DEVELOPMENT AND VALIDATION OF INSULIN ADHERENCE QUESTIONNAIRE (IAQDM) AND DETERMINATION OF FACTORS ASSOCIATED WITH NON-ADHERENCE AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

by

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologist
ACE	American College of Endocrinology
ADA	American Diabetes Association
ADEs	Adverse drug events
ADRs	Adverse drug reactions
β - Cell	Beta cell
BMI	Body mass index
BP	Blood pressure
CFA	Confirmatory factor analysis
CGMS	Continuous glucose monitoring system
CI	Confidence interval
CPG	Clinical practice guideline
CRF	Case report form
DCHUSM	Diabetic Centre Hospital Universiti Sains Malaysia
DCCT	Diabetes Control & Complications Trial
DM	Diabetes mellitus
EFA	Exploratory factor analysis
EGO	Endogenous glucose output
FA	Factor analysis

FPG	Fasting plasma glucose
GDM	Gestational Diabetes Mellitus
HbA1c	Glycated haemoglobin A_{1C}
HBM	Health Belief Model
HCP	Health care practitioner
HDL – C	High density lipoprotein cholesterol
HUSM	Hospital Universiti Sains Malaysia
IAQDM	Insulin Adherence Questionnaire for diabetes mellitus
ID	Identification number
LDL – C	Low density lipoprotein cholesterol
MDA	Malaysian Diabetes Association
mg/dl	Milli gram per litre
mmHg	Milli metre of mercury
mmol/L	Milli mol per litre
OADs	Oral antidiabetics
OR	Odds ratio
PAF	Principal axis factoring
PCA	Principal component analysis
RA	Reliability analysis
RPG	Random plasma glucose

SD	Standard deviation
SMBG	Self-monitoring blood glucose
SPSS	Statistical Package for Social Science
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TC	Total cholesterol
TG	Triglycerides
UKPDS	United Kingdom Prospective Diabetes Study
USM	Universiti Sains Malaysia
WC	Waist circumference
WHO	World Health Organization

ABSTRAK

PENGHASILAN DAN PENGESAHAN SOAL SELIDIK KEPATUHAN INSULIN (IAQDM) DAN PENGENALPASTIAN FAKTOR-FAKTOR BERKAITAN DENGAN KETIDAKPATUHAN DALAM KALANGAN PESAKIT KENCING MANIS JENIS 2

Pengenalan:

Prevalen penyakit kencing manis jenis 2 (T2DM) sedang meningkat di seluruh dunia dan di dalam negara. Walaupun pelbagai rawatan telah diberi untuk mengawal tahap glukos dalam darah, sasaran glisemik yang ditetapkan masih tidak tercapai. Buat masa sekarang, terapi insulin menjadi terapi utama kerana keberkesanannya dalam mengawal tahap glukos dalam darah. Walau bagaimanpun, rawatan insulin secara suntikan sangat komplek dan boleh menyumbang kepada masalah ketidakpatuhan terhadap rawatan insulin dalam kalangan pesakit diabetes.

Objektif: Untuk menghasil dan mengesahkan satu soal selidik baru untuk mengukur kepatuhan terhadap terapi insulin dalam kalangan pesakit kencing manis jenis 2. Kajian ini juga bertujuan untuk menentukan kadar ketidakpatuhan, kawalan glisemik, dan faktor-faktor yang berkaitan dengan terapi insulin.

Metodologi: Kajian ini menggunakan kaedah secara kualitatif di awal kajian untuk memilih tema yang sesuai bagi menghasilkan IAQDM dan kajian selainnya menggunakan kaedah kuantitatif. Temubual telah dijalankan kepada 30 orang pesakit

kencing manis jenis 2 yang menerima terapi insulin menggunakan panduan soal selidik semi-struktur untuk temuduga. Item untuk IAQDM baru telah dipilih dari temuduga pesakit, kajian literatur, dan konsultasi dengan pakar.

Soal Selidik IAQDM telah diukur kesahihannya terhadap 156 orang pesakit kencing manis jenis 2 yang menerima rawatan insulin di Pusat Diabetes, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia. Tahap ketidakpatuhan terhadap terapi insulin, kawalan glisemik dan faktor-faktor berkaitan dengan ketidakpatuhan terapi insulin telah diukur dalam kalangan 355 orang pesakit kencing manis jenis 2. Transkrip dari awal kajian telah dianalisa untuk tema yang berkaitan menggunakan perisian NVivo versi 10.0. Data untuk sosiodemografi, kadar ketidakpatuhan insulin, kawalan glisemik, dan faktor-faktor yang berkaitan dengan terapi insulin telah dianalisa secara kuantitatif menggunakan “Statistical Package of Social Science” (SPSS) versi 22.

Keputusan: IAQDM mengandungi 35 item yang terdiri dari empat domain: domain 1 (halangan terhadap suntikan insulin), domain 2 (pemantauan kendiri insulin dan glukos dalam darah), domain 3 (kepatuhan terhadap suntikan insulin) dan domain 4 (pelarasan pemakanan dalam terapi insulin). Nilai keseluruhan Cronbach’s alpha bagi 35 soalan IAQDM ialah 0.82. Cronbach’s alpha untuk keempat-empat domain masing-masing adalah 0.82, 0.88, 0.85 dan 0.82. Kadar ketidakkepatuhan terhadap terapi insulin dalam kalangan pesakit kencing manis jenis 2 adalah 81%. Majoriti (98%) pesakit diabetes jenis 2 yang menerima rawatan insulin tidak mencapai sasaran tahap HbA1c < 6.5%. Jangka masa penggunaan insulin, kekerapan suntikan

insulin dan tahap gula semasa berpuasa telah dikenalpasti sebagai faktor yang bebas dan ketara yang mempengaruhi ketidakpatuhan terhadap terapi insulin.

Kesimpulan: Satu Soal Selidik baru IAQDM dengan ciri-ciri psikometrik yang sangat baik untuk mengukur kepatuhan terhadap terapi insulin telah berjaya dihasilkan. Kepatuhan terhadap terapi insulin dalam kalangan pesakit kencing manis jenis 2 sangat rendah. Pengenalpastian faktor-faktor yang mempengaruhi ketidakpatuhan insulin boleh memberi panduan yang amat berguna untuk penyaringan, pengurusan, pemantauan, dan penambahbaikan kepatuhan kepada terapi insulin.

ABSTRACT

DEVELOPMENT AND VALIDATION OF INSULIN ADHERENCE QUESTIONNAIRE (IAQDM) AND DETERMINATION OF FACTORS ASSOCIATED WITH NON-ADHERENCE AMONG PATIENTS WITH TYPE 2 DIABETES

Introduction: Prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide and locally. Although various treatments were prescribed to control blood glucose level, the glycaemic target is still not achieved. At present, insulin therapy becomes the mainstay of treatment because of its effectiveness to control blood glucose. However, insulin injection is complex and can contribute to non-adherence problem among insulin treated patients with diabetes.

Objective: To develop and validate a new questionnaire to measure adherence with insulin therapy in patients with T2DM. This study also aimed to determine rate of non-adherence, glycaemic control and factors associated with insulin therapy.

Methodology: This study used qualitative design in the initial part of the study to choose appropriate themes for the IAQDM and quantitative design was utilised for the rest of the study. Interviews were conducted among 30 patients with T2DM on insulin therapy using developed and validated semi-structured interview guide. Items for the new IAQDM were selected from patients' interviews, literature reviews, and consultation with the experts. The IAQDM was validated among 156 patients with T2DM on insulin therapy at the Diabetic Centre, Hospital Universiti Sains Malaysia,

Kubang Kerian, Kelantan, Malaysia. Rate of insulin non-adherence, glycaemic control and factors associated with insulin non-adherence were measured in 355 patients with type 2 diabetes mellitus. Transcript data from the initial interviews were analysed for relevant themes using NVivo software version 10.0. Data for sociodemography, insulin non-adherence rate, glecemic control and factors associated with insulin therapy were analysed quantitatively using Statistical Package of Social Science (SPSS) version 22.

Result: The IAQDM consisted of 35 items and four domains: domain 1 (barriers with insulin injection), domain 2 (self-monitoring of insulin and blood glucose), domain 3 (adherence with insulin injection) and domain 4 (dietary adjustment with insulin therapy). Overall Cronbach's alpha value for all the 35 items in the IAQDM was 0.82. Cronbach's alpha values for each domain are 0.82, 0.88, 0.85 and 0.82 respectively. Non-adherence rate with insulin therapy among patients with type 2 diabetes was 81%. Majority (98%) of patients on insulin therapy did not achieve the target HbA1c of < 6.5%. Duration of insulin therapy, frequency of insulin injections and fasting plasma glucose were identified as independent and significant factors to non-adherence with insulin therapy.

Conclusion: A new IAQDM with very good psychometric properties to measure adherence with insulin therapy has been developed. Adherence with insulin therapy and glycemic control among patients with T2DM were very poor. Identification of several factors contributed to insulin non-adherence can provide a very useful guide for screening, managing, monitoring, and improving adherence with insulin therapy.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Type 2 diabetes mellitus (T2DM) continues to increase worldwide and in Malaysia. Globally, in 1995, the number of population in the developing country affected by diabetes was estimated to be 135 million in the year 2000 and increased to 154 million in the year 2025 (King *et al.*, 1998; Mafauzy, 2006). It is the most common disease causing significant mortality and morbidity is in nearly all the countries (Vijan *et al.*, 2005; Danaei *et al.*, 2011; Whiting *et al.*, 2011).

In Malaysia, the First National Health and Morbidity Survey (NHMS) 1986 reported a prevalence of diabetes mellitus of 6.3% and in the Second NHMS I in 1996, the prevalence had risen to 8.2% (Mafauzy, 2006). Based on the latest results of the NHMS 2011 and projections by the Disease Control Division, Ministry of Health (MOH), the prevalence of diabetes among adults in Malaysia is projected to rise to 21.6% by the year 2020.

Furthermore, studies in Malaysian had shown that diabetes was most prevalent amongst Indians (38%) and Malays (24%) with the current overall prevalent of 23% compared to the year 2006 with only 12% (Wan Nazaimoon *et al.*, 2013).

Type 2 diabetes mellitus (T2DM) is a chronic disease and causes many problems such as financial, psychosocial and disability to the sufferer, family and community (Boyle *et al.*, 2010). Short-term complications of T2DM are hypoglycemia and hyperosmolar hyperglycemic nonketotic syndrome, which is very high blood glucose. Long term complications of T2DM are macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) (Fowler, 2008). Morbidity and mortality substantially increased with elevation of blood glucose (Lavernia, 2008). Therefore, proper management and treatment are very important aspect in dealing with T2DM especially with insulin therapy.

At the beginning of the diagnosis, majority of patients can control their glycaemic status with diet, exercise and oral hypoglycaemic agents (OHA). However, sooner or later, these T2DM patients will eventually need to take insulin, as their ability to produce their own insulin from pancreatic beta-cells increasingly declined (Hirsch et al, 2005, Hamaty, 2011).

Most importantly, T2DM is a progressive disease and treatment with oral hypoglycaemic agents often lose their effectiveness with increased duration of disease. Consequently, there is a need to add insulin therapy to maintain glycaemic control. The use of insulin therapy among patients with T2DM has continued to increase with the awareness of the need to maintain strict glycaemic control and good adherence towards prevention of acute and chronic complications of diabetes (Ministry Of Health Malaysia, 2010).

Even though the use of insulin has increased, its use is still generally low in Malaysia and varies across different states in the country. This happens because of low acceptance from health care providers, patients, family members, probably due to lack of knowledge, awareness, guidance and support. Therefore, diabetes focused health education and counselling will hopefully improve awareness, acceptance and adherence to insulin therapy among T2DM patients.

Insulin therapies have now become a common prescription for out-patient departments (DeWitt & Dugdale, 2003). Many uncontrolled T2DM patients with symptoms, regardless whether haemoglobin A1c (HbA1c) more than 10% or fasting blood sugar (FBS) of more than 13 mmol/L, will be started on subcutaneous insulin injection (Practical guide to insulin therapy in T2DM, 2010).

Insulin therapy is very complex if not properly guided. Usually, T2DM will start with a single type of insulin therapy such as subcutaneous glargine (Lantus®), detemir (Levemir®), or insulatard (NPH®) (DeWitt & Dugdale, 2003, Hamaty, 2011). These types of insulin must be injected before bedtime. The aim for these types of insulin is to reduce fasting blood sugar till near normal, about four to six mmol/L (4 – 6 mmol/L) without hypoglycaemic symptoms. Subsequently, if a single type of insulin still cannot achieve the near normal target, most T2DM patients will need to inject two times, three times, or four times a day.

Furthermore, even though the majority of T2DM at Diabetic Centre, Hospital Universiti Sains Malaysia were prescribed with more than one injection per day, glycaemic status are still unsatisfactory. Three years data from 2012 to 2014 revealed that majority of patients had Glycosylated Haemoglobin A1c (HbA1c) levels of more than 8% (Figure 1.1).

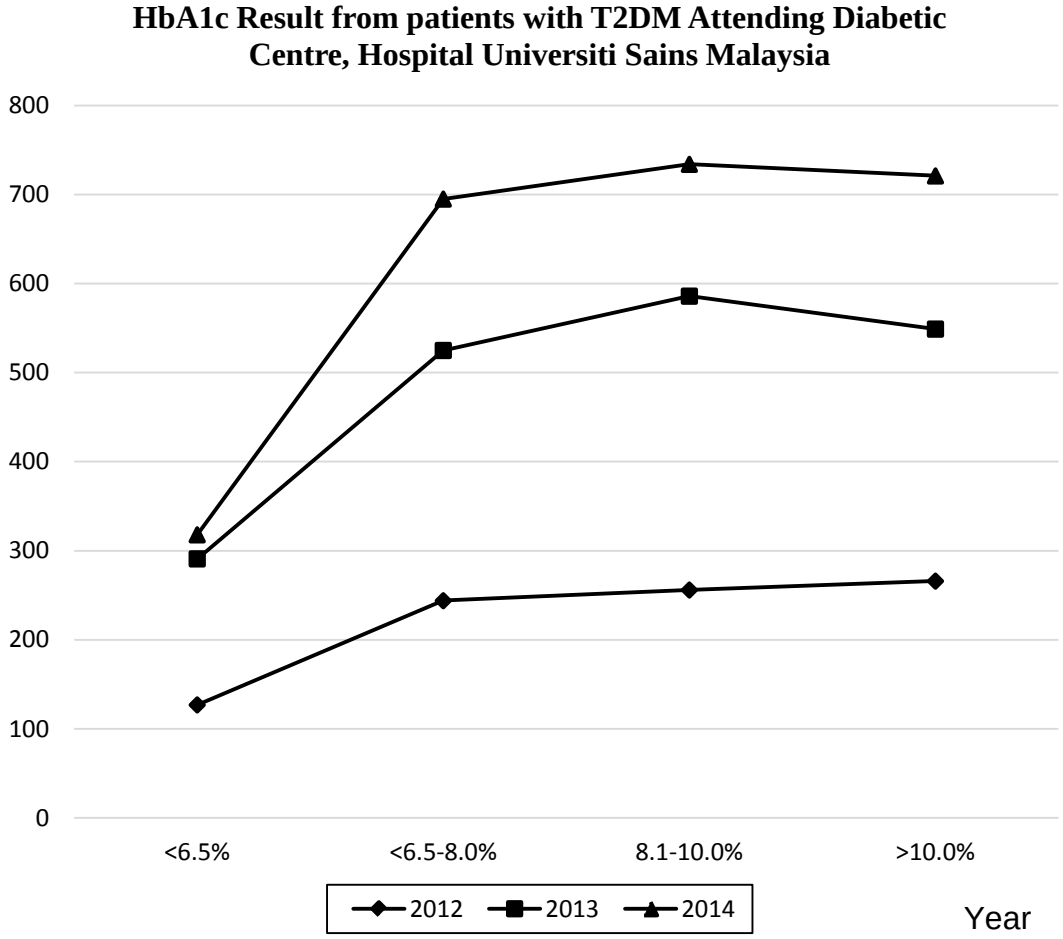


Figure 1. 1 HbA1c result from patients with T2DM Attending Diabetic Centre, HUSM, Kelantan, Malaysia from 2012 to 2014

(Data from the Diabetic Centre, HUSM, 2015).

1.2 Justification of the study

At the moment, there is no standard tool for measuring adherence among patients with T2DM on insulin therapy. Even though numerous studies had been conducted in relation with insulin therapy (Bradley et al, 2007, Naegeli & Haynes, 2010, Franz M, 2010, Nishigaki et al, 2012), none was focusing specifically on measuring insulin adherence. Since adherence is very crucial for the success of diabetic therapy (Chisholm-Burns & Spivey, 2012), availability of a new tool to measure insulin is certainly justified. Therefore, this study has been conducted to develop a new tool to measure adherence among patients with T2DM on insulin therapy.

Non-adherence to medication can resulted in failure of patient's condition to improve, worsen or relapse (especially in long term therapy), and this effect has negative economic impact on the entire health care system (Chisholm-Burns & Spivey, 2012). Obtaining information about the level of non-adherence among T2DM with insulin therapy is a first step in formulating intervention program among insulin treated diabetes patients. Given this point, vigilant assessment is critical in planning for the interventions needed, to improve effectiveness of pharmacological care, and to safeguard the sustainability of healthcare systems especially in patients with insulin therapy.

Ability of health care practitioners such as clinicians, pharmacists, nurses, dieticians and others to identify and document insulin non-adherence and its associated factors among patients with T2DM is very important for the successful outcomes of therapy. These documentations using evidence-based approach can provide further understanding on the complex and dynamic behaviour of adherence with insulin therapy. Therefore, prevention and intervention strategies can be implemented to reduce problems, complications, disease progression, cost, morbidity and mortality.

1.3 Rationale of the study

The rationale of conducting this study was to obtain more information regarding adherence among patients with T2DM on insulin therapy. Furthermore, since there was no specific assessment tool to be used in assessing adherence to insulin therapy, especially in the local population, a new tool was developed and validated. Although quality of life of patients has been constantly-targeted as an important matter in the patients' treatment management (Pera, 2011, Oliva *et al.,* 2012), understanding regarding basics of insulin therapy is still limited. In addition, most of the available information was obtained from different settings (Wei, *et al*., 2002, Farsaei, *et al*., 2014) which may not be applicable locally. Adherence is a dynamic and complex behaviour and may differ with different setting and population. Thus, the findings of this study will serve the purpose of providing as much information as possible regarding adherence in the local

setting to improve the services provided by the health care practitioners among patients with type 2 diabetes on insulin therapy.

1.4 Conceptual framework of the study

The modified Health Belief model (HBM) (Figure 1.2) was used to study patients' responses to symptoms and their behaviour in response to diagnosed illness, particularly adherence with medical regimens were mainly used in the development of the questionnaire (Janz and Becker, 1984, Carpenter, 2010). The HBM is generally effective in identifying factors associated with the adoption of preventive action in a variety of different populations. The model also relates patient's susceptibility to illness, severity of consequences, and benefits and barriers to adherence with prescribed therapy.

The HBM by Janz and Becker (1984) is a framework for understanding patient adherence to health behaviours. The HBM focus on two aspects of a person's conceptualization of health and health behaviour which are threat perception and behavioural evaluation. Threat perception is dependent on perceived susceptibility to illness and anticipated severity of the consequences. For the behavioural evaluation, it concerns the benefits of a health behaviour and the barriers to enacting the behaviour's (Carpenter, 2010). Therefore, according to the HBM, the likelihood of individuals with T2DM adhering to their regimens may be determined by five factors.

The first factor, which is susceptibility to illness, refers to the perception of vulnerability to diabetes and its complications. This includes patients' perception of chance that they may have for developing problems due to diabetes. The second factor is severity, which is the perception of diabetes as a serious illness, ranging from perceiving few complications to viewing diabetes as a life-threatening disease. The third factor is benefits of adherent behaviour which concerns the perception that the regimen is effective, so that the individual feels physically better from taking medications.

The fourth factor is barriers to adherence. This refers to the perceived cost of adhering to a regimen and how inconvenient the regimen is perceived to be. Lastly, cues to action concerns either external (e.g., time of day, reminders from family) or internal (e.g., feeling high and low blood sugars) cues that the individual associates with taking action. However, it was noted that the cues to action was the most underdeveloped factor and rarely measured in research (Carpenter, 2010).

Inconsistent results have been obtained in several studies which investigated risk perception and adherence to recommended diabetes management activities in adults (Janz & Becker, 1984, Woolridge *et al.*, 1992). These findings highlight the importance of modifying and examining individual components of health beliefs, rather than directly using the HBM (Carpenter, 2010).

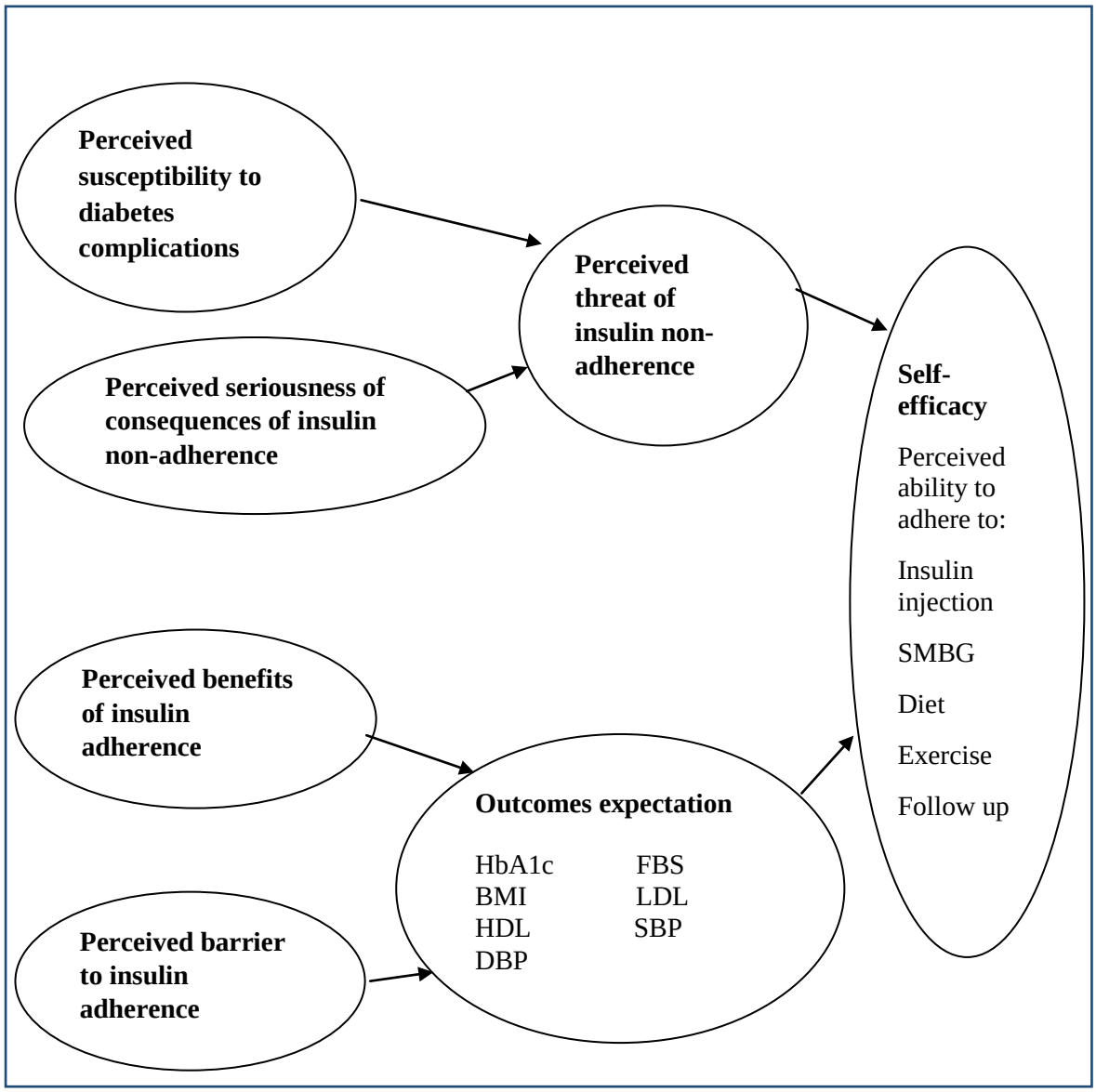


Figure 1. 2 Modified conceptual framework of the Health Belief Model on insulin adherence among patients with T2DM

1.5 Research questions

1. Is the newly developed Insulin Adherence Questionnaire valid and reliable?
2. What is the rate of non-adherence among patients with T2DM on insulin therapy?
3. What is the rate of glycaemic control among patients with T2DM on insulin therapy?
4. What are the factors associated with non-adherence with insulin therapy?

1.6 Research objectives

1.6.1 General objectives

The general objective is to develop and validate a new questionnaire to measure adherence with insulin therapy in patients with T2DM at the Diabetic Centre, Hospital Universiti Sains Malaysia, Kelantan, Malaysia.

1.6.2 Specific objectives

1. To develop and validate a new Insulin Adherence Questionnaire to measure adherence with insulin therapy.
2. To determine rate of non-adherence among T2DM on insulin therapy.
3. To determine rate glycaemic control among patients with T2DM on insulin therapy.
4. To identify factors associated with non-adherence with insulin therapy.

CHAPTER 2

LITERATURE REVIEW

2.1 Definition and causes of T2DM

Type 2 diabetes mellitus is a complex metabolic disorder resulting from relatively decreased pancreatic insulin secretion, insulin action or insulin resistance (Inzucchi, 2002). It has serious complications and reduce life expectancy by 8–10 years (Astrup and Finer, 2000). It is the most prevalent form of diabetes (90–95%) and rapidly becoming one of the major disease in the world (LaSalle, 2010).

Type 2 diabetes is the condition in which the body does not produce or properly use insulin (Simo and Hernández, 2002, Organization, 2006). Insulin is a hormone that is required to convert glucose into energy needed for daily life. Insulin insensitivity is an early phenomenon partly related with obesity, with gradual decline of pancreatic β-cell function over time before the onset of clinical hyperglycaemia (Alberti and Zimmet, 1998; Scheen, 2003, Hirsch *et al.*, 2005, Stumvoll *et al.*, 2005, Inzucchi et al, 2012).

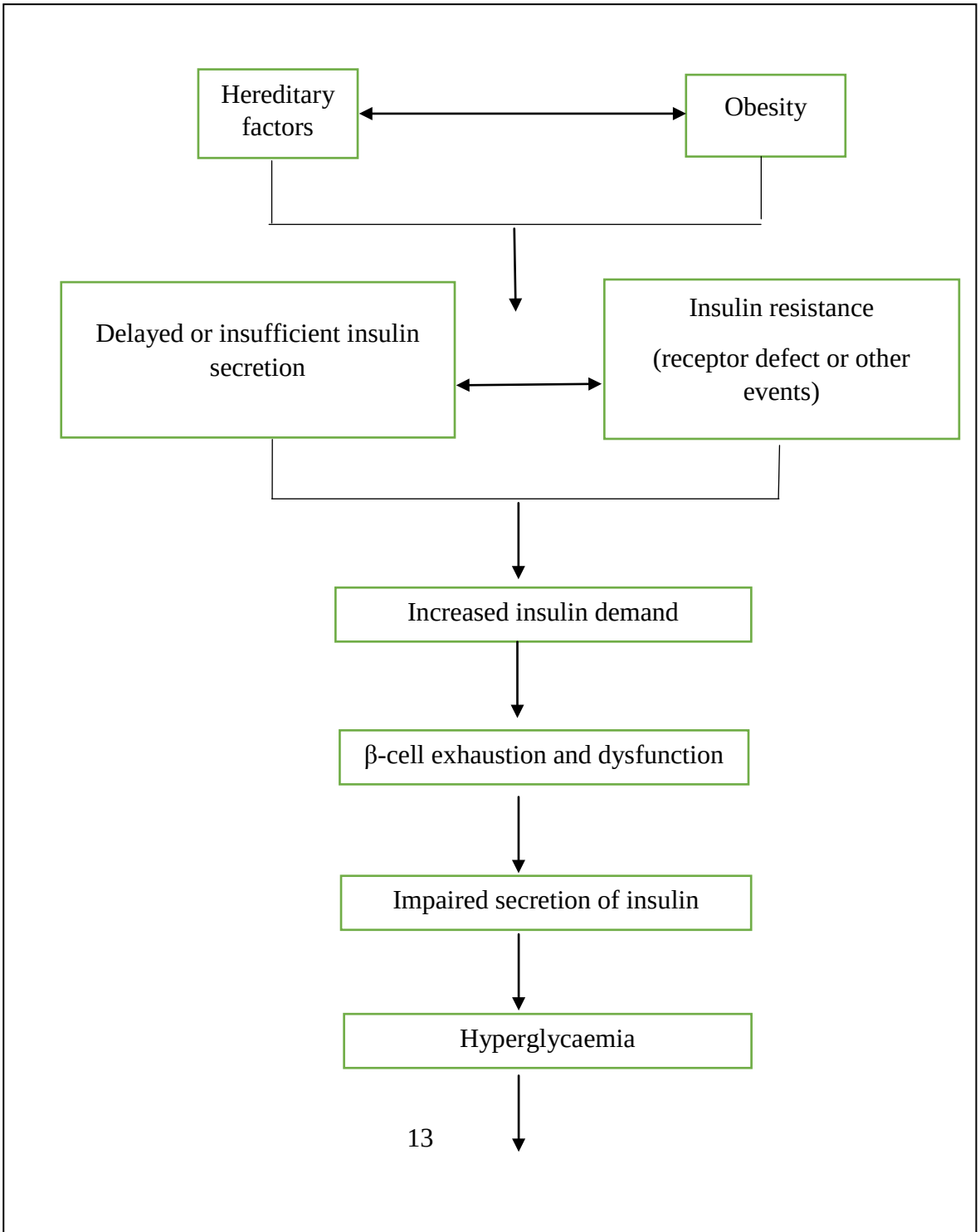
The causes of diabetes stem from both from genetics and environmental factors. Obesity and lack of exercise also appear to play important roles (Stern, 1995, Astrup and Finer, 2000, Chen *et al.*, 2012).

2.2 Pathophysiology of T2DM

Type 2 diabetes mellitus is a heterogeneous syndrome characterized by abnormalities in carbohydrate and fat metabolism. It is characterised by high blood glucose in the context of insulin resistance and relative insulin deficiency (Meltzer *et al.*, 1998, Rodbard *et al.*, 2009). The causes of T2DM are complex and multifactorial and include both genetic and environmental elements that affect beta-cell function and tissue (muscle, liver, adipose tissue, and pancreas) which in turn affect insulin sensitivity. Majority of individuals suffering from T2DM are obese with central visceral adiposity. Therefore, adipose tissue plays a crucial role in the pathogenesis of T2DM (Scheen, 2003).

Type 2 diabetes mellitus is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and pro-inflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat (American Diabetes Association, 2008, American Diabetes Association, 2009, American Diabetes Association, 2010).

For T2DM to occur (Figure 2.1), both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes only develops in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for their level of glycaemia (Rodbard *et al.*, 2009, MOH, 2016).



Non-Insulin Dependent Diabetes Mellitus (NIDDM)
or T2DM

Figure 2. 1 Pathophysiology of T2DM

(Adapted from Hope, 2012)

2.3 Diagnosis of T2DM

Diagnosis of diabetes mellitus can be made through clinical presentation such as increased thirst and urine volume, recurrent infections, unexplained weight loss, and in severe cases, drowsiness and coma. Furthermore, high levels of glycosuria are usually present (Stride *et al.,* 2005, Clinical practice guidelines, 2016).

According to The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Alberti and Zimmet, 1998, The International Expert Committee, 2009), diabetes may be diagnosed in three ways: symptoms of diabetes plus casual plasma glucose concentrations ≥ 11.1 mmol/L, fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or two hours plasma glucose (2 - hPG) ≥ 11.1 mmol/L during an oral glucose tolerance test (OGTT).

In addition, the diagnosis of diabetes in an asymptomatic subject should never be made on the basis of a single abnormal blood glucose value or test. For an asymptomatic patient, at least one additional plasma/blood glucose test result with a value in the diabetic range is essential, either fasting blood glucose, random (casual) blood glucose, or from the oral glucose tolerance test.

In epidemiological studies, one fasting plasma glucose measurement is adequate. Meanwhile, The WHO has reserved the use of fasting plasma glucose or 2 hours plasma glucose measurements for epidemiological purposes and suggested that ideally, both values should be used (World Health Organization, 1999). The diagnostic value interpretations of the fasting and 2 hours post load concentrations in non-pregnant subjects are listed in Table 2.1.

Table 2. 1 Fasting and 2 hours post- load glucose values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

Category	Sampling time	Glucose concentration, mmol/L (mg/dl)			
		Whole Blood		Plasma	
		Venous	Capillary	Venous	Capillary
Diabetes Mellitus	Fasting	≥ 6.1 (110)	≥ 6.1 (110)	≥ 7.0 (126)	≥ 7.0 (126)
	2-hours post glucose load	≥ 10.0 (180)	≥11.1 (200)	≥ 11.1 (200)	≥ 12.2 (220)
Impaired Glucose Tolerance (IGT)	Fasting	< 6.1 (110)	<6.1 (110)	< 7.0 (126)	< 7.0 (126)
	2-hours post glucose load	≥ 6.7 - < 10.0 (120 – 180)	≥ 7.8 - < 11.1 (140 – 200)	≥ 7.8 - < 11.1 (140 – 200)	≥ 8.9 - < 12.2 (160 – 220)
Impaired Fasting Glycaemia (IFG)	Fasting	≥ 5.6 - < 6.1 (100 – 110)	≥ 5.6 - < 6.1 (100 – 110)	≥ 6.1 - < 7.0 (110 – 126)	≥ 6.1 - < 7.0 (110 – 126)
	2-hours post glucose load	< 6.7 (120)	< 7.8 (140)	< 7.8 (140)	< 8.9 (160)

Adapted from the WHO Consultation Report (1999)

Even though the Oral Glucose Tolerance Test is the "gold standard" for diagnosing diabetes, it is known to be poorly reproducible and is often not performed. In addition, the use of an HbA_{1c} level to diagnose diabetes is more convenient, because therapeutic decisions are based on this value, regardless of the findings of the OGTT. An HbA_{1c} level of 7.0% or higher often requires pharmacological intervention and is most often associated with the diagnosis of diabetes by World Health Organization standards. An HbA_{1c} level below 7.0% should generally be treated with diet and exercise, regardless of the diagnosis of IGT or diabetes by OGTT. Thus, measurement of HbA_{1c} levels may represent a reasonable approach to identify treatment-requiring diabetes (Peters *et al.*, 1996). However, all these methods have their limitations in certain area because lack of accessibility and equipment to perform the test.

The International Expert Committee (2009) with the members appointed by ADA, the European Association for the study of Diabetes, and the International Diabetes Federation had convened in 2008. This committee urged consideration for the current and future means of diagnosing diabetes in non-pregnant individuals by using HbA1c. The International Expert Committee hoped that its report would serve as a stimulus to both the international community and professional organizations to use this measure.

2.4 Management of T2DM

Diabetes is a chronic disease that needs continuous of self-management and appropriate treatment. Patients need to adopt and maintain multiple self-care behaviours to achieve and sustain good glycaemic control (Savoca and Miller, 2001). The aims of diabetes management are to improve quality of life and prevent premature death by reducing hyperglycaemia and body fat, relief of symptoms and prevention of acute and chronic complications (Boulé *et al.,* 2001). In addition, continuous maintenance of good glycaemic control, identification of associated risk factors, appropriate treatment and proper patients' education should be conducted.

Management of diabetes is very complex and needs to address the prevention of cardiovascular and microvascular diseases. Diabetic management includes not only diet and exercise, but also combinations of anti-hyperglycaemic drugs, lipid-lowering drug, anti-hypertensives, and anti- platelet therapies (Inzucchi *et al.,* 2012).

In recent years, new evidence has accumulated on lifestyle intervention since life-style factors affects the incidence of T2DM (Hu *et al.,* 2001). Self-management through education by self-monitoring and many other new treatments have been introduced.

Once a diagnosis is confirmed, structured education is very important to patients and their family members. Structured education is an integral part of diabetes care and

should be organized annually with constant reinforcement (Home *et al.*, 2008). Most importantly, structured education programme should be based on evidence-based approach. It should be tailored to individual needs, enhance self-management and has a formal curriculum. Structured education is usually delivered by trained educators using defined education resources or any trained paramedic staffs that deal with diabetic patients.

The International Diabetes Federation Europe and the World Health Organization had stated an obligation to optimize the management with the aim of decreasing the risk of long-term complications (World Health Organization, 1999). Self-care behaviours is very important since persons with diabetes are expected to follow a complex set of behavioural actions and modification such as dietary adjustment, physical activity, and adherent to diabetes medications (McNabb, 1997, Meltzer *et al.*, 1998).

The mainstay of diabetes management is diet control since diet is known to influence body weight (Meyer *et al.*, 2000). Maintaining a desirable body weight and optimal glycaemic control can reduce morbidity and mortality associated with diabetes (Savoca and Miller, 2001). Doctors or paramedics should refer patients to registered dieticians or diabetes educators to help them to formulate a healthy eating plan. Patients with T2DM need to monitor their intake of carbohydrates and reduce total daily calories. Controlling total fat and protein consumptions are also recommended.

A study was conducted by Nelson, *et al.,* (2002) in the Third National Health and Nutrition Examination Survey (NHANES III) among 1,480 adult with T2DM had

shown that only two thirds of the patients consumed more than 30% of their daily calories from fat with more than 10% of total calories from saturated fat. Thirty six percent of them were overweight and another 36% were obese. These results further complicated the diabetes management and patients might be exposed to various cardiovascular problems. Therefore, Medical Nutrition Therapy (MNT) is very important for the effective management of diabetes (Morris *et al.*, 1997) by providing individualized nutritional recommendations taking into consideration the personal, cultural, and lifestyles preference to achieve optimum treatment (Nisak *et al.*, 2013)

In clinical practice, diabetic patients must strictly adhere to the diet prescriptions by dietitians. A well balanced diet which consists of carbohydrates, protein, fats and minerals is a basic requirement for every patient. On top of that, a high fibre diet plays an important roles to reduce cholesterol level in the blood. The American Diabetes Association (ADA) recommended a moderate increase in the intake of dietary fibre to 20–35 g per day (Chandalia *et al.*, 2000). They should avoid foods with high total calories, low dietary fibre intake, and high glycaemic load. A low fibre diet with a high glycaemic index has been associated with increased diabetes complications (Pon *et al.*, 2006). A validated full block questionnaire consisted of approximately 100 food items, plus additional questions on the consumption of food from restaurants and the frequency of use and type of cooking fat was available and able to capture all nutrient in the diet (Block *et al.*, 1990).

A cross sectional study was conducted by Nthangeni, *et al.,* (2002) among 288 T2DM to determine the dietary intake, practice, knowledge and barriers to dietary adherence at the urban and rural areas in South Africa. They found that urban subjects had higher intake of animal protein and lower ratios of polyunsaturated fat to saturated fat than rural subjects. Poor glycaemic control was found in both urban and rural areas, with more than half of the subjects having fasting plasma glucose above 8 mmol/L, and more than 35% having plasma glycosylated haemoglobin levels above 8.6%. High triglyceride levels were found in 24 to 25% of men and 17 to 18% of women. The team also noted that obesity (body mass index $\geq$ 30 kg/m^2) was higher in women with 35 to 47% and elevated blood pressure ($\geq$ 160/95 mmHg) is higher (42.4%) in men at the urban area.

Savoca and Miller (2001) conducted a qualitative study using semi-structured interview among 45 subjects with T2DM. They explore the belief and perspectives among patients with T2DM on dietary requirement, food selection, eating patterns and attitude in self-management practices. They noted that dietary self-efficacy, social support, and time management were identified as mediating variables that can influence dietary behaviours. At the same time, diabetes nutrition education programs increase awareness of eating behaviours and support from family members.

Another study was conducted by Tan, *et al.,* (2011) among 150 patients with T2DM at the Hospital USM to determine dietary compliance and its association with glycaemic control using a questionnaire-based interview. They found that only 16.4% of subjects adhered to dietary regimen provided by dietitians. There was a

significant association between gender and fasting blood sugar with the compliance status.

In another study by Hu, *et al.,* (2001) among 84,941 nurses free from cardiovascular disease, diabetes, and cancer at the base line for 16 years, 3300 new cases from the subjects developed T2DM. Overweight or obesity was the single most important predictor of diabetes. In addition, lack of exercise, poor diet control, current smoking, and abstinence from alcohol use were also associated with a significantly increased risk of diabetes, even after adjustment for body-mass index.

Exercise or physical activity improved quality of life and reduced the risk for several leading causes of death (Evenson and McGinn, 2005). Physical activity also reduced blood sugar, body fat, blood pressure, and helped to prevent cardiovascular disease. Therefore, it is recommended that people with type 2 diabetes get regular 30 minutes of moderate exercise on most days. A deliberate weight loss of 0.5 – 9.0 kilogram is associated with 30 – 40% reduction in diabetes related mortality (Astrup and Finer, 2000).

Regular physical activity is recommended for patients with T2DM since it may have beneficial effects on metabolic risk factors responsible for the development of diabetes complications. The non-pharmacological nature of physical activity further enhance the effectiveness of insulin therapy (Boulé *et al.,* 2001). Lack of exercise among patients with diabetes has been associated with significant and increased risks of diabetes complications (Hu *et al.,* 2001).

The Third National Health and Nutrition Examination Survey was performed in 1,480 subjects with T2DM (NHANES III). The results showed that 31% reported no regular physical activity and another 38% reported less than recommended levels of physical activity. Lower income and increasing age were associated with physical inactivity, with 36% of the subjects were overweight and another 46% were obese (Nelson *et al.*, 2002).

Other than regular physical exercise, stress management is also very important. Stress is particularly worrisome for people with diabetes because it increases blood pressure and blood glucose levels. Many people with diabetes find that relaxation techniques can help to manage their condition. Examples include visualization, meditation, or breathing exercises. Taking advantage of social support networks is also helpful, like talking with a relative or friend, support group or counsellors. It is widely recognized that stress had negative effects on health in patients with diabetes (Surwit *et al.*, 2002). Proper stress management was associated with small (0.5%) but significant reduction in HbA1c levels.

Type 2 diabetes is a progressive disorder which can be initially treated with oral agent monotherapy, but eventually will require addition of others drugs (DeFronzo, 1999, Qaseem *et al.*, 2012). Oral medication is recommended for people with T2DM who cannot adequately control their blood sugar with diet and exercise. Many types of oral diabetes medications are available and usually used in combination for best

results. Certain drug increases insulin production, others improve the body's use of insulin, while still others partially block the digestion of starches.

Due to the progression of the disease, majority of patients with T2DM need multiple therapies such as regular diet control, regular exercise, insulin therapy, and oral diabetic agents such as sulphonylurea or metformin (Qaseem *et al.,* 2012). This combination therapies were known to improve glycaemic control among T2DM (Giugliano *et al.,* 1993; Turner *et al.,* 1999, Qaseem *et al.,* 2012). Whatever treatment that patients with T2DM received, most of them need to monitor their own blood sugar levels to achieve optimal glycaemic control. Self-monitoring of blood glucose is very important tool to help in optimizing glycaemic control, minimizing hypoglycaemia and maintaining quality of life (Bergenstal and Gavin III, 2005). Although self-monitoring of blood glucose (SMBG) is an integral part of disease management for patients with both type 1 and type 2 diabetes, it is still underutilized.

Progression of diabetes means that patients are going through the following treatment stages: for the early part, diet and physical activity are aimed to achieve weight loss and reduce insulin needs and resistance. Then, treatment with a single drug, usually metformin. If not controlled, treatment with two oral drugs, usually by adding a sulphonylurea to the metformin. If still not controlled, treatment with three oral drugs in addition to insulin, usually with once-daily long-acting (basal) insulin, taken along with metformin and a perhaps reduced dose of sulphonylurea. Finally, when all the treatment above fail to achieve optimum glycaemic control, moving to more complex insulin regimens, such as adding short-acting insulin at mealtimes, or twice-daily

mixed insulins, with sulphonylurea being discontinued (Clar *et al.*, 2010). This progression needs to be self-monitored regularly by diabetic patients.

2.5 Insulin therapy among T2DM

Diabetes mellitus affects people all over the world with 90% - 95% are T2DM. Type 2 diabetes mellitus can be caused by insulin resistance, which impaired the ability of insulin to suppress hepatic glucose production and stimulate peripheral glucose uptake and secondly, progressive impairment of insulin secretion (Wallia and Molitch, 2014). Many patients with T2DM will eventually need insulin, as their ability to produce their own insulin from pancreatic beta cells decline over time (Hamaty, 2011). Up to 60% of patients with T2DM require insulin within 6 to 10 years of initial diagnosis (Barag, 2011).

Insulin is a potent well known drug used in treating patients with diabetes mellitus. Guideline by the American Diabetes Association (ADA) and the National Institute for Health and Clinical Excellent (NICE) stated that insulin is the most effective glucose-lowering agent (Davies *et al.*, 2013). Among the various pharmacologic treatments, insulin is among the most widely used drug, encompassing all cases of type 1 diabetes mellitus and between 20% and 30% of adult cases of T2DM (Anderson *et al.*, 2004). However, delay in insulin initiation is common since about 50% of patients with poor control T2DM did not timely start insulin therapy. The initiation was usually three to five years after failure of oral hypoglycaemic agents (Hassan *et al.*, 2013). The first patients treated with insulin therapy in the year 1922 was 14 years old boy Leonard Thompson with type 1 diabetes. Before the discovery