According to the pathophysiology of type 2 diabetes, metformin lowers the blood glucose level in type-2 diabetics. However, it does not cause hypoglycemia even in non diabetic individuals unless given in overdose (Bailey & Turner 1996). Unlike sulfonylureas, metformin does not stimulate the release of insulin from the pancreas, and there is evidence that metformin lowers fasting blood glucose concentration by decreasing gluconeogenesis which will decrease hepatic glucose production. It is also seen to decrease the peripheral resistance to insulin by enhancing glucose utilization and clearance as well as reduction in plasma insulin concentration. It also lowers free fatty acid plasma level and subsequent oxidation which may attribute to its ability to reduce hepatic glucose production and increase the glucose disposal in the muscle mediated by insulin (Kirpichnikov et al. 2002).

Use of metformin is effective in lowering glycosylated hemoglobin (HbA1c) by 1 to 2 percentage points when used as monotherapy or in combination with other antidiabetic drugs (Stephen et al. 2003). In addition, metformin produces small decrements (5%-10%) in the total cholesterol level and (10%-20%) in triglycerides level, small increments or no change in HDL (high-density lipoprotein). It increases LDL (low-density lipoprotein) production which lead to increased LDL particle size as a result (Ohiro et al. 2007). Unlike sulfonylureas, thiazolidinediones and insulin, metformin have a positive effect on clotting factors, platelets function, vascular function and weight loss other than weight gain. These effects generated interest in the potentially favorable effects of metformin on cardiovascular disease and clinical outcomes (UKPDS 28, 1998).
1.5 Clinical presentations

The signs and symptoms associated with hyperglycemia in type-2 diabetes in general are fatigue, polyuria, polydipsia, and polyphagia. In addition, symptoms like weight loss, genital itching, stomatitis, balanitis, visual disturbances, and confusion irrespective of age, sex, BMI (Body Mass Index). As well, the presence of diabetic complications should be considered. It is diagnosed by routine physical examination (Stephen et al. 2003). The pre-diagnostic duration is short and associated with glycemic level (Dravishlom et al. 2005). The signs and symptoms in elderly often present atypically (Stephen et al. 2003). Classical symptoms associated with diabetes may be masked by other illnesses, absent, or may be explained away by the normal aging process like (Misbin 1999):

- Fatigue and visual disturbances, often are counted as a part of aging process.
- Polyuria, which may be minimized by higher glucose renal threshold or confounded by urinary incontinence or prostate problem.
- Thirst, which is commonly blunted in elderly patients, increasing their risk of dehydration and electrolyte disturbance.
- Hunger, which may be altered by medications or depression

Based on the above reasons, type-2 diabetes is commonly in elderly is under-diagnosed and under-treated (Stephen et al. 2003).

1.6 Diagnosis
The diagnostic criteria of the American Diabetes Association (ADA) are the same for children, adolescents, and adults (Copeland et al. 2005). Beside the signs and symptoms, diagnosis of type-2 diabetes must be confirmed by measurement of venous plasma glucose level (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD), and Academy of Medicine, 2004). The venous sample should be taken before initiating pharmacological therapy (Fonsaca et al. 2000). Diabetes is now diagnosed by one of three criteria:

1- Typical signs and symptoms of diabetes type-2 with random plasma glucose level (RPG) ≥ 11.1 mmol/l. It is defined as sampling at any time of day without consideration of the time of the last meal (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD), Academy of Medicine, 2004).

2- A fasting plasma glucose level (FPG) of ≥ 7.0 mmol/l. It is the most significant change from RPG and was proposed to be the major diagnostic criteria to abolish confusion over the role of FPG versus an oral glucose tolerance test (OGTT) (ADA, 2004).

3- A two-hour level ≥ 11.1 mmol/l (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD), Academy of Medicine, 2004) during a load of 75g oral glucose tolerance test OGTT (ADA, 2004). It is recommended for patients with high risk factors for diabetes mellitus with normal glucose level and for patients who have risk factors with crucial FPG of 5.6-6.9 mmol/l or RPG of 6.5-11.0 mmol/l. According to Clinical Practice Guidelines of Malaysia, one abnormal glucose value is diagnostic for the symptomatic patients, and two abnormal glucose values are required for the diagnosis in asymptomatic patients (Malaysian Ministry of Health, Persatuan Diabetes
Blood glucose values can be expressed in mg/dl, by multiplying the mmol/l value by factor 18 (Koda-Kimble et al. 2005).

1.7 Treatment

The most important point of glucose lowering therapy in diabetic patients is to prevent or delay the development of complications of this disease that menace the balance of life quality. There are three major components to the treatment of type-2 diabetes: diet, pharmacologic therapy (oral hypoglycemic agents, and insulin) and exercise. Diet and exercise therapy remains the cornerstone of management and should be adopted alone first. However, the extent and duration of advantage from this intervention is inadequate for most patients with type-2 diabetes (Consoli et al. 2004), as discussed below:

1.7.1 Dietary therapy

Current dietary advice for the management of diabetes mellitus provide guidelines that is in general the same for what would be measured prudent recommendation for general community (Willett 1994). Good glycemic control was assumed to be helpful to prevent complications, particularly microvascular complications of type-2 diabetes. Weight loss is still to be a goal for obese patients with type-2 diabetes to improve glycemic control and lipid profile (The Diabetes Control and Complications Trial Research Group, 1993). For fat, reduced body fat and increased intake of polyunsaturated or
vegetable polyunsaturated fats (Garg et al. 1994) may lead to the improvement of glycemic control. Consequently, this may correct or set up risk factors for type-2 diabetic complications like Coronary Artery Disease (CAD) (Hu 2003). For carbohydrates, viscous soluble fibers are considered to have a very small effect on decreasing serum cholesterol levels (ADA, 1994; Franz et al. 1994).

In comparison with starch, fructose may raise the level of low-density lipoprotein cholesterol (LDL) (Bantle et al. 1986; Swanson et al. 1992) despite its glycemic benefit (Franz et al. 1994). Reducing the rate of nutrient delivery like slowing carbohydrates absorption has been known as having a potential benefit in the management of type-2 diabetes (Kuo et al. 2007).

### 1.7.2 Exercise

Exercise plays an important therapeutic role in the management of type-2 diabetes and is often prescribed along with diet and pharmacologic therapy (American Council on Exercise (ACE), 2001). Moreover, there is now strong evidence to indicate that physical exercise prevents the development of type-2 diabetes in high risk populations. This supports the recommendation that increase physical exercise, together with the avoidance or treatment of obesity by dietary restriction is an important factor of lifestyle modification. This change in lifestyle is crucial for people with predisposing factors like impaired glucose tolerance, history of gestational diabetes mellitus, or family history of type-2 diabetes mellitus. Benefits of exercise can be observed by the lower blood glucose concentration during and after exercise. As well, it can be seen in improved insulin sensitivity, and the reduction in cardiovascular risk factors.
through the improvement of lipid profile and weight reduction (American Collage of Sport of Medicine, 2003).

1.7.3 Pharmacologic therapy

Sulfonylurea and insulin only were available to treat type 2 diabetes until 1995, after that, metformin, α-glucosidase inhibitors, thiazolidenidiones and non-sulfonylureas have been approved by the FDA (Food and Drug Administration), and many different agents with different mechanism of action are under development (Koda-Kimble et al. 2005). Furthermore, type-2 diabetic patients usually are prescribed several other medications for treating their complications like cardiovascular diseases, dyslipidemia, hypertension, and other chronic illnesses that develops with the aging process. On this base, the regimen of type 2 diabetic patient should be the simplest and the safest regimen that give the best glycemic control and treat the complications properly (Bailey & Day 2003).

1.7.3.1 α-Glucosidase inhibitors

Two members belong to this group, acarbose (refer to appendix A) 25, 50 and 100mg and miglitol (Bailey & Day 2003). They do not cause weight gain. Their adverse effects are bloating and diarrhea. Diarrhea can be avoided by starting treatment with low doses (ADA a, 2007). They act by inhibiting the
digestion of carbohydrates and consequently, glucose absorption (Bailey & Day 2003).

1.7.3.2 Nonsulfonylurea insulin secretagogues

Repaglinide 0.5, 1 and 2 mg, and nateglinide 60 and 120 mg (refer to appendix A), are members of insulin secretion-stimulating group (Bailey & Day 2003). Repaglinide was approved by FDA (Food and Drug Administration) of United States in December 1997. Nateglinide was approved in December 2000 (Culy & Jarvis 2001; Novartis Pharmaceutical Companion, 2002). It is recommended to take the dose right before meals, and skip the dose with skipped meal (ADA a, 2007).

1.7.3.3 Sulfonylureas

There are seven members of different sulfonylureas (refer to appendix A). The first generation consists of four members which are: Acetohexamide, chlorpropamide, tolazamide, and tolbutamide (ADA, 2007). The second generation members are: glipizide and glyburide. Glimipride was approved for use in 1997 which represents the third generation. Sulfonylureas can cause hypoglycemia, although this occurs much less often than with insulin. Even if they have the same effectiveness, they are different from each other in their pharmacokinetic parameters and adverse effects (Zimmerman, 1997). Sulfonylureas, unlike metformin and the thiazolidinediones, can induce hypoglycemia when insulin production overshoots (Patlak 2002).
1.7.3.4 Thiazolidenidiones (TZDs)

Rosiglitazone and pioglitazone (refer to appendix A) were approved by FDA of the United States in 1999. Troglitazone was approved by FDA of the United States in 1997, but it was taken off the market in March 2000 because it's hepatotoxic effect (Mudaliar & Henry 2001). TZDs can increase peripheral glucose utilization in skeletal muscle and adipose tissue, reduce hepatic glucose production. They increase fatty acid uptake and reduce lipolysis in adipose cells which will eventually leads to a reduction in fasting and post-prandial plasma glucose, insulin and circulating free fatty acid (FFA) levels (Olefsky 2000). They are contraindicated in patient with liver impairment and significant heart problems (O'Moore-Sullivan & Prins 2002). The UKPDS showed that; although monotherapy with sulfonylureas, metformin or insulin can achieve good glycaemic control initially. Sustained control with these agents fails in 50% of patients after three years. Most patients will require multiple therapies to obtain adequate long term glycaemic control (UKDPS 49, 1999).

1.7.3.5 Metformin

Metformin 500 mg, 850mg, and sustained release metformin (refer to appendix A), the only licensed member in biguanide group of oral hypoglycemic agents. Phenformin, the first biguanide, was available in the United States till 1977 and withdrawn from market because of its association with lactic acidosis, according to the recommendation of the FDA of the
United States (Koda-Kimble et al. 2005). Unlike sulfonylureas, metformin will not produce hypoglycemia when it is used within the therapeutic dose, does not stimulate insulin secretion from pancreas. Metformin also does not promote weight gain. Metformin decrease fasting plasma glucose level by decreasing the hepatic glucose production rate (Hundal et al. 2000). Metformin also helps to lower blood glucose concentration by increasing muscle tissue sensitivity to insulin (Kimmel & Inzucchi 2005) and it is considered to be the first-line anti-hyperglycemic drug of choice in overweight diabetic patients (with body mass index > 25kg/m²). Metformin has a great role in type-2 diabetes treatment (National Institute of Clinical Excellence (NICE), 2002), but it has certain contraindications in its use and that is the main topic of this study.

1.7.3.6 Insulin

Exogenous insulin is a crucial product for type-1 diabetic patient survival due to the destroyed β-cells in pancreas. It also plays an important role in the treatment of individuals in type-2 diabetes. The most common indications for exogenous insulin are the failure to achieve glycemic control with diet, exercise, and oral hypoglycemic drugs. Insulin also used in conditions which include acute illness, surgery, pregnancy, glucose toxicity. Contraindications in type-2 diabetes to oral antidiabetic agents are among insulin indications (Mayfield & White 2004). Other conditions that indicate insulin prescription are breast-feeding and severe metabolic disorders (e.g. diabetic ketoacidosis, severe hypertriglyceridemia, lactic acidosis and hyperosmolar non-ketotic
coma (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD),
Academy of Medicine, 2004). The percentage of type-2 diabetic patient who
use insulin is 27% (Koro et al. 2004). Many types of exogenous insulin are
found with different immunogenicity, pharmacokinetic and pharmacodynamic
properties, physical and chemical characteristics (Koda- Kimble et al. 2005).
Types administered parenterally are, rapid-acting insulin analogs solution
(Insulin lispro and insulin aspart) for subcutaneous administration. As well,
insulin can be found as short-acting (regular), intermediate-acting (neutral
protamine hagedorn or isophane NPH; Lente and neutral protamin lispro NPL)
(Holleman et al. 1997), and long-acting (Ultra lente, and insulin glargin) (Bolli
& Owin 2000). Other forms of insulin like pre-mixed insulin which is a
combination of particular percentages of intermediate-acting and short-acting
insulin in one container or insulin pen (Koro et al. 2004; ADA b 2007) (refer
to Appendix A).

Scientists have been working in number of new advanced alternative
insulin delivery systems such as transdermal insulin through skin patches.
Although some pharmaceutical companies are hoping to develop products that
could provide boluses of insulin through the skin for mealtime, any
achievement for transdermal delivery is to be expected to come with basal
delivery of relatively small amounts over time. Inhaled insulin is the most
about lately and only one type that has passed the final phase of testing for
approval by the FDA of the United States. It is the form that is approved for
adults only. Buccal insulin is similar to the inhaled one, but the delivery into
the oral cavity and the spray instead of going to the lung, the insulin will be
absorbed in the lining at the back of the mouth and throat (ADA c 2007). Already, it is known that insulin is not suitable for oral route due to the rapid break down in the stomach. Some scientists are trying to produce insulin by using a special coating technique, or by changing the insulin structure to get more stable insulin pill in stomach conditions.

Using insulin in combination with oral anti-diabetic agents shows glucose levels improvement in patients with failure in glycemic control despite maximal combination of oral anti-diabetic drugs (Pugh et al. 1992). Insulin can be combined with metformin (Ponssen et al. 2000), sulfonylureas (UKPDS 57, 2002), thiazolidinediones (TZDs) (Raskin et al. 2001), and α-glucosidase inhibitors (Coniff et al. 1991). Insulin therapy may be used initially in type-2 diabetes especially in marked hyperglycemia (Mayfield & White 2004).

1.8 Complications of type-2 diabetes

All complications independently predispose mortality in patient with type-2 diabetes and the degree of mortality is increased with deterioration of complications (Cusick et al. 2005). Diabetes ranks as the sixth source of death in the United State, approximately > 71,000 deaths a year (Center of Medicare and Medicaid Services (CMS) Public Affairs Office, 2004). The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study group (1999) found that assessed 25,364 patients from 13 cohort studies. DECODE examined the risk of death according to ADA and WHO diagnostic criteria for diabetes. They found that patients with diabetes
had a doubling of mortality risk over 10 years compared with non diabetic patients (DECODE, 1999; Stancoren & McGuire 2007). Along with diabetic type-2 patients, the macrovascular complications of cardiovascular and cerebrovascular diseases constitute the major proportion of deaths (Winer & Sawers 2004). Diabetes is also correlated with microvascular complication morbidity like retinopathy, neuropathy, and nephropathy. It is the leading cause of end-stage renal impairment, non-traumatic amputation, and blindness in adults (Sheetz & King 2002).

In Malaysia, the rate of microvascular complications is high among people with diabetes. A wide survey in 1997 in Malaysia showed that 57% of diabetes had retinopathy, 58% had neuropathy, and 52% had microalbominuria. Malaysian people are at risk of macrovascular complications like ischemic heart disease (IHD) and stroke because of the delayed diagnosis, poor glycemic control and metabolic syndrome association like obesity. About 43-52% of diabetic patients who are obese and overweight (most of them are Malay and Indian females), and 63-76% had hyperlipidemia (Mustaffa 2004). There are two types of complications, acute complications which include hypoglycemia and hyperglycemia. The other type is the chronic complications that divided into two categories, macrovascular and microvascular complications. Macrovascular complications are represented by cardiovascular diseases, peripheral vascular diseases, and cerebrovascular diseases. Microvascular complications are nephropathy, neuropathy, and retinopathy (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD), Academy of Medicine, 2004).
1.9 Prevention

Reducing the long-term consequence of diabetes mellitus has been classified as primary, secondary, tertiary prevention. Primary prevention is the intervention before the onset of the disease. Secondary intervention is after onset of the disease but before the development of complications. Diabetes mellitus treatment with the goal of normoglycemia is a secondary intervention that delays development of microvascular complications and decrease the rate of disease progression (UKPDS 34, 1998). Tertiary intervention is after the development of complications but before the progression to end-stage consequence (World Health Organization Study Group on Prevention of Diabetes Mellitus, 1994).

Laser photocoagulation, administration of angiotensin converting enzyme inhibitors (ACEI), and preventive foot care are tertiary interventions that have been shown to reduce the risk of sever vision loss, end stage renal disease (ESRD), lower extremity amputation in patients with diabetes mellitus respectively. These interventions take place after the development of significant retinopathy, macroprotienuria, and distal sensomotor neuropathy (The Diabetic Control and Complications Trial Research Group, 1993). People at high risk for the development of diabetes mellitus can be identified by screening, demographic factors, ethnic factor, BMI, physical activity, gestational diabetes mellitus history, sensitivity to glucose and insulin, and glucose tolerance status. They are known to influence the risk of progression to diabetes mellitus (National Diabetes Data Group (NDDG), 1997; Martin et al. 1992). The risk progression to diabetes is also correlated with the duration
and severity of impaired glucose tolerance (Saad et al. 1988). Rate of progression from impaired glucose tolerance to diabetes mellitus is 10% in year. It is likely to be noticed in those with severe glucose tolerance, in specific racial and ethnic groups at high risk of diabetes mellitus and in women with history of gestational diabetes (Edelstein et al. 1997). Epidemiologic studies show a contrary relationship between diabetes and moderate exercise (Errikson & Landgrade 1990; Manson et al. 1991). Interventions lead to weight loss or weight gain prevention, reduction in dietary fat, increase the intake of complex carbohydrates and increase exercise change the lifestyle in a way that reduce insulin resistance and preventing type-2 diabetes consequently (Pan et al. 1997).

Cardiovascular disease (CVD) is the leading cause of death among patients with diabetes with approximately between two thirds and three fourths death of some form of CVD (UKDPS 38, 1998). The Systolic Hypertension in Europe (Syst-EUR) Trial (Voyaki et al. 2001) have shown that the good control for blood pressure can improve CVD outcomes, especially stroke (UKDPS 38, 1998; Chobanian 2003) and decrease the rate of CVD by 33-50% in patients with diabetes (UKDPS 38, 1998). It has been found that each 10 mmHg reduction in mean systolic blood pressure was correlated with decreasing the risk of 12% of any complications. For diabetic-related death it was 15%, 11% of myocardial infarction (MI), and 13% of microvascular complications in diabetic patients (UKPDS 36, 2000). This might also delay or prevent diabetic nephropathy (ADA, 2005).
About 20-30% of patients with type-2 diabetes mellitus develop nephropathy (Dobesh 2006), resulting in ESRD if nephropathy is not treated effectively (Sowers 2003). It has been found that 2% of type 2 diabetic patients developed microalbuminuria per year. As well, 2.8% progressed from microalbuminuria to macroalbuminuria per year. Consequently, 2.3% progressed from macroalbuminuria to high serum creatinine level (≥ 175 µmol/l) or hemodialysis (U.S. Renal Data System (USRDS) 2005 annual data report, 2005). Besides that, nephropathy associated with type-2 diabetes is also associated significantly with high risk cardiovascular morbidity and mortality that can not be ameliorated by hemodialysis or renal transplantation (Gerstein et al. 2001).

According to clinical studies, renin-angiotensin system (RAS) is involved in the pathophysiology of diabetic nephropathy (Dobesh 2006). Drugs that suspend the RAS like angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II-receptor blockers (ARBs) are effective in the prevention treatment of diabetes nephropathy in addition to their ability to lower blood pressure (ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001; Lewis et al. 2001).

1.10 Monitoring

Several measurements may be used by the clinicians and patients in self monitoring to assess glycemic control (Goldstein et al. 2004).
1.10.1 Urine ketone test

Urine ketones should be elevated when the blood glucose level is more than 300 mg/dl or 16.7mmol/l, and during acute illness (Goldstein et al. 2004) that indicates insulin deficiency. Ketonuria can lead to lipolysis and ketoacidosis, or they may be found in people with extremely low caloric intake. It can be seen in first morning sample of pregnant women with gestational diabetes (Koda-Kimble et al. 2005).

1.10.2 Plasma glucose

Fasting plasma glucose (FPG) reveal glucose derived from hepatic glucose output because liver represent the primary source of glucose in the postabsorptive state. The target value of FPG is 4.4-6.1 mmol/dl (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD), Academy of Medicine, 2004). Postprandial (1-2 hour after start of meal) glucose concentration reflect the efficiency of insulin-mediated glucose uptake at the peripheral tissues. It is used to review glycemia level when FPG values are within normal range or when there is a need to assess the effect of treatment with a specific drug like α-glucosidase inhibitors on the glycemic control after meal (Goldstein et al. 2004). The normal value of postprandial glucose test is < 7.8 mmol/L within two hours after meal. It is preferred to use plasma sample rather than whole blood sample because these values are not subject to any change in hematocrit. Blood glucose level is less than the plasma glucose level in 10-15% because there is no distribution through the hemoglobin (Koda-Kimble et al. 2005).
1.10.3 Glycosylated hemoglobin (HbA\textsubscript{1c})

HbA\textsubscript{1c} is an accurate way for the evaluation of glycemic control over a definite period of time by measuring the percentage of HbA that has been irreversibly glycosylated at the N-terminal of the β-chain. It represents as an indicator of glycemic control over the former 2-3 months due to red blood cell (RBC) life span is approximately 120 days (Michael \textit{et al.} 2007). The normal value is between 4-6% of the total hemoglobin (Goldstein \textit{et al.} 2004). The target for type-2 diabetes is < 6.5% (Malaysian Ministry of Health, Persatuan Diabetes Malaysia (PMD), Academy of Medicine, 2004). Any change in RBC life span such as during anemia, acute or chronic blood loss and uremia may affect HbA\textsubscript{1c} values that lead to inaccurate assessment for glycemic control (Ceriello \textit{et al.} 1991). For HbA\textsubscript{1c}, no needs for special preparations like fasting. It does not replace the ordinary monitoring of blood glucose concentration like FPG and postprandial glucose concentration that are essential for detecting the acute change in blood glucose concentration (Misbin 1999). Lowering HbA\textsubscript{1c} may lower the risk of myocardial infarction and cardiovascular death (ADA c, 2003).

1.10.4 Glycated serum protein (GSP), glycated serum albumin

Fructosamine assay is one of the most commonly used ways for measuring glycated proteins that reveal the extent of various serum proteins glycation (Cefalu \textit{et al.} 1999). The normal value is 2-2.8 % mmol/l. Fructosamine provides an indication of glucose control over a shorter period of time (1-2