ADHERENCE TO INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS PATIENTS TREATED AT THE GOVERNMENT'S PRIMARY HEALTH CARE CENTERS IN KLANG, SELANGOR

AZRI BIN NASRUDDIN

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LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CI	Confidence Interval
DM	Diabetes Mellitus
FBS	Fasting Blood Sugar
GOF	Goodness of Fit
HbA_{1c}	Haemoglobin A_{1c}
IAQDM	Insulin Adherence Questionnaire for Diabetes Mellitus
IQR	Interquartile Range
MOH	Ministry of Health Malaysia
MTAC	Medication Therapy Adherence Clinic
RBS	Random Blood Sugar
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SE	Standard Error
SMBG	Self-monitoring of blood glucose
TCM	Traditional and Complementary Medicine
T2DM	Type 2 Diabetes Mellitus
OR	Odds Ratio
OHA	Oral Hypoglycaemic Agents
VIF	Variance Inflation Factor
WHO	World Health Organization

LIST OF SYMBOLS

α	Level of significance
1-ß	Power
Δ	Precision
n	Sample size
Z	1.96 for Z value with two standard deviations of standard normal distribution
σ	Standard deviation
b	Regression coefficient
p	P-value
%	Percentage
=	Equal to
<	Less than
$\leq$	Less than and equal to
>	More than
$\geq$	More than and equal to
r_j	Pearson Residual
r_{sj}	Standardized Pearson Residual
d_j	Deviance Residual
h_j	Leverage Residual
ΔX^2	Hosmer-Lemeshow Delta Chi-Square
ΔD_j	Hosmer-Lemeshow Delta Deviance
$\Delta\hat{ß}_j$	Pregibon Delta Beta

KEPATUHAN KEPADA RAWATAN INSULIN DALAM KALANGAN PESAKIT DIABETES MELLITUS JENIS 2 YANG MENERIMA RAWATAN DI PUSAT-PUSAT PENJAGAAN KESIHATAAN PRIMER DI DAERAH KLANG, SELANGOR

ABSTRAK

Pesakit Diabetes Mellitus Jenis 2 (DMJ2) memerlukan terapi insulin bagi mencapai tahap glisemik yang disasarkan dan mencegah komplikasi berkaitan dengan diabetes mellitus. Kajian ini bertujuan untuk menentukan kadar pematuhan terhadap terapi insulin kepada pesakit yang mendapatkan rawatan di pusat-pusat penjagaan kesihatan primer Kementerian Kesihatan dan untuk mengenalpasti faktor-faktor yang berkaitan kepada kepatuhan. Kaitan antara tahap kepatuhan dan tahap glisemik (HbA_{1C}, RBS dan FBS) juga telah dinilai. Kajian keratan rentas ini telah dijalankan ke atas pesakit DMJ2 yang berumur 18 tahun ke atas yang menggunakan terapi insulin sekurang-kurangnya dua bulan. Kaedah persampelan tujuan telah digunakan. Kajian ini melibatkan 249 subjek dari lima pusat-pusat penjagaan kesihatan primer Kementerian Kesihatan di Klang, Selangor. Pesakit telah ditemubual dan data mengenai sosio-demografi, faktor-faktor yang berkaitan dengan penyakit, faktor-faktor berkaitan rawatan dan parameter klinikal telah didokumenkan. Satu soal selidik Kepatuhan Terhadap Insulin yang telah disahkan dan dijawab sendiri oleh pesakit telah digunakan. Regresi Logistik Binari telah digunakan untuk mengenalpasti faktor-faktor yang signifikan berkaitan dengan kepatuhan terhadap terapi insulin. Peratusan kepatuhan kepada terapi insulin hanya 8.43% (95% selang keyakinan (SK): 0.05, 0.12). Selepas pelarasan semua faktor-faktor yang berkait, tiga faktor didapati

signifikan. Faktor-faktor yang berkaitan dengan kepatuhan insulin adalah pemantauan kendiri glukosa darah yang mempunyai 5.49 kali kebarangkalian kepatuhan kepada terapi insulin (Nisbah ods terlaras (NOT)=5.39, 95% SK: 1.20, 24.13). Seorang pesakit yang mengamalkan aktiviti senaman mempunyai 3.38 kali kebarangkalian kepatuhan kepada terapi insulin (NOT=3.38, 95% SK: 1.37, 10.03). Terdapat peningkatan 63% ke atas kebarangkalian kepatuhan kepada terapi insulin pada setiap satu unit peningkatan dalam kekerapan dos insulin sehari (NOT=1.63, 95% SK: 1.09, 2.44). Tiada kaitan antara tahap kepatuhan dan tahap glisemik. Kepatuhan kepada terapi insulin adalah rendah. Pesakit yang mengamalkan pemantauan glukosa darah kendiri, senaman dan kekerapan dos insulin sehari adalah faktor-faktor yang mempengaruhi kepatuhan ke atas terapi insulin. Hasil klinikal pesakit DMJ2 boleh dipertingkatkan melalui identifikasi yang lebih baik dan spesifik ke atas faktor-faktor yang membawa kepada pematuhan terapi insulin.

Kata Kunci: insulin, pemantauan kendiri glukosa darah, pematuhan, senaman, kekerapan dos insulin dalam sehari, kepatuhan insulin, diabetes mellitus

ADHERENCE TO INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS PATIENTS TREATED AT THE GOVERNMENT'S PRIMARY HEALTH CARE CENTERS IN KLANG, SELANGOR

ABSTRACT

Insulin therapy is necessary for Type 2 Diabetes Mellitus (T2DM) patients to accomplish targeted glycaemic level and to prevent diabetes-related complications. This study aimed to determine the proportion of adherence to insulin therapy in patients who attended Ministry of Health's primary care centers and its associated factors. The association between adherence level and glycaemic control was also studied. This cross-sectional study was conducted among T2DM patients aged 18 years and above and who were on insulin therapy for at least two months. A purposive sampling method was used. This study involved 249 subjects from five Ministry of Health's primary care centers in Klang. Patients were interviewed, and records were accessed to collect data on socio-demographic characteristics, disease-related factors, treatment-related factors and clinical parameters. A self-administered validated questionnaire was used. Significantly associated factors were identified by using Binary Logistic Regression. The proportion of adherence to insulin therapy was only 8.43% (95% CI: 0.05, 0.12). After adjusting for confounders, three variables were found to be significant. Factors associated with insulin adherence were self-monitoring of blood glucose (SMBG) (Adjusted OR=5.39, 95% CI: 1.20, 24.13), exercise (Adjusted OR=3.38, 95% CI: 1.37, 10.03), and number of daily insulin injections (Adjusted OR=1.63, 95% CI: 1.09, 2.44). There was no association between adherence level and glycaemic parameters. Insulin therapy was poor. Patient who

practiced SMBG, exercised and had more frequent daily insulin injections significantly affected the adherence to insulin therapy. T2DM patients' clinical outcomes could be improved through a better and specific identification of factors that could lead to the adherence to insulin therapy.

Keywords: insulin, self-monitoring of blood glucose, exercise, daily insulin injections, insulin adherence, type 2 diabetes mellitus

CHAPTER 1

INTRODUCTION

1.1. Background of the Study

Type 2 Diabetes Mellitus (T2DM) is demonstrated by elevated blood glucose levels and other metabolic imbalances. It is mainly due to inadequate insulin secretion and resistance in the body. There is a progressive loss of β-cell function and consequently, impairment of insulin secretion and subsequently, defects in insulin action (American Diabetes Association, 2015; Ministry of Health Malaysia, 2015a).

T2DM is one of the most common non-communicable diseases globally and increasing all over the world year after year (Wallia and Molitch, 2014). In 2011, it was estimated that 366 million people worldwide had diabetes mellitus (DM), corresponding to a global prevalence of 8.3% (Cani *et al.*, 2015). In 2012, diabetes caused 1.5 million deaths worldwide, and the uncontrolled level of blood glucose contributed to a further 2.2 million deaths due to increasing risks of cardiovascular and other complications (World Health Organization, 2016). A study by Guariguata *et al.* (2014) estimated that in 2035, 592 million of the world population would have DM and large proportions of them live in the low and middle-income countries. As most countries moving towards an aging nation, the shift of demographic pattern would result in increased number of people more than 65 years of age with DM (Wild *et al*., 2004).

In Malaysia, there is a rising trend on the prevalence of T2DM. National Morbidity Surveys conducted routinely by the Ministry of Health Malaysia showed increasing

trend from 6.3% in 1986 to 8.3% in 1996, 11.6% in 2006, 15.2% in 2011, 17.5% in 2015 and projected to rise to 20.6% in 2020. The latest survey found out that one in five Malaysians was diabetic. Categorically by age group, in 2015, 9.4% of those aged 30 to 34 had diabetes, almost double from 4.9% in 2006. For 35 to 39 years old, it was increased from 6.4% to 10.9% for the same period. For those aged 40 to 44, it rose from 10.3% to 17.6%, and those aged 45 to 49 saw a rise from 15% to 20.6% (Ministry of Health Malaysia, 2015b). Among patients with known T2DM, 25.1% were on insulin therapy (Ministry of Health Malaysia, 2015a).

A key component to ensure the success of a therapeutic regime is to ensure that patients adhere to the recommended and tailored medication regime set up by the healthcare professionals.

1.2. Justifications of the Study

Patients with chronic diseases require long-term treatments and monitoring. Among chronic diseases, diabetes had significant medical, social and economic burdens, as well as physical and cognitive impairments (Sabaté, 2003).

Recent studies in Malaysia showed that diabetes control was poor among patients attending public hospitals in Malaysia (Mafauzy *et al.*, 2011; Ministry of Health Malaysia, 2015a; Mohamed, 2016). The percentage of diabetic patients which were under optimum control was only 13% in tertiary centers and 24% for primary care centers (Ministry of Health Malaysia, 2015a).

Patients with T2DM is manifested by a chronic hyperglycemic state and this is primarily due to insulin deficiency and/or resistance (Ministry of Health Malaysia, 2015a). Furthermore, despite the advancement of treatment and the progression of knowledge on T2DM, treatment adherence to pharmacological treatment is still unsatisfactory and a serious concern. A study by Purran *et al.* (2015) showed that the proportion of adherence to insulin therapy in a tertiary centre was unsatisfactory (19%). This study was conducted among Malay diabetic patients in the East Coast of Malaysia. Therefore, adherence rate in other races in Malaysia was still unknown.

Generally, T2DM is an important risk factor for other comorbidities such as cardiovascular diseases and long-term complications such as retinopathy, neuropathy, nephropathy and cerebrovascular complications Lerman *et al.* (2009) & Rhee *et al.* (2005). Non-adherence may lead to complications of DM related diseases and a financial burden to the patients and the government.

Therefore, it is of prime importance for a further study to measure insulin adherence in the primary settings using the same research tool. The chosen area of Klang district has multi-racial and well-balanced races between Malay, Chinese and Indian. Therefore, this study can generate a more general result on adherence to insulin therapy which can be inferred to the multi-racial Malaysian population.

1.3. Research Questions

1. What was the level of adherence to insulin therapy in T2DM patients treated at the government's primary health care centers?

2. What were the factors associated with adherence to insulin therapy in T2DM patients who were treated in the government's primary health care centers?
3. Was adherence to insulin therapy associated with a well-controlled glycaemic levels (HbA_{1c}, RBS, and FBS) in T2DM patients who were treated in the government's primary health care centers?

1.4. General Objectives

To study the adherence of insulin therapy and its associated factors in T2DM patients who were treated in the government's primary health care centers in Klang, Selangor.

1.5. Specific Objectives

1. To determine the proportion of adherence to insulin therapy in T2DM patients treated at the government's primary health care centers in Klang by using a validated Bahasa Malaysia version of Insulin Adherence Questionnaire for Diabetes Mellitus.
2. To identify the factors associated with adherence to insulin therapy in T2DM patients who were treated at the government's primary health care centers in Klang.
3. To determine the association between adherence to insulin therapy with a well-controlled glycaemic levels (HbA_{1c}, RBS, and FBS) in T2DM patients who were treated at the government's primary health care centers in Klang.

1.6. Hypotheses Statements

1. There were significant associations between adherence to insulin therapy in T2DM patients who were treated at the government's primary health care centers in Klang and patient-related factors, therapy-related factors, condition-related factors and socio-economic factors.
2. Adherence to insulin therapy was significantly associated with a well-controlled glycaemic levels (HbA_{1c}, RBS, and FBS) in T2DM patients who were treated at the government's primary health care centers in Klang.

CHAPTER 2

LITERATURE REVIEW

2.1. Overview of T2DM

There are three types of DM. Type 1 DM (T1DM) is an autoimmune condition which is caused by the body attacking its pancreas and genetic predisposition. The damaged ß-cells in people with T1DM resulted in the inability of the pancreas to produce insulin. The other type is gestational DM which is triggered by pregnancy leading to insulin resistance. It is often diagnosed in the second or third trimester (American Diabetes Association, 2010).

The third type of DM is T2DM which is characterized by insulin resistance with progressive loss of ß-cell function and insulin deficiency. T2DM is a chronic disease (American Diabetes Association, 2015) and an important risk factor of other comorbidities such as cardiovascular diseases and long-term complications such as retinopathy, neuropathy, nephropathy and cerebrovascular complications (Lerman, 2005; Rhee *et al.*, 2005; Boriani, 2016).

2.2. T2DM Complications

Uncontrolled T2DM may lead to a variety of complications, and it greatly affects individual's quality of life. Diabetic kidney disease, diabetic retinopathy, diabetic peripheral neuropathy and diabetic autonomic retinopathy are associated with microvascular complications of diabetes (World Health Organization, 2016). Twenty to forty percent of patients with diabetes develop kidney disease and subsequently

end-stage renal disease. A local study performed by Abougalambou and Abougalambou (2012) reported that the prevalence of nephropathy secondary to DM was 54.3%.

Autonomic neuropathy consists of hypoglycaemia, tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sweating (Sarbacker and Urteaga, 2016). In addition, the presence of atherosclerotic cardiovascular disease complications is the leading cause of morbidity and mortality in individuals with T2DM (American Diabetes Association, 2015). Therefore, it is of prime importance for patients with T2DM to achieve glycaemic control and lower HbA_{1c} to reduce onset or progression of complications (Krass *et al.*, 2015; Sarbacker and Urteaga, 2016).

2.3. Glycaemic Indicator for DM Control

There are three types of glycaemic control to measure the amount of glucose or sugar in the body which are fasting blood sugar (FBS), random blood sugar (RBS) and HbA_{1C}. A blood glucose test and the glycaemic levels can help to diagnose and determine the severity of DM.

In Malaysia, RBS test is an easier method to screen a patient with T2DM (Ministry of Health Malaysia, 2015a) as patients are not required to fast before undergoing the procedure. However, it is less sensitive compared to FBS and HbA_{1C} (American Diabetes Association, 2015). An individual with ≥11.0 mmol/L is considered to have T2DM (Ministry of Health Malaysia, 2015a). Based on the clinical practice guideline,

there is no statement on the frequency of RBS test needed to be done on T2DM patients. However, RBS test is commonly and routinely being practiced in facilities under Ministry of Health Malaysia.

The American Diabetes Association (American Diabetes Association, 2015) has recommended the use of FBS for the initial screening of DM because it is easier, faster, has less intra-individual variation and has high predictive value for the development of the microvascular complications of DM. The major disadvantage of FBS test is that patients need to fast overnight before undergoing the procedure. An individual with ≥7.0 mmol/L is considered to have T2DM, and the test should be done annually on all T2DM patients (Ministry of Health Malaysia, 2015a).

Unlike FBS which needed the patient to fast before the procedure, the HbA_{1C} test can be performed at any time of the day. This advantage has made it the ideal test for assessing glycaemic control in people with diabetes (Committee, 2009; World Health Organization, 2011). On top of that, HbA_{1c} mimics average plasma glucose over the past eight to 12 weeks (Nathan *et al.*, 2007). Therefore, it can avoid the issue of inaccurate and variability of glycaemic values (World Health Organization, 2011). The recommended cut-off point for HbA_{1C} is set at 6.5%. A value of more than that 6.5% indicates that the glycaemic levels of the patient are uncontrolled (World Health Organization, 2011; Ministry of Health Malaysia, 2015a).

HbA_{1C} was initially recognized as an 'unusual' haemoglobin in patients with diabetes (Rahbar *et al.*, 1969). From there on, studies were done considering the relationship of HbA_{1C} and glucose levels in the body. Based on numerous studies, it is now well

established that there is a strong correlation between HbA_{1C} and average glucose across a range of diabetes types and patient populations (Nathan *et al.*, 2007). In the 1980s, HbA_{1C} was introduced and used in clinical settings and later became a gold standard for identifying and diagnosing diabetic patients (Massi-Benedetti, 2006).

To prevent long-term complications of patients with T2DM, HbA_{1c} level ought to be maintained at 7% or less. In addition, HbA_{1c} goals must be personalized according to patient's age, comorbidities, available resources, and risks of hypoglycaemia (Wallia and Molitch, 2014; Ministry of Health Malaysia, 2015a). A retrospective cohort study in the United Kingdom in between 1995 to 2005 involving 14 824 T2DM patients discovered that majority of patients had poor glycaemic control (Calvert *et al.*, 2007). In addition, Holman *et al.* (2008) also reported that majority of patients did not achieve the required level of HbA_{1c}.

A study done by Al Balushi *et al.* (2014) found out that only 2.4% patients achieve the targets of six diabetes-related factor which are HbA_{1c}, blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. In addition, HbA_{1c} level in Malaysia was found to be suboptimal where ethnicity, insulin, and medications were found to be the predicting factors (Ahmad *et al.*, 2011). In addition, a study performed by Cani *et al.* (2015) showed a decrease in HbA_{1c} by 0.57% ($P < 0.001$) in insulin-treated patients with T2DM.

To reduce the long-term complications of T2DM, proper control of glycaemic levels is important (American Diabetes Association, 2015). Apart from pharmaceutical

intervention, behavioral modifications such as changes in dietary lifestyle and education regarding physical activity are also paramount in managing T2DM.

2.4. Treatment Recommendations for T2DM

2.4.1. Behavioral Modifications

The management of T2DM involves multitudes of therapies. The therapies depend on the duration and severity of illness and individual's overall state of health and lifestyle (Edelman, 1997). The initial treatments are to initiate changes in lifestyle. In principle, all patients with T2DM should undergo lifestyle modification, which consists of proper dietary therapy and increased physical activity (Ministry of Health Malaysia, 2015a).

Proper diet is crucial in the management of T2DM at any stage and including those on medication. This proper dietary habit can be achieved through healthy food choices. The role of a dietitian is crucial to guide T2DM patients to control their dietary habit better and therefore, to control their glycaemic level (Ministry of Health Malaysia, 2015a). Lifestyle changes alone including healthy food and regular exercise are sufficient for glycaemic control in many patients with newly diagnosed T2DM.

In addition to diet changes, enhancement of physical activity and exercise are also essential in DM management. The primary goal is to assist in weight loss and control of glycaemic levels in the blood (American Diabetes Association, 2015; Gardner, 2015). Increased physical activity can improve glycaemic control, assist with weight

maintenance, and reduce the risk of complication due to DM (Ministry of Health Malaysia, 2015a).

Compared with dietary manipulation alone, intensified therapy in the form of oral antidiabetic agents or insulin significantly has more impact towards the management of proper glycaemic control and reduced the development of microvascular complications (UK Prospective Diabetes Study Group, 1998). In addition, poor adherence to lifestyle modifications in Malaysia (Hussein *et al.*, 2015) are common, and therefore, the introduction of pharmacological management is needed.

2.4.2. Pharmacological Management

There are broad classes of pharmacologic management in treating T2DM patients. It depends on their modes of action, safety profiles, and tolerability and can be classified into either oral hypoglycaemic agents (OHA) and/or insulin therapy.

2.4.2 (a) Oral Hypoglycaemic Agents

The OHA include agents that stimulate insulin secretion (sulphonylureas and rapid-acting secretagogues), reduce hepatic glucose production (biguanides), delay digestion and absorption of intestinal carbohydrate (α-glucosidase inhibitors) or improve insulin action (thiazolidinediones) (Krentz and Bailey, 2005).

The preferred pharmacological therapy for T2DM is metformin (Krentz and Bailey, 2005). Other second-line agents include sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors,

sodium–glucose cotransporter 2-inhibitors, glucagon-like peptide receptor agonists, and amylin mimetics (American Diabetes Association, 2015; Ministry of Health Malaysia, 2015a; Sarbacker and Urteaga, 2016). The necessary factors in deciding the need for oral medications or insulin therapy depending on the clinical condition of the patient, state of glycaemic control and presence of any complications (Ministry of Health Malaysia, 2015a).

A study done locally by Mohamed (2016) found that the most commonly prescribed oral anti-hyperglycaemic agents was metformin (78.6%) and followed by sulphonylureas (35.4%).

2.4.2 (b) Insulin Therapy

Over time, insulin secretion capability deteriorates, and most individuals with T2DM would eventually require the usage of insulin therapy to maintain their glycaemic controls (American Diabetes Association, 2015). It is the most effective therapy for better management of glycaemic control (Sarbacker and Urteaga, 2016), especially when combination therapy has failed (Korytkowski, 2002). A study by Bennett *et al.* (2011) found out that individual oral hypoglycaemic agents (OHA) usually do not decrease the levels of HbA_{1c} by more than 1%. Therefore, insulin therapy is eventually necessary to achieve better glycaemic control (Raskin *et al.*, 2005; Garber *et al.*, 2006; Inzucchi *et al.*, 2012; Home *et al.*, 2014).

Many evidence suggests that insulin therapy should be initiated earlier in diabetes treatment (Garber, 2003). Inability to achieve adequate glycaemic control with a

combination of OHAs is likely to indicate that the natural history of DM has progressed to a state of severe β-cell failure. At this juncture, it is necessary to switch to insulin therapy (Krentz and Bailey, 2005). A delayed introduction or ineffective insulin therapy would contribute to poor glycaemic control and increase the likelihood of patients to develop complications (Cahn *et al*., 2015).

The type of insulin introduced need to be individualized, based on the pathophysiology of T2DM, the clinical condition of the patient, dietary pattern and lifestyle modification (Wallia and Molitch, 2014; Ministry of Health Malaysia, 2015a).

There is a wide range of treatment options and regiments of insulin which can be initiated in patients with T2DM. Currently, there are two types of insulin which are commonly prescribed to T2DM patients in Malaysia. These are human insulin derived recombinant technology and insulin analog (genetically modified human insulin). Both types of insulin are further divided into prandial, basal and premixed as per their pharmacokinetic profiles.

Prandial insulin is administered before-meal because of its short or rapid onset of activity in controlling postprandial glucose. Basal insulin is given to a patient requiring insulin therapy once or twice daily. The intermediate or long-acting pharmacokinetic profile covers the basal insulin requirements in between meals and night time. Premixed insulin combines both the short or rapid-acting insulin with intermediate-acting insulin into one formulation to cover for both postprandial glucose excursion as well as basal insulin needs (Ministry of Health Malaysia, 2015a).

Basal insulin can be added to OHAs initially while prandial insulin can be added later using one of the multiple strategies in a stepwise fashion based on the clinical condition of the patient (Home *et al.*, 2014; Wallia and Molitch, 2014). A survey on utilization of medications in diabetic patients was conducted in the United States of America in 2012. The study discovered that only 2.9 million people (14%) used insulin only and 3.1 million (14.7%) used a combination of insulin and oral medications. Furthermore, 11.9 million (56.9%) used only oral medications only, and 3 million (14.4%) did not use any medicines (Sarbacker and Urteaga, 2016).

The Diabetes, Wishes and Needs (DAWN) study concluded that initially, both health-care professionals and patients might have a negative attitude towards starting insulin therapy (Alberti, 2002) and therefore leading to the barriers towards adherence of patients to insulin therapy.

2.5. Medication Adherence and Its Importance in T2DM

The terminologies ‘adherence’ and ‘compliance’ have been used interchangeably to define the way patients take their prescribed medications. Previously, the term ‘compliance’ was widely used in which patients were blindly and passively following the instruction of medicines consumption. Nowdays, the term ‘adherence’ was more widely accepted in the medical field as it describes what is the extent patients were taking their medication, their involvement in the medication decision prescribed and overall lifestyle changes to improve their clinical symptoms (Ahmed and Aslani, 2014). In addition, World Health Organization (WHO) states adherence as “the extent

to which the persons' behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider." (Sabaté, 2003).

Adherence to medication is complex and involves multi-factorial scope that can influence patient's behavior and treatment effects (Gardner, 2015). Non-adherence leads to poor clinical outcomes, increase in morbidity, higher death rates, and unnecessary healthcare expenditure (Johnson *et al.*, 1999; Brown and Bussell, 2011; Mafauzy *et al.*, 2011).

The effectiveness of treatment is mainly dependent on the level of adherence towards the prescribed medication (Paes *et al.*, 1998; Ahmad *et al.*, 2013) and accurate reporting of adherence problems (Vitolins *et al.*, 2000). Multiple factors leading to poor adherence are socioeconomic factors, therapy-related factors, patients-related factors, condition-related factors and health system-related factors (Sabaté, 2003). The conceptual framework of the study which consists of factors leading adherence to insulin therapy is shown in Figure 2.1.

Studies by Mann *et al.* (2009) and Aikens and Piette (2013) in the United States of America showed that the adherence to hypoglycaemic agents including insulin therapy was 28%. A study done by AlHewiti (2014) reported that 56.9% had low-adherence and it is associated with negative views to medications. Recently, a study was done by Yavuz *et al.* (2015) in Turkey found out that the adherence was 78%.

A systematic review was done by Cramer (2004) from previous studies deduced that the adherence to oral anti-diabetic agents drugs ranged from 36% to 93% and

specifically between 62-64% adherence rates for insulin therapy. These findings were consistent with a study done by Ahmad *et al.* (2013) in Malaysia which stated that 53% T2DM patients did not adhere to hypoglycaemic agents including insulin therapy. However, a study done by Mashitani *et al.* (2013) found out that the adherence rate in the Japanese population to be as high as 70.65%. The rate of adherence, or the variables affecting adherence may vary according to nationality, tools used to measure adherence, culture or subculture (Sabaté, 2003).

A study by Purran *et al.* (2015) of 156 patients showed that the proportion of adherence to insulin therapy in a tertiary hospital in Kelantan was only 19% and 98% of patients did not achieve the desired level of HbA_{1c} of less than 6.5%. Reasons for non-adherence are multifactorial. Studies done in different settings with various type of sample population regarding races, culture, lifestyle, education and income might yield different findings.

Rubin *et al.* (2009) identified several characteristics of diabetic management that may lead to non-adherence of therapy. Firstly, is the individual's perspective of the effects of diabetes of his or her personal lifestyle and secondly is the complexity of the regime. Edelman and Pettus (2014) commented that "once insulin therapy is initiated, adherence to treatment often is poor with many patients omitting or altering their insulin doses." Furthermore, the authors also deduced that the risks of future complication and financial burden would be increased if the patients were non-adherent to insulin therapy. The involvement of both patient and health care provider is essential in the accomplishments of adherence of medications to T2DM and therefore, effective insulin therapy (Peyrot and Rubin, 2011).

Adherence to insulin therapy is crucial in the management of diabetes. The adherence and control of insulin therapy would result in the improved levels of postprandial blood glucose, fasting blood glucose and HbA_{1c} and thus, reduce the risk of developing complications secondary to T2DM (Doggrell and Warot, 2014). However, only a small number of patients in the primary settings achieved the desired level blood glucose and diabetes control (Spann *et al.*, 2006).

A study conducted by Garcia-Perez *et al.* (2013) discovered that variety of factors might influence adherence to medication for DM patients. Factors associated with reduced adherence are the complexity of medication regimens, adverse events, the perception of efficacy and safety, financial considerations and patient-healthcare provider relationship. On the other hand, factors associated with improved adherence are reduced treatment complexity, education and increased knowledge, ensure benefits outweigh costs and improved continuity of care.

Enhancing the effectiveness of adherence towards medication regime may contribute a significant impact on the health of the population than any other improvement in specific medical treatment (Haynes *et al.*, 2008). Furthermore, adherence to pharmacotherapy intervention is crucial in glycaemia controls, reduce long-term complications and improve patient's health outcomes (American Diabetes Association, 2015; Krass *et al.*, 2015).

2.6. Assessment Tools Used in Measuring Adherence

An important component to measure the adherence of a patient towards medication is identifying its occurrence. The extent of treatment's adherence can be directly or indirectly measured. Direct measurements can be monitored by directly observing the treatment received, therapeutic drug monitoring and biomarkers (Vermeire *et al.*, 2001). However, most often, health care providers do not have access or limited opportunities to assess medication adherence by using direct measurement. Therefore, indirect measurements by way of record review, clinical assessment, pill count and questionnaire (Vermeire *et al.*, 2001; Horne *et al.*, 2005) may assist health care providers to assess medication adherence of a patient.

According to Sabaté (2003), studies conducted from 1980 to 2001 in measuring the adherence to DM regime yielded inconsistent findings. These inconsistent results might be due to several factors which were due to variability in research design, sampling frame employed, the use of general measures, sample sizes and lack of control of potentially confounding variables. The complexity of regime in managing T2DM has been recognized as a challenge to adherence to therapy.

A systematic review that was done by Stolpe *et al.* (2016) reported that there were numerous approaches to measuring adherence to insulin, namely using a self-administered questionnaire or filling of medicines. Reported methods which were commonly used in research studies were medication possession ratio, the proportion of days covered, persistence, daily average medication consumption, and the Morisky Adherence Scale. However, all methods were associated with a variety of challenges concerning the accuracy of estimated adherence, the complexity of data collection, the

absence of validated cut-off points for good adherence and reliability of adherence outcomes. This is due to the complexity of the measuring adherence level for injectable therapies as compared to oral medications.

Every adherence measurement tools have its strength and weaknesses (Williams *et al.*, 2013). A high number of patients with diabetes use insulin injection as one of their medication. Presently, there is no gold standard available for measuring medication adherence. Interestingly, questionnaires have been found to provide a more accurate assessment of adherence in comparison with other methods such as pill counts or biological assays (Arroyo *et al.*, 2011).

Previous studies measuring adherence level to insulin used a general version of questionnaires (Cramer, 2004; Peyrot *et al.*, 2010; Peyrot *et al.*, 2012) and did not specifically measure all the factors related to insulin therapy. Purran *et al.* (2015) had developed and validated an Insulin Adherence Questionnaire for Diabetes Mellitus (IAQDM) with good internal consistency and reliability specifically to measure the adherence to insulin therapy. The IAQDM consist of 34 items measuring the factors that leading to the adherence to insulin therapy.

2.7. Associated Factors of Adherence to Medication

The proportion of non-adherence to insulin therapy appear to be influenced by a variety of factors. Although plenty of studies were done to detect the factors associated with adherence to insulin, there was still inconsistency among studies (Rubin *et al.*, 2009; Peyrot *et al.*, 2012).

2.7.1. Socio-demographic Factors

In accordance with previous studies, there was a clear indication that the older the age, the higher the adherence to medication (Ahmad *et al*., 2013; Curkendall *et al*., 2013; Tunceli *et al*., 2015; Yavuz *et al*., 2015). Adherence was higher among patients aged 65 through 79 (Adjusted OR=1.36, 95% CI: 1.21, 1.52) and aged 80 years and older (Adjusted OR=1.41, 95% CI: 1.25, 1.59), compared to those aged 55 through 64 (Curkendall *et al.*, 2013). A study done by Tunceli *et al*. (2015) found out that patients aged less than 45 years old were 65% less likely to adhere to medications than older patients aged 45 to 65 years old (Adjusted OR=0.35, 95% CI: 0.33, 0.36). In Malaysia, Ahmad *et al.* (2013) found out similar outcome where younger age was 3% less likely to adhere compared to older age (Adjusted OR=0.97, 95% CI: 0.95, 0.99). It is possible that younger patients were less aware of their disease and thus more likely to be more non-adherent.

Male were more adherent to antihyperglycemic agents compared to female (Adjusted OR=1.14, 95% CI: 1.11, 1.17) (Tunceli *et al.*, 2015). However, a study done locally found out that females were more adherent to antihyperglycemic agents compared to male (Adjusted OR=2.33, 95% CI: 1.10, 4.93) (Ahmad *et al.*, 2013). The contradictory findings might be the result of different culture and belief among the sample population.

A study by Napolitano *et al.* (2016) in Italy found out that patients with a college degree or tertiary level of education were more likely to adhere to pharmacotherapy compared to those with a lower education level among patients with chronic conditions (Adjusted OR=2.05; 95% CI: 1.37, 3.06). Those with secondary school

(Adjusted OR=1.68; 95% CI: 1.08, 2.61) and with at least a college degree level of education (Adjusted OR=2.42; 95% CI: 1.53, 3.81) were more likely to adhere to medicines than those with a primary school or lower level. This study was similar to a study by Koprulu *et al*. (2014) which found that secondary and tertiary educated patients were 83% less likely to adhere to medications compared to those with none and primary level of education (Adjusted OR=0.17, 95% CI: 0.09, 0.31). A study done locally found out that patients with a secondary level of education were 2.72 times more adhere to medications compared to those in primary school and no formal education (Adjusted OR=2.72, 95% CI: 1.13, 6.55) (Bakar *et al.*, 2016). Findings were conclusive where people who were more educated was more likely to remember to take their medications.

2.7.2. Disease-Related Factors

The presence of DM comorbidities such as hypertension, dyslipidemia or both (Adjusted OR=1.78, 95% CI: 1.06, 2.98) resulted in higher non-adherence rate (Ahmad *et al.*, 2013). This was similar to a study by Koprulu *et al.* (2014), where patients with co-morbidities have 76% lower odds to adhere to medications (Adjusted OR=0.24, 95% CI: 0.11, 0.51). T2DM patients with comorbidities have more drugs of different pharmacological classes. This complex treatment regimen could be a factor that contributes towards non-adherence.

Furthermore, duration of illness also plays a contributing factor in non-adherence to insulin therapy as studied by Feldman *et al*. (2014) and Yavuz *et al.* (2015). These findings deduced that longer duration of illness leads to better adherence to therapy. Patients with a shorter duration of diabetes of 4.8 years (SD 4.3) were having

significantly lower adherence to insulin therapy than the longer duration of diabetes of 8.8 years (SD 6.3) (Yavuz *et al.*, 2015). In addition, a study by Feldman *et al.* (2014) found that long (more than 60 months) (Adjusted OR=2.48, 95% CI: 2.38, 2.59) and intermediate disease (36-59 months) duration (Adjusted OR=1.46, 95% CI: 1.39, 1.54) of illness were associated with higher adherence compared to those with short disease duration (1-35 months). Of those diabetes patients with longer duration of illness, many are taking multiple diabetes medications that are being actively managed by the patients or by their physician.

2.7.3. Treatment-Related Factors

There was an increased likelihood of non-adherence for patients who were on fewer than three concomitant medications compared to patients with no other concomitant medications (Adjusted OR=0.87; 95% CI: 0.84, 0.89) (Tunceli *et al.*, 2015). Patients who took a lower number of total pills per day (Adjusted OR=1.75; 95% CI: 0.66, 0.87) had 75% higher odds to adhere to medicines than patients who took more medicines per day (Napolitano *et al.*, 2016). Furthermore, patients were found to be 75.6% less likely to adhere to their medications with each unit increase in the number of prescribed medications (Adjusted OR=0.24, 95% CI: 0.08, 0.63) (Jarab *et al.*, 2014). Those studies were consistent with a study by Tunceli *et al.* (2015) who found out that patients on a twice-daily dose were 17% less likely to adhere to medications compared to patients with a once-daily dose (Adjusted OR=0.82; 95% CI: 0.80, 0.84). Donnelly *et al.* (2007) also reported that patients with poor adherence were significantly prescribed higher doses (66.4 IU/day) compared to those with better adherence (40.8 IU/day). These findings were conclusive where patients with higher

number of concomitant medications were having poorer adherence to medications. Patients with higher number of concomitant medications might a difficulty to adhere to the complex pharmacotherapy regime compared to patients with lower number of concomitant medications.

Patients had 64% lesser odds (Adjusted OR=0.36, 95% CI: 0.24, 0.87) to adhere to their medications if they reported adverse effects on the use of antihyperglycaemic agents compared to those who did not experience any adverse effects (Jarab *et al.*, 2014). Adverse effects which are typically happened in patients receiving insulin therapy are weight gain and hypoglycaemia (Russell and Khan, 2007; Wallia and Molitch, 2014).

Patients who had used insulin therapy for a shorter duration with a mean (SD) of 5.2 months (2.4) were more likely to non-adherent to insulin therapy than those on longer duration with a mean (SD) of 10.7 months (2.4) (Yavuz *et al.*, 2015). In addition, patients with a last visit to the clinic of more than one month has 14 times more likely to be non-adherent to medications compared to patients with a last visit of less than one month (Adjusted OR=14.0, 95% CI: 6.52, 10.04) (Koprulu *et al.*, 2014).

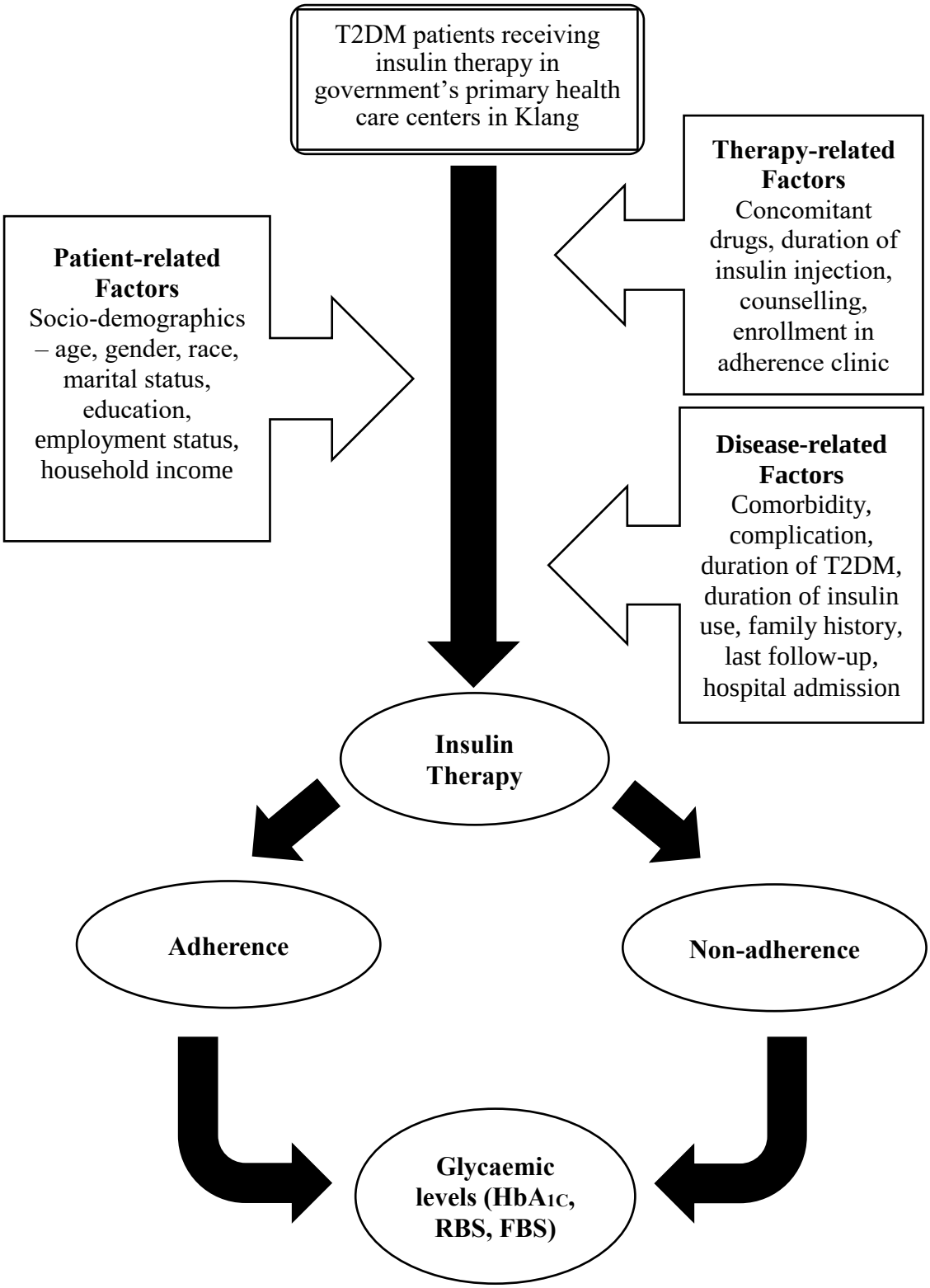

Figure 2.1: Conceptual Framework of the Study