SAFETY AND EFFICACY OF BASAL-BOLUS INSULIN REGIMEN VERSUS PREMIXED INSULIN REGIMEN AMONG TYPE 2 DIABETES MELLITUS (T2DM) PATIENTS: AN OBSERVATIONAL STUDY

BY

PENWALLA NAZIA IQBAL

A thesis submitted in fulfilment of the requirement for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice)

Kulliyyah of Pharmacy
International Islamic University Malaysia

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic condition due to insulin resistance or relative insulin deficiency. In Malaysia, although various insulin regimens are recommended for the management of T2DM, premixed (PM) regimen is relatively more commonly prescribed compared to Basal-Bolus (BB) regimen probably due to the convenience of injecting fewer number of injections per day. Yet, there is still limited comparison data regarding the optimal use of these two regimens. Thus, the BB and PM insulin regimens were compared in regards to their safety and efficacy outcomes. A retrospective study involving 271 T2DM subjects treated with BB or PM regimen in an outpatient setting was conducted in Hospital Tengku Ampuan Afzan and Klinik Kesihatan Beserah observing patient data over one year period. Among the safety outcomes measured was the mean increment in weight, number of patients experiencing hypoglycemia, hospitalization rate and mortality rate. Consequently, efficacy outcomes measured were mean reduction in the Glycosylated Haemoglobin (HbA1c), mean reduction in the Fasting Plasma Glucose (FPG), and mean increment in the Total Daily Insulin (TDI) dose. After one year, mean reduction in HbA1c for BB versus that of the PM regimen was 0.9% versus 0.2% (difference: 0.66, 95% CI -0.06, 1.37, p=0.070), showing no significant difference between the arms. Also, there was no statistical significant difference between BB and PM arm in terms of mean reduction in FPG over a year,0.7 mmol/L versus 0.9 mmol/l (difference: 0.25, 95% CI –2.02, 1.52, p = 0.780), and mean increment in the TDI Dose, 15.1 U/day versus 11.8 U/day (difference: 3.37, 95% CI -8.38, 1.64, p = 0.184). On safety parameters, the difference between BB and PM arm in terms of number of patients experiencing hypoglycemia was 25.6% versus 17.1% (p=0.108) and the mean increment in weight was 0.9 kg versus 1.3kg (p = 0.581) , showing both parameters to be comparable over the one year period. Even though it was found that a significantly higher number of patients were hospitalized over the one year in the BB arm compared to the PM arm, hospitalization specifically due to hypoglycemia with 3 subjects in BB arm versus none in PM arm was found to be statistically not significant (p=0.245).No mortality was reported in either arm. From this first local comparative analysis of these two insulin regimens, it can be concluded that the BB regimen and PM regimen were equally safe, effective and comparable for use in T2DM patients at the involved study sites. Nevertheless, it is recommended for further research that such study should use larger sample size and extend the scope of study to other states in Malaysia.

خلاصة البحث

يعرف داء السكري النمط الثاني T2DMعلى أنه حالة مزمنة ناتجة عن نقص أو مقاومة الأنسولين.على الرغم من وجود عدة حميات أنسولين ينصح بها في ماليزيا للسيطرة على T2DM إلا أن Premixed (PM) تعتبر أكثر شيوعاً بالمقارنة مع Basal-Bolus (BB), وذلك قد يكون لقلة عدد الحقن اليومية. ولمحدودية البيانات المقارنة بين الاستعمال الأمثل لهاتين الحميتين تمت المقارنة بينهما من حيث مخرجات الأمان والفعالية. تم تصميم دراسة ارتجاعية تتضمن 271 شخص مصاب بداء السكري النمط الثاني خضع للعلاج بحمية BBأو PM في العيادات الخارجية سواء بمشفى تنكو أمبوان أفزان او في عيادة بصرى. وتمت مراقبة بيانات المرضى لمدة عام واحد. تتضمن عوامل السلامة كلا من نسبة تعرض المريض لهبوط سكر الدم الحاد و متوسط تغيرات الوزن و الحاجة للاستطباب في المشفى و معدل الوفيات. بينما تضمنت عوامل الفعالية المدروسة كلا من متوسط تغير الهيموغلوبين السكري (HbA1c) ومعدل انخفاض سكر الدم الصيامي (FPG)ومعدل زيادة جرعة الأنسولين اليومية الكلية(TDI). بعد سنة واحدة كان متوسط تغير ال HbA1c لحمية BB-0.9% مقابل -0.2% لحمية PM (الفرق: -0.06, 95% CI -0.66, 1.37, P=0.070) مع عدم وجود اختلاف احصائي مهم بين الحميتين بالنسبة لمتوسط تغير ال HbA1c وايضا لم يلاحظ اختلاف احصائي مهم بين الحميتين بالنسبة لمتوسط تغير ال FPGو معدل ارتفاع جرعة ال TDI. بالنسبة لعوامل السلامة، الإختلاف بين BB , PM من حيث عدد المرضى الذين واجهوا انخفاض حاد في سكر الدم كان 25.6% مقابل 17.1% (p=0.108) ومعدل ارتفاع الوزن كان 0.9 كغ مقابل 1.3 كغ (p = 0.581) مبدياً نتائج متقاربة بكلا العاملين المدروسين خلال السنة. على أي حال، وجد أن عدد المرضى الذين احتاجوا الى استطباب في المشفى على مدار سنة واحدة في حالة حمية ال BB كان أعلى بشكل ملحوظ احصائيا منه في حالة حمية PM. والاستطباب في المستشفى تحديداً كان لثلاثة مرضى في حمية BBبسبب انخفاض حاد في معدل سكر الدم مقارنة بعدم تسجيل أي حالة دخول مستشفى لمستخدمي حمية PM و الاستطباب نتيجة هبوط سكر الدم الحاد لم يبد اختلافا احصائيا مهما بين الحميتين (p=0.245). لم يتم تسجيل أي حالة وفاة في كلا الحميتين. أظهرت نتائج أول دراسة محلية لمقارنة حميتي انسولين أن كلا من حمية Basal-Bolus (BB) و حمية Premixed اثبتتا تساوياً في الفعالية والأمان للاستخدام في حالة T2DM فيمن شملتهم الدراسة. ومع ذلك ينصح باستكمال البحث في دراسة مشابهة تستعمل عدد عينة أكبر وتوسع من المناطق المدروسة في ماليزيا.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice).

……..
Nor Ilyani Mohamed Nazar
Supervisor

……..
Noordin Othman
Co-Supervisor

……..
Nik Nur Fatnoon Nik Ahmad
Co-Supervisor

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice).

……..
Ahmad Marzuki Omar
Internal Examiner

……..
Noorizan Abd. Aziz
External Examiner

This thesis was submitted to the Department of Pharmacy Practice and is accepted as a fulfilment of the requirements for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice).

……
Nor Ilyani Mohamed Nazar
Head, Department of Pharmacy Practice

This thesis was submitted to the Kulliyyah of Pharmacy and is accepted as a fulfilment of the requirements for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice).

……
Siti Hadijah Shamsuddin
Dean, Kulliyyah of Pharmacy

DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Penwalla Nazia Iqbal

Signature……. Date ….....

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Affirmed by Penwalla Nazia Iqbal.

…… ……..
Signature Date

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AGI	Alpha-Glucosidase Inhibitors
ALT	Alanine transaminase
BB	Basal Bolus
CI	Confidence Interval
CKD	Chronic Kidney Disease
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl Peptidase-4
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
HbA1c	Glycosylated Hemoglobin
HTAA	Hospital Tengku Ampuan Afzan
IDDM	Insulin Dependent Diabetes Mellitus
IMT	Intima Media Thickness
IREC	IIUM Research Ethical Committee
KKBK	Klinik Kesihatan Bandar Kuantan
MEMS	Malaysian Endocrine and Metabolic Society
MOH	Ministry of Health
MREC	Medical Research & Ethics Committee
NHMS	National Health and Morbidity Survey
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NMRR	National Medical Research Register
NPH	Neutral Protaminated Hagedorn
OHA	Oral Hypoglycaemic Agents
PG	Plasma Glucose
PM	Premixed
PS	Power & Sample Size Calculation
SAEs	Serious Adverse Events
SMBG	Self Monitored Blood Glucose
SPSS	Statistical Package for Social Sciences
TDI	Total Daily Insulin
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study
1,5-AG	1,5- Anhydroglucitol

LIST OF SYMBOLS

δ	Population Mean
σ	Standard Deviation

CHAPTER ONE

INTRODUCTION

1.1 DEFINITION OF DIABETES

1.1.1 Definition of Diabetes

Diabetes Mellitus is a chronic disorder characterized by chronic hyperglycemia and other metabolic abnormalities, related to insulin deficiency and/or insulin resistance (Ministry of Health Malaysia, 2009). The two common types of Diabetes are Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM), in addition to Gestational Diabetes Mellitus (GDM) as well as specific types of diabetes due to other causes (American Diabetes Association, 2015).

1.2 TYPES OF DIABETES

1.2.1 Type 1 Diabetes Mellitus (T1DM)

Only 5-10% of all cases of Diabetes Mellitus consist of T1DM (Daneman, 2006). This type of diabetes is considered an autoimmune disorder leading to damage of the beta cells of the islets of Langerhans in human pancreas resulting in insulin deficiency (Van Belle, Coppieters, & Von Herrath, 2011). This type of diabetes is also called Insulin Dependent Diabetes Mellitus (IDDM) and patient diagnosed with IDDM is dependent on insulin to control hyperglycemia.

1.2.2 Type 2 Diabetes Mellitus (T2DM)

Type 2 Diabetes Mellitus (T2DM) is the majority type of all cases of diabetes in the world. T2DM is usually associated with increasing age and obesity. It is a complex

metabolic condition described by existence of multiple factors such as resistance of insulin in the muscle and adipose tissue, decline in pancreatic insulin secretion, increase in liver glucose production and various hormone related deficiencies (Ferrannini, 1998; UK Prospective Diabetes Study (UKPDS) Group, 1998; Van Belle et al., 2011). This type of diabetes is also called Non-Insulin Dependent Diabetes Mellitus (NIDDM) and patients diagnosed with NIDDM will have options of oral hypoglycemic agents as well as insulin therapy in order to control the hyperglycemia.

1.2.3 Gestational Diabetes Mellitus (GDM)

Gestational Diabetes Mellitus (GDM) is any level of intolerance to glucose detected first during pregnancy (The Royal Australian College of General Practitioners and Diabetes Australia, 2014). The recommended criterion for diagnosis is based on a 2 hour test by consuming 75 gram of oral glucose. The test is called the Oral Glucose Tolerance Test (OGTT). A Fasting Plasma Glucose (FPG) level $\geq$ 5.1 mmol/L (92 mg/dl) , post one hour glucose level of $\geq$ 10.0 mmol/L (180 mg/dl), or a post two hour glucose level of $\geq$ 8.5 mmol/L (153 mg/dl) is used for diagnosis of GDM (Wendland et al., 2012).

1.2.4 Specific types of diabetes due to other causes

There are specific types of diabetes that occurs due to other causes. Among the causes are beta cell function and insulin related defects, pancreas related diseases and chemical or drug induced effects (The Royal Australian College of General Practitioners and Diabetes Australia, 2014). For example, the use of nucleoside reverse transcriptase inhibitors (NRTIs) or protease inhibitors may lead to insulin

resistance and increase risk of diabetes mellitus among HIV infected patients (Frasco et al., 2014).

1.3 PREVALENCE OF DIABETES

1.3.1 Global Prevalence of Diabetes

Diabetes Mellitus is becoming one of the most highly concerned health problems in this 21st century (George, Cebioglu, & Yeghiazaryan, 2010). In 2014, according to the International Diabetes Federation (IDF), the world prevalence of diabetes among adults was about 387 million people and it was projected that this figure will rise to be over 592 Million adults by 2035 (International Diabetes Federation, 2014). The IDF had also estimated a one hundred percent increment of the global expenditure of diabetes to USD 490 billions from year 2010 to 2030 (van Avendonk & Rutten, 2009). As T2DM adds on to the financial burden to all nations, the highest burden is held upon developing countries as more than 80% cases occur in these countries (Ramachandran, Snehalatha, Shetty, & Nanditha, 2012). The implications of diabetes is so huge that IDF had grouped Diabetes Mellitus as an "International Disaster" and pursued United Nation to accept the global threat of the diabetes epidemic (Mastura et al., 2011).

1.3.2 Prevalence of Diabetes in South East Asia

The prevalence of diabetes in Asian population is increasing rapidly. In 2013, there were 72.1 million diabetes patients in South East Asia and it is predicted that by 2035 the prevalence of diabetic patients will reach 123 million people (International Diabetes Federation, 2013). In line with the increasing prevalence of diabetes, the overweight and obesity statistics are also rising sharply. This could be due to the

economic growth, diet changes and unhealthy lifestyle among the Asian population (Chan et al., 2009) .

1.3.3 Prevalence of Diabetes in Malaysia

In Malaysia, the Ministry of Health (MOH) conducts a population based national survey on a 10 yearly basis initially and shortened to every four years currently. The first National Health and Morbidity Survey (NHMS) in Malaysia was conducted in 1986 where diabetes prevalence among adults of age ≥35 years old was 6.3% (Noor, Lua, & Nik, 2011). The second survey, NHMS II, conducted ten years later in 1996 revealed an increase in prevalence of further 2% to 8.3% in patients of and above 30 years old (Letchuman et al., 2010). In 2006, NHMS III showed a significant rise of almost 80% in the prevalence to 14.9%, with estimated 95% of this population having T2DM (Letchuman et al., 2010; Malaysian Endocrine and Metabolic Society (MEMS), 2011). In 2011, according to NHMS IV, the prevalence of diabetes increased up to 20.8% among adult 30 years and above thus rendering one in every five Malaysian adult, a diabetic (Ministry of Health Malaysia, 2011).

1.4 INSULIN AND ITS TYPES

1.4.1 History of Insulin

Insulin is a complex molecule with also a similarly complex mechanism of action (Conlon, 2001). Insulin is a protein hormone extracted first in 1921 (Sleigh, 1998). In 1958, Fred Sanger discovered its amino acid sequences (Pickup J, 1997; Sleigh, 1998) as in Figure 1.1. Since its discovery, insulin has become an essential component in the management of diabetes (Kalra, Balhara, Sahay, Ganapathy, & Das, 2013) not only in

Type 1, but a growing evidents show its benefitial contribution in the management of T2DM.

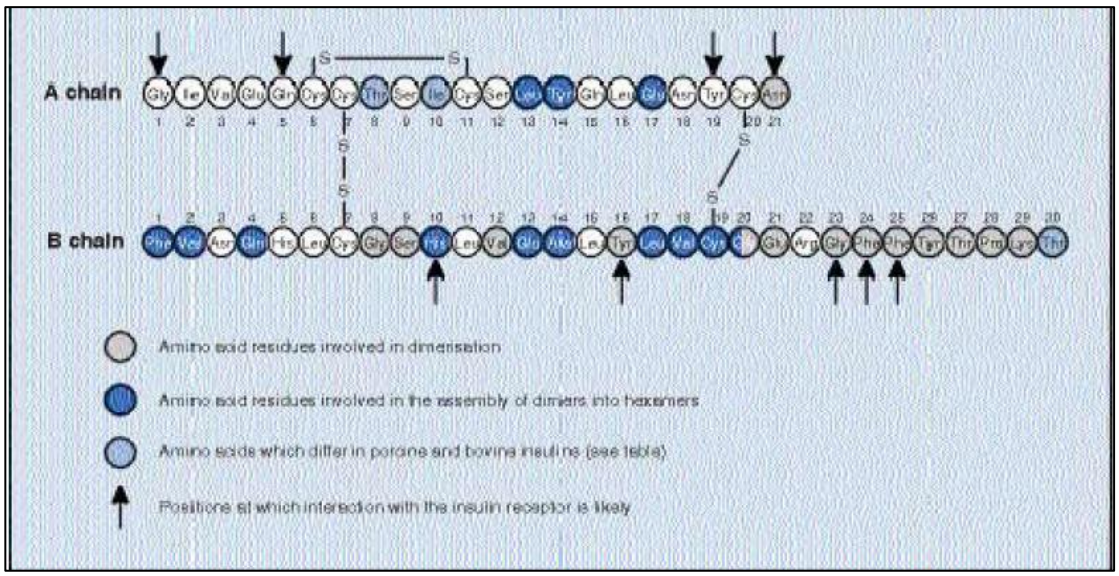

Figure 1.1 Amino acid sequence of insulin (Sleigh,1998).

Prior to genetic advancements, purified animal-origin insulin was the only type of insulin available to diabetic patients. The first genetically engineered, synthetic 'human' insulin was produced in a laboratory in 1977 by Arthur Riggs, Keiichi Itakura, and Herbert Boyer using *E. Coli* (Eilertsen & Berntsen, 2011). In 1982, a group of researchers together with Eli Lilly Company were the first ones to sell the first commercially available biosynthetic human insulin under the brand name of *Humulin,* ended the need of extracting insulin from animal pancreas (Melmer, Hellwig, Hehmann, & Dahlems, 2011; Rendell, 2008). Furthermore, modification in the amino acid arrangements of insulin has given rise to analogue insulins such as rapid acting and long acting insulins (Rendell, 2008).

1.4.2 Types of Insulin in Malaysia

In Malaysia, the available recombinant human insulins are either manufactured from native human insulin, that is, regular human insulin, or insulins that are structurally modified, also known as analogue insulins. The types of insulin preparation available in Malaysia, their pharmacokinetic profiles, as well as the insulin regimens and frequency of injections per day are shown in Figure 1.2 ,Figure 1.3, and Figure 1.4 respectively (Malaysian Endocrine and Metabolic Society (MEMS), 2011).

Insulin Type	Conventional	Analogue
Prandial	Short-acting regular human insulin - Actrapid® - Humulin R®	Rapid-acting - Novorapid® (Aspart) - Humalog® (Lispro) - Apidra® (Glulisine)
Basal	Intermediate-acting or Neutral Protaminated Hagedorn (NPH) Insulin - Insulatard® - Humulin N®	Long-acting - Lantus® (Glargine) - Levemir® (Detemir)
Premixed	Combination of short & intermediate-acting: 30% regular insulin + 70% NPH - Mixtard® 30 - Humulin® 30/70	Combination of rapid-acting & protaminated analogue - NovoMix® 30 (30% aspart + 70% aspart protamine) - Humalog Mix® 25 (25% lispro + 75% lispro protamine)

(Note: Adapted from the *Practical Guide to Insulin therapy in Type 2 Diabetes Mellitus* by Malaysian Endocrine and Metabolic Society,2011)

Figure 1.2 The Insulin Preparations available in Malaysia

Brand (Generic) Name	Onset	Peak (Hr)	Duration (Hr)	Timing of insulin
a) Short-acting, regular - Actrapid®* - Humulin R®*	 30 min 30 min	 1-3 2-4	 8 6-8	30 mins before meal
b) Rapid-acting analogue - Novorapid® (Aspart)* - Humalog® (Lispro)* - Apidra® (Glulisine)	 10-20 min 0-15 min 5-15 min	 1-3 1 1-2	 3-5 3.5-4.5 3-5	5-15 mins before or immediately after meals
c) Intermediate-acting, NPH - Insulatard®* - Humulin N®*	 1.5 Hr 1 Hr	 4-12 4-10	 18-23 16-18	Pre-breakfast / Pre-bed
d) Long-acting analogue - Glargine®* - Detemir®*	 2-4 Hr 1 Hr	 peakless peakless	 20-24 17-23	Same time everyday at anytime of the day
e) Premixed human (30% regular insulin+ 70% NPH) - Mixtard® 30* - Humulin® 30/70*	 30 min 30 min	 dual dual	 18-23 16-18	30-60 mins before meals
f) Premixed analogue - NovoMix® 30 (30% aspart + 70% aspart protamine)* - Humalog Mix® 25 (25% lispro + 75% lispro protamine*	 10-20 min 0-15 min	 dual dual	 18-23 16-18	5-15 mins before meals

** Available at Ministry of Health, Malaysia.*

(Note: Adapted from the *Practical Guide to Insulin therapy in Type 2 Diabetes Mellitus* by Malaysian Endocrine and Metabolic Society,2011)

Figure 1.3 Pharmacokinetic profiles of various types of insulin

No. of injections per day	Insulin regimen	Type of insulin and timing
1	BASAL	Intermediate acting (NPH) insulin pre-bed
	BASAL	Long-acting analogue once daily
	PREMIXED OD	Premixed/ premixed analogue pre-dinner
2	BASAL	Intermediate acting (NPH) pre-breakfast and pre-dinner
	PREMIXED BD	Premixed insulin pre-breakfast and pre-dinner
	BASAL-PLUS (1)	Basal insulin once daily + 1 prandial insulin
3	BASAL-PLUS (2)	Basal insulin once daily + 2 prandial insulin
	PRANDIAL	Prandial insulin pre-breakfast, pre-lunch and pre-dinner
	PREMIXED TDS	Premixed analogue pre-breakfast, pre-lunch and pre-dinner
	PREMIXED-PLUS	Premixed insulin pre-breakfast, pre-dinner + 1 prandial insulin pre-lunch
	PREMIXED-PLUS	Prandial insulin pre-breakfast and pre-lunch + premixed insulin pre-dinner
4	BASAL-BOLUS	Basal insulin once daily + prandial insulin pre-breakfast, pre-lunch and pre-dinner
5	BASAL-BOLUS	Intermediate acting (NPH) insulin pre-breakfast and pre-dinner + prandial insulin pre-breakfast, pre-lunch and pre-dinner

(Note: Adapted from the *Practical Guide to Insulin therapy in Type 2 Diabetes Mellitus* by Malaysian Endocrine and Metabolic Society,2011)

Figure 1.4 Insulin regimens and frequency of injections per day

1.5 INSULIN USE IN THE MANAGEMENT OF T2DM

1.5.1 General Principle

Findings from the UKPDS revealed that affected Type 2 Diabetes Mellitus (T2DM) patients usually have lost half of their β-cell functions at the point of diagnosis, with a further decline of 5% every year (Harris, Klein, Welborn, & Knuiman, 1992). Most patients need to start on oral anti-diabetic agents together with lifestyle modification strategy. As in reality, normal glycemic control is difficult to achieve with lifestyle changes alone (Ligthelm et al., 2006) .

In T2DM patients, with time, oral anti-diabetic agents usually lose their effectiveness and patients need to seek exogenous insulin therapy. Generally, implementation of successful insulin therapy requires three stages of treatment including insulin initiation, optimization and intensification (Malaysian Endocrine and Metabolic Society (MEMS), 2011).

According to the Malaysian Clinical Practice Guidlines (CPG) for T2DM published in 2009, among the insulin regimens suggested are basal insulin, once daily premixed, multiple daily premixed or basal-plus regimen (Ministry of Health Malaysia, 2009) whereas the local Practical Guide to Insulin Therapy Guidelines published in 2011 suggests the use of premixed, basal-plus, premixed-plus or basal-bolus insulin regimens (Malaysian Endocrine and Metabolic Society (MEMS), 2011).

1.5.2 Pattern of Insulin Prescribing in Malaysia

According to local statistics, 73.5% of patients with known diabetes receive treatment at MOH facilities due to its low cost of treatment compared to 20.3% from private clinics (Letchuman et al., 2010; Ng, Lee, et al., 2013). However, on an overall basis, the usage of insulin in primary health care facilities, both government and non-

governmental settings, is still low and diversified across different states in Malaysia (Malaysian Endocrine and Metabolic Society (MEMS), 2011). According to National Health and Morbidity Survey III (NHMS III), only 7.2% of the patients were on insulin alone or in combination therapy (Letchuman et al., 2010).

According to the largest cohort study in T2DM patients in public health care setting in Malaysia, the usage of intermediate acting insulin was the highest (54.9%) followed by the premixed (36.1%) and short acting insulin (15.8%), respectively (Mastura et al., 2011). The use of analogue insulins, rapid or long acting which is known for its lower risk for hypoglycemia was very low, as cost was of concern in public healthcare setting (Mastura et al., 2011; Ng, Lee, et al., 2013).

1.6 PROBLEM STATEMENT: WHY COMPARISON OF BASAL-BOLUS REGIMEN VERSUS PREMIXED INSULIN REGIMEN?

Despite no strong evidence to support the superiority among different types of insulin preparation, premixed insulin is the highest prescribed worldwide (Lasserson, Glasziou, Perera, Holman, & Farmer, 2009). Local audits and surveys have also shown that among the most prescribed insulin regimens are premixed insulin (45% cases), basal-only regimens (39% cases), and bolus or basal bolus regimens (13% cases) respectively (Malaysian Endocrine and Metabolic Society (MEMS), 2011). BB insulin regimen, comprising four insulin injections a day provides a physiological insulin-like activity but there have been concerns with regards to the multiple number of injections involved and its impact on patients lifestyle (Ligthelm et al., 2006; Masuda et al., 2008). Thus, most prescribers and diabetic patients look for convenient fewer injections regimens such as premixed insulin regimen providing both fast or rapid and intermediate insulin coverage (Fritsche, Larbig, Owens, & Häring, 2010;