# EVALUATION OF ILLNESS PERCEPTIONS AND THEIR ASSOCIATIONS WITH GLYCAEMIC CONTROL, CHRONIC KIDNEY DISEASE AND MEDICATION ADHERENCE IN TYPE 2 DIABETES MELLITUS PATIENTS AT HOSPITAL PULAU PINANG

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**by**

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| | |
|---|---|
| BIPQ | Brief Illness Perception Questionnaire |
| CI | Confidence Interval |
| CSM | Common Sense Model of Self - Regulation of Leventhal |
| DALY | Disability Adjusted Life Years |
| DCF | Data Collection Form |
| ESRD | End Stage Renal Disease |
| GDM | Gestational Diabetes Mellitus |
| HPP | Hospital Pulau Pinang |
| IDF | International Diabetes Federation |
| IP | Illness Perception |
| IPQ | Illness Perception Questionnaire |
| IPQ-R | Revised Illness Perception Questionnaire |
| MOH | Ministry of Health |
| MMAS-8 | Eight-Item Morisky Medication Adherence Scale |
| MREC | Medical Research Ethics Committee |
| NHMS | National Health Morbidity Survey |
| OAD | Oral Anti-diabetic Agent |
| OR | Odds Ratio |
| PMP | Per Million Population |
| QoL | Quality of Life |

| | |
|---|---|
| RCT | Randomised Controlled Trials |
| r | Pearson Correlation Coefficient |
| rs | Spearman's Rank Correlation Coefficient |
| SD | Standard Deviation |
| SMBG | Self-Monitoring of Blood Glucose |
| SPSS | Statistical Package for Social Science |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| UK | United Kingdom |
| US | United States |
| USM | Universiti Sains Malaysia |
| WHO | World Health Organization |

**PENILAIAN PERSEPSI PENYAKIT TERHADAP KAWALAN GLISEMIK, PENYAKIT BUAH PINGGANG KRONIK DAN TABIAT PENGAMBILAN UBAT DALAM KALANGAN PESAKIT YANG MENGHIDAPI DIABETES MELLITUS JENIS 2 DI HOSPITAL PULAU PINANG**

## ABSTRAK

Malaysia mempunyai kadar kelaziman diabetes tinggi iaitu 16.9% dan kawalan glisemik suboptimal kerana hanya 23.8% pesakit mencapai HbA1C <7%. Persepsi penyakit (IP) melibatkan strategi dan tingkah laku pesakit yang boleh mempengaruhi kawalan glisemik. Objektif kajian adalah untuk menilai IP dan hubungan dengan kawalan glisemik, penyakit buah pinggang kronik (CKD) dan tabiat pengambilan ubat dalam kalangan pesakit diabetes jenis 2 (T2DM). Kajian keratan rentas telah dijalankan dalam 384 pesakit T2DM atas 18 tahun di bawah rawatan susulan dengan menggunakan Soal Selidik Persepsi Penyakit dan "Morisky Medication Adherence Scale" (MMAS-8). Umur median pesakit adalah 58.1 tahun dan tempoh median diabetes adalah 13 tahun. Responden terdiri daripada 38.8% Melayu, 31.0% Cina dan 28.9% India dengan 55.7% wanita. Kadar 79.4% mempunyai kawalan paras glisemik tidak sempurna dan 39.6% mempunyai kadar pengambilan ubat rendah. Skor median Garis Masa Akut / Kronik, Akibat, Kawalan Peribadi, Kawalan Rawatan, Pemahaman Penyakit, Garis Masa Kitaran dan Perwakilan Emosi adalah masing-masing 23, 18, 22, 18, 19, 12 dan 14. Pesakit yang mempunyai kawalan glisemik baik mempunyai skor Garis Masa Akut / Kronik ($p = 0.048$) dan Perwakilan Emosi ($p = 0.032$) yang lebih tinggi daripada pesakit yang kurang dikawal, pesakit tersebut percaya bahawa diabetes adalah penyakit kronik dan mengganggu emosi. Pesakit dalam peringkat CKD yang lebih teruk mempunyai skor Garis Masa Kitaran

yang lebih tinggi ($\chi 2 = 18.718$, $p = 0.001$) dan mempercayai bahawa diabetes tidak dapat diramalkan. Pesakit dengan tabiat pengambilan ubat baik mempunyai skor tinggi dalam Pemahaman Penyakit ($\chi 2 = 21.385$, $p < 0.001$) tetapi skor Akibat ($\chi 2 = 17.592$, $p < 0.001$) dan Perwakilan Emosi adalah rendah ($\chi 2 = 16.849$, $p < 0.001$), oleh itu pesakit tersebut mempunyai pemahaman baik dan tidak dipengaruhi oleh persepsi negatif. Pesakit dengan tabiat pengambilan ubat tidak sempurna mempunyai persepsi negative iaitu Identiti ($\chi 2 = 15.25$, $p < 0.001$) dan Garis Masa Kitaran ($\chi 2 = 16.370$, $p < 0.001$) yang tinggi. Pematuhan ubat dan HbA1c mempunyai hubungan linear yang lemah. Dimensi Akibat mempunyai skor yang lebih tinggi dalam pesakit di bawah umur 65 tahun ($p = 0.003$) yang berpendapat diabetes mempunyai kesan besar terhadap hidup. Dimensi IP mempunyai hubungan yang signifikan dengan kawalan glisemik, CKD, pengambilan ubat dan umur, oleh itu persepsi pesakit boleh mempengaruhi kawalan glisemik dan tabiat pengambilan ubat. Kajian lanjut perlu dijalankan di Malaysia dengan pendidikan dimensi IP yang tersasar untuk meningkatkan kawalan paras gula secara optimal dengan objektif IP dimasukkan dalam Panduan Klinikal Diabetes di masa depan.

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## ABSTRACT

Malaysia has a high prevalence of diabetes at 16.9% and suboptimal glycaemic control with only 23.8% achieving HbA1C of <7%. Illness perceptions (IP) involve coping strategies and behavioural responses that influence glycaemic control. The objective of this study was to evaluate IP and their associations with glycaemic control, chronic kidney disease (CKD) and medication adherence in Type 2 diabetes mellitus patients (T2DM). A cross-sectional study was conducted in a purposive sample of 384 T2DM patients using Revised Illness Perception Questionnaire and 8-Item Morisky Medication Adherence Scale. T2DM patients >18 years under regular follow-up were included. The patients' median age was 58.1 years and median duration of diabetes was 13 years. There were 55.7% females and an ethnic distribution of 38.8% Malays, 31.0% Chinese and 28.9% Indians. A staggering 79.4% of patients had poor diabetes control and 39.6% of patients had low medication adherence. The median score of Timeline Acute/Chronic, Consequences, Personal Control, Treatment Control, Illness Coherence, Timeline Cyclical and Emotional Representations was 23, 18, 22, 18, 19, 12 and 14, respectively. Patients with good glycaemic control had a higher Timeline Acute/Chronic (p=0.048) and Emotional Representations (p=0.032) score than poorly controlled patients, indicating they believed that diabetes is chronic and experienced negative emotions. Patients in more advanced stage of CKD had a significantly higher Timeline Cyclical score

($\chi 2$=18.718, p=0.001), believing that their diabetes was unpredictable. Highly adherent patients had a significantly higher Illness Coherence ($\chi 2$=21.385, p<0.001) score but a significantly lower Consequences ($\chi 2$=17.592, p<0.001) and Emotional Representations score ($\chi 2$=16.849, p<0.001), hence they had good understanding of the disease and less negative perceptions of disease burden. Patients with low adherence had a significantly higher Identity ($\chi 2$=15.25, p<0.001) and Timeline Cyclical ($\chi 2$=16.370, p<0.001) score, therefore attributing more symptoms and a cyclical nature to diabetes. Medication adherence and HbA1c were weakly correlated. The Consequences dimension had a significantly higher score for patients below the age of 65 years (p=0.003), therefore younger diabetics felt that their lives were negatively affected. IP dimensions had significant associations with glycaemic control, CKD, medication adherence and age, showing that patients' beliefs can affect illness outcomes and adherence behaviour. Further studies should be conducted in Malaysia involving targeted patient education of IP dimensions to establish exact relationships with glycaemic control for concrete recommendations to be included in future Clinical Practice Guidelines to improve outcomes of diabetes.

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the study

Diabetes mellitus is a disease with multiple complications, which is caused by hyperglycaemia. The pathophysiology behind the chronic state of hyperglycaemia is reduced or complete defects in insulin secretion; or insulin resistance (World Health Organization, 1999). Worldwide, approximately 424.9 million or 8.8% of adults between the ages of 20 and 79 years are estimated to suffer from diabetes (International Diabetes Federation, 2017). The prevalence of diabetes in adults in Malaysia has increased alarmingly from 11.6% in 2006 (Ministry of Health Malaysia, 2013) to 17.5 % in 2015 (Institute for Public Health, 2015), which is an increase of 50.9% within the space of 11 years. Malaysia has an increasing and alarming prevalence of diabetes, which was the reason this disease was chosen as a focus of this study.

Diabetes can be classified into Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and specific types of diabetes due to other causes, such as monogenic diabetes syndromes, diseases of the exocrine pancreas and drug- or chemical-induced diabetes (American Diabetes Association, 2015; World Health Organization, 2006).

T2DM, which is the focus of this study, was previously referred to as "non- insulin-dependent diabetes". It is the most common form of diabetes and constitutes 90-95% of all diabetes cases (American Diabetes Association, 2015). In T2DM, hyperglycaemia occurs due to peripheral insulin resistance, impaired regulation of

hepatic glucose production and beta-cell dysfunction, with relative rather than absolute insulin deficiency as opposed to T1DM (Kahn, 2003; Mahler & Adler, 1999). Beta-cell dysfunction is a critical factor in the development of T2DM and worsens progressively with increasing glucotoxicity (Stumvoll, Goldstein, & van Haeften, 2005). Stumvoll et al. also pointed out the important link between obesity, physical inactivity and insulin resistance. The "deadly quintet" of hypertension, hyperlipidemia, obesity, procoagulability, and hyperglycemia have been postulated as the cause of oxidative stress and endothelial dysfunction that underlie the dysmetabolic syndrome, which is a precursor of diabetes (Boyle, 2007).

T1DM is known to be caused by immune-associated destruction of insulin-producing pancreatic β-cells, ultimately leading to absolute insulin deficiency and requiring exogenous insulin replacement for life (Atkinson, Eisenbarth, & Michels, 2014). T1DM comprises approximately 5-10% of cases and even though T1DM can be diagnosed at any age, it is commonly first diagnosed in childhood with peaks in presentation occurring between 5- 7 years of age and at or around the time of puberty (American Diabetes Association, 2015; Atkinson et al., 2014). GDM is a form of diabetes which is usually diagnosed in the second or third trimester of pregnancy in patients with no known previous diagnosis of diabetes (American Diabetes Association, 2015; World Health Organization, 1999). Specific types of diabetes, such as monogenic diabetes syndromes and diseases of the exocrine pancreas constitute a small percentage of all diabetes patients, comprising less than 5% in total (American Diabetes Association, 2015).

Diabetes is a disease which often leads to a lifetime of suffering with multiple debilitating complications. Acute complications of diabetes which can be life-threatening include diabetic ketoacidosis, hyperglycaemic hyperosmolar state and malignant hyperthermia-like syndrome with rhabdomyolysis (Pinhas-Hamiel & Zeitler, 2007). Diabetes causes long-term microvascular complications: retinopathy, nephropathy and neuropathy; and macrovascular complications: cardiovascular disease, peripheral vascular disease and stroke (Alva, Gray, Mihaylova, Leal, & Holman, 2015; DCCT Research Group, 1995; Stephenson & Fuller, 1994; Stratton et al., 2000; Stumvoll et al., 2005; World Health Organization, 1999).

Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb with an estimated 1.6 million deaths being directly caused by diabetes in 2015 (World Health Organization, 2016). The World Health Organization (WHO) predicted that diabetes will be the seventh leading cause of death in 2030. A collaborative meta-analysis of 102 prospective studies found that diabetes doubles the risk for coronary heart disease, major stroke and fatalities related to vascular diseases (The Emerging Risk Factors Collaboration, 2010).

Diabcare Malaysia was initially started in 1997 as an initiative to assess the prevalence of diabetes as well as the level of care in the Malaysian setting (Mafauzy, Hussein, & Chan, 2011). It was found by Mafauzy et al. in Diabcare 2008 that there was a high rate of complications in their study population of 1549 patients with 75% of patients having microvascular complications and 28.9% of patients having macrovascular complications. Severe late complications (legal blindness, myocardial infarction, coronary artery bypass graft/ angioplasty/ stents, cerebral stroke, end stage renal

disease and lower limb amputation) were documented in 25.4% of patients (Mafauzy et al., 2011). According to these findings, it is obvious that the rate of high complications in the Malaysian setting is worrisome.

It has been demonstrated that patients in Malaysia are not meeting their targets with HbA1c, although it has been proven that good glycaemic control is essential in diabetes (Abougalambou, Mafauzy, Syed Azhar, Abougalambou, & Mohamed Azmi, 2010; Mafauzy et al., 2011). Illness perceptions have been known to have significant associations with glycaemic control and medication adherence but there is a lack of data in Malaysia as no study has looked at these associations in Malaysian T2DM patients (Bean, Cundy, & Petrie, 2007; Broadbent, Petrie, Main, & Weinman, 2006; Davies et al., 2008; Kucukarslan, 2012). The more patients believe that their treatment will be effective, the more they are likely to have better self-care with improved glycaemic control (Skinner & Hampson, 2001). Therefore, it is important to understand the possible associations between illness perceptions and glycaemic control in the Malaysian setting.

### 1.2 Statement of the Problem

Diabetes is a chronic disease which has major implications on health with both microvascular and macrovascular complications. The prevalence of diabetes is rising worldwide and incidence is highest in developing countries, especially in Asia with a high economic cost (Ramachandran, Ching, & Snehalatha, 2010).

Diabetes is on a relentless course of high prevalence and an increasing number of patients in Malaysia with T2DM comprising more than 92.8% of the diabetes patient

population in Malaysia (Mafauzy et al., 2011). It is essential to bring this disease under control and prevent patients from progressing with the deadly complications of diabetes.

Good knowledge of diabetes and high medication adherence are significant predictors of good metabolic control (Al-Qazaz et al., 2011). Glycaemic control has been shown to be associated with medication adherence (Ahmad, Islahudin, & Paraidathathu, 2014; Chua & Chan, 2011; C. S. Lee, Tan, Sankari, Koh, & Tan, 2017). There is a link between medication adherence and glycaemic control, which is why these two variables were included in this study in association with illness perceptions to understand the possible link to the psychology behind this phenomenon.

A major complication of diabetes is chronic kidney disease. The major cause of end stage kidney disease requiring dialysis was reported to be caused by diabetes, comprising 61% of cases. It is important that factors associated with glycaemic control are identified, so that glycaemic control can be achieved to help delay the progression of kidney disease in diabetic patients (Huri, Lim, & Lim, 2015).

In Malaysia, it has been found that diabetes care is far from satisfactory as the majority of patients are not able to achieve good glycaemic control and there is a high prevalence of complications (Mafauzy, 2006). Mafauzy recommended that steps are taken to improve the management of diabetes by educating health professionals, improving patients' awareness of the disease, providing more resources, encouraging self-care in diabetes and improving the communication between healthcare professionals and patients. As glycaemic control is of paramount interest in diabetes

management, diabetic treatment has to be optimized through a multidisciplinary method with the patient in the center of management. It is necessary to understand how to help these patients in a holistic manner, in terms of pharmacological, psychological and social management.

The Common Sense Model (CSM) of self-Regulation explains that patients develop distinct cognitive illness representations which are defined as identity, cause, timeline, consequences and control (H Leventhal, Brisette, & Leventhal, 2003; H Leventhal, Meyer, & Nerenz, 1980). Illness perceptions which include both cognitive and emotional representations of illness provide an insight into how patients develop coping strategies as a result of a health threat and how subsequently these coping strategies affect the self-management behaviour (Weinman, Petrie, Moss-Morris, & Horne, 1996). Illness perceptions can affect health outcomes such as medication adherence and metabolic control (Davies et al., 2008; Kucukarslan, 2012). As good glycaemic control is an essential part of diabetes management, it was of interest to find out whether there is a link between illness perceptions as a psychological parameter and glycaemic control as a measure of disease outcome.

The Clinical Practice Guidelines (CPG) 2015 for T2DM (Ministry of Health Malaysia, 2015) mentioned that psychological and social factors are important influences on the ability of patients to cope with chronic disease such as diabetes as they may affect the overall success of the management. However, there is no mention of illness perceptions in the Clinical Practice Guidelines. It is surely of relevance to investigate whether illness perceptions have a role to play when it comes to glycaemic control, chronic kidney disease which is a very worrisome complication of diabetes and

medication adherence. This exploratory study will hopefully reveal whether illness perceptions have significant associations with the variables being studied. To the best of my knowledge, no other study in Malaysia has placed its focus on illness perceptions in association with all three variables: glycaemic control, chronic kidney disease and medication adherence in T2DM. Ultimately, this study might enable more research to be conducted in this area and open up the avenue for illness perceptions to be included in future clinical guidelines with regards to psychosocial assessment and care of diabetes.

## 1.3 Objectives of the Study

### 1.3.1 General objective:

To assess the associations between illness perceptions, glycaemic control, medication adherence and chronic kidney disease in patients with T2DM in a tertiary care setting in the multi-ethnic Malaysian setting.

### 1.3.2 Specific objectives:

- To explore the associations between various domains of illness perceptions and glycaemic control based on HbA1c in T2DM patients
- To explore the associations between illness perceptions and chronic kidney disease in T2DM patients
- To explore the associations between illness perceptions and medication adherence in T2DM patients
- To explore whether there are differences in illness perceptions among younger patients and elderly patients, defined as 65 years old and above

## 1.4 Conceptual Framework of the Study

The concept of illness perceptions was developed by Weinman et al. (1996) in order to provide a quantitative assessment of the illness representations based on the CSM of self-regulation of Leventhal (H Leventhal et al., 1980). Illness perceptions comprise both cognitive and emotional representations of illness which can ultimately influence the way a patient responds to psychological treatment and whether a patient adheres to the treatment prescribed (Howard Leventhal, Leventhal, & Contrada, 1998; Weinman & Petrie, 1997). The concept of illness perceptions comprises nine dimensions which include both negative and positive perceptions: Identity, Timeline Acute/Chronic, Consequences, Personal Control, Treatment Control, Timeline Cyclical, Illness Coherence, Emotional Representations and Cause. These dimensions are described in detail in Section 3.6.2.

Both cognitive and emotional representations give rise to coping strategies that have an influence on medication adherence (Kucukarslan, 2012), glycaemic control (Mc Sharry, Moss-Morris, & Kendrick, 2011) and chronic kidney disease (Clarke, Yates, Smith, & Chilcot, 2016). Glycaemic control and medication adherence have been shown to be associated with each other (Ahmad et al., 2014; Al-Qazaz et al., 2011; Chua & Chan, 2011; S. F. Lee, Teh, Malar, Ong, & James, 2017). Therefore, it was the purpose of my study to explore whether positive illness perceptions led to good glycaemic control and medication adherence; likewise, whether patients with negative illness perceptions had poor glycaemic control and medication adherence. The perceptions in T2DM patients might also differ according to whether they have CKD and in which stage they are. Patients in advanced stage of chronic kidney disease may

have more negative perceptions of illness as compared to patients in earlier stages of the disease. Figure 1.1 shows the possible associations between the different variables.

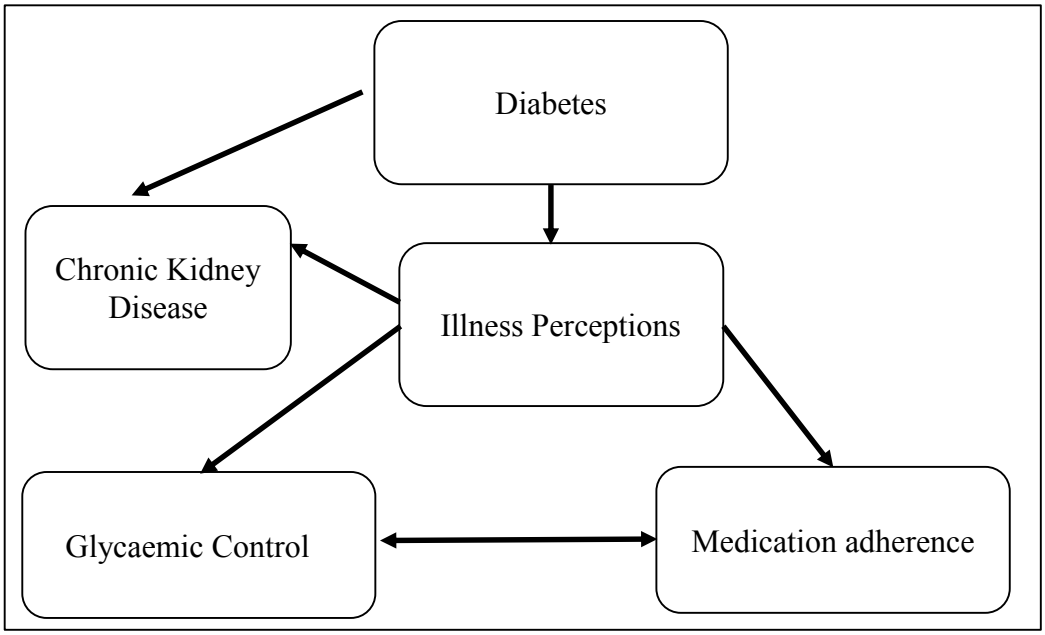


*Figure 1.1* Conceptual framework of illness perceptions and their associations with glycaemic control, chronic kidney disease and medication adherence in T2DM

## 1.5 Significance of Study

The application of this exploratory study is to provide baseline data for the possible significant associations between illness perceptions and the three variables being studied. With this baseline data, further studies can be conducted with the potential of targeted intervention of dimensions of illness perceptions being included as part of psychological management in the T2DM CPG Ministry of Health Malaysia (MOH). There has been evidence that a family-based intervention on poorly controlled T2DM patients showed significant improvements in HbA1c and improved socio-psychological beliefs (Keogh et al., 2011). A group education programme was provided to T2DM patients by healthcare professionals who had been specifically trained to empower patients psychologically and improve self-care (Davies et al., 2008). This intervention managed to motivate patients to improve their negative perceptions as well as initiate positive lifestyle changes. In the future, guidelines with targeted dimensions of illness perceptions can be formulated with regular assessment of illness perceptions using tools such as the IPQ-R or BIPQ.

It is important to establish a close collaboration between medical doctors, pharmacists, diabetes specialist nurses and mental health care providers who are involved in the care of T2DM patients. Patients who have poor glycaemic control, poor medication adherence and patients who are known to have renal derangement can be identified. All healthcare personnel in primary, secondary and tertiary care who are involved in the care of T2DM can be trained to deliver psychological counselling with the aim of improving negative perceptions, medication adherence and glycaemic control. Pharmacists can use the opportunity during the Medication Therapy Adherence Clinic (MTAC) and medical doctors during the follow-up clinic visit to identify patients who

have poor adherence and poor glycaemic control. These patients can then be counselled in separate sessions or the counselling can be incorporated into the clinic visit. Patients can be empowered during counselling sessions by improving their negative perceptions and being encouraged to improve their adherence and self-care of diabetes.

A computerised health database could be used by the health personnel involved in the care of T2DM to update the perception status of patients and whether there is an improvement in clinical outcomes. However, a health database must be handled in such a way that patient confidentiality is maintained. The database can be used to keep track of continuous assessment of illness perceptions using tools such as the IPQ-R, monitoring of familial or social support, monitoring of self-care, regular assessments of adherence by pharmacists, assessment of glycaemic control and referral to members of the healthcare team that are trained in illness-perception based psychological intervention (clinicians, pharmacists, nurses and mental health team).

## 1.6 Chapter Outline

This is a brief outline of the chapters that are presented in this thesis:

**Chapter 2 -** This chapter is a review of the literature tied to the objectives of this study. The first part introduces the complications and burden of the disease, with reference to the Malaysian setting. This is then expanded to include topics relevant to this study comprising metabolic control, chronic kidney disease in diabetes and diabetes in the elderly. The second part is about medication adherence, which is also tied to the objectives of this study and explains why medication adherence is an essential component of patient management. The third and final part is about illness perceptions, the concept on which this study is based and the quantitative measure of illness perceptions, the Revised Illness Perception Questionnaire (IPQ-R), which is a parameter to measure illness perceptions in patients.

**Chapter 3** - In this chapter, the explanation and justification behind this study are presented in detail. The components of this chapter are study design, study setting, study period, study population, sample size, sampling techniques, ethical approval and instruments utilised. The final section in this chapter is the description of the study procedure and data analysis.

**Chapter 4** - The results of the study are presented in details in this chapter. A complete overview of the statistical analysis showing the dimensions of illness perceptions as well as their associations with metabolic control, medication adherence and CKD are described and presented in tables and figures.

**Chapter 5** - This chapter includes a detailed description of the findings in this study as well as the learning points that can be derived from the results. A comparison of the similarities and differences with other studies are also listed here.

**Chapter 6** - This chapter is a conclusion and final summary with the strengths and limitations of the study. The implications for the Malaysian setting, including inclusion of illness perceptions in future CPGs and recommendations for further research are included in this chapter.

# Chapter 2

# Literature Review

## 2.1 Diabetes

### 2.1.1 Burden of diabetes

Diabetes is growing at endemic proportions increasing the burden on healthcare systems worldwide. Although in fact the total number of people with diabetes worldwide was projected to rise from 171 million in 2000 to 366 million in 2030 (Wild, Roglic, Green, Sicree, & King, 2004), this figure had already been surpassed in 2013 with 382 million patients and was expected to rise to 592 million by 2035 (Guariguata et al., 2014). In 2017, diabetes caused 4.0 million deaths globally and USD 727 billion dollars in health spending (International Diabetes Federation, 2017). In Malaysia, it was estimated that diabetes would have cost the government RM 1.40 billion in the year 2011 which was almost 10% of the entire MOH healthcare budget (Idzwan Mustapha et al., 2017). Additionally, it was also estimated by Idzwan Mustapha et. al that the total cost of diabetes including its complications was RM 2.04 billion annually and the yearly cost of dialysis was RM 42, 362 per patient. In a nutshell, diabetes is a chronic and devastating disease with a high economic burden for both patients and healthcare systems.

The global status report on non-communicable diseases 2014 (World Health Organization, 2014), clarified that diabetes was directly responsible for 1.5 million deaths in 2012 and 89 million Disability Adjusted Life Years (DALY), which is the sum of years of potential life lost due to premature mortality and the years of

productive life lost due to disability. According to the same report, non-communicable diseases, of which cardiovascular diseases, cancer, chronic respiratory diseases and diabetes are responsible for more than 82% of deaths, currently cause more deaths than all other causes combined and these deaths are projected to increase from 38 million in 2012 to 52 million by 2030.

However, what used to be known as traditional complications of diabetes are not solely applicable as there are many new aspects to newly known complications especially in association with the metabolic syndrome as well as high lipid levels, therefore physicians must be made aware of the new complications such as non-alcoholic fatty liver disease, polycystic ovary syndrome and eating disorders in addition to well-known complications such as stroke and cardiovascular disease (Twigg & Wong, 2015). It is of paramount importance to individualise the treatment of diabetes to prevent these serious complications and optimise every single avenue of treatment, may it be pharmacological or psychological management.

Globally, the number of diabetics has increased alarmingly from 108 million in 1980 to 422 million in 2014 (NCD Risk Factor Collaboration, 2016). The same study showed that the rate of increase in prevalence was highest in countries with low and middle incomes. In 2014, it was found that the highest number of patients with diabetes were from east and south Asia with 106 million and 86 million diabetics, respectively (NCD Risk Factor Collaboration, 2016). All these figures clearly show that diabetes is becoming a real threat and optimal management of diabetes is crucial.

From 2009 to end of 2012, there were a total of 657,839 patients enrolled in the NRD in Malaysia, which was established to keep track of the target achievement and clinical outcomes of patients with diabetes managed at primary healthcare clinics under the MOH. Nearly all the patients enrolled, 653,326, were diagnosed with T2DM indicating the huge burden of T2DM in Malaysia, as patients diagnosed with T1DM or other forms of DM comprised only a minimal 0.7% of the patients in the registry (Ministry of Health Malaysia, 2013). In the National Health and Morbidity Survey (NHMS) 2015 in Malaysia, the overall prevalence of diabetes mellitus among adults of 18 years and above was 17.5% out of 19,935 respondents. A general increasing trend in prevalence with age was observed in the NHMS from 5.5% in the 18-19 years age group with a peak of 39.1% among the 70-74 years age group (Institute for Public Health, 2015). It was also noted that the Indians had the highest prevalence at 22.1%, followed by the Malays at 14.6% and the Chinese at 12.0%, a trend which was also observed in the previous NHMS in 2006 (Institute for Public Health, 2015; Letchuman et al., 2010) . It can be deduced that Malaysia has a high prevalence of T2DM with all ethnic groups at risk, with Indians having the highest prevalence.

### 2.1.2 Metabolic Control in Diabetes

Glycated haemoglobin, HbA1c was shown to correlate with the average glucose control over the previous 8 – 12 weeks based on continuous glucose monitoring (Nathan, Turgeon, & Regan, 2007). HbA1c shows how the glycaemic control in patients has been maintained over the preceding 3 months. Therefore, it has been recommended that the HbA1c test should be conducted as a routine measure in all patients at the initial phase of diabetes assessment and at routine intervals on a 3-monthly basis to determine whether patients' have been able to achieve their

glycaemic targets and maintain them. Additionally, how frequently HbA1c is tested should also be individualised based on the clinical situation, the treatment regimen and the consultant or physician's decision (American Diabetes Association, 2015).

The United Kingdom Prospective Diabetes Study (UKPDS), which ran from 1977 to 1997 and included 5102 patients at 23 centres across the United Kingdom was a landmark study in showing the importance of blood glucose control in diabetes (Home, 2008; King, Peacock, & Donnelly, 1999; UK Prospective Diabetes Study (UKPDS) Group, 1998a, 1998b, 1998c). It was the largest and longest study ever undertaken in diabetes. Patients were followed for an average of 10 years to determine whether intensive use of pharmacological therapy to lower blood glucose levels would result in clinical benefits and whether the use of various sulfonylurea drugs, the biguanide drug metformin, or insulin have specific therapeutic advantages or disadvantages. The UKPDS results established that retinopathy, nephropathy, and possibly neuropathy are benefited by lowering blood glucose levels with intensive therapy. A median HbA1c of 7.0% was achieved with intensive therapy as compared with conventional therapy with a median HbA1c of 7.9%. Epidemiological analysis of the UKPDS data showed a continuous relationship between the risks of microvascular complications and glycaemia; for every decrease of 1% in HbA1c there was a 35% reduction in the risk of complications (King et al., 1999; UK Prospective Diabetes Study (UKPDS) Group, 1998b). It has been concluded that treatment of T2DM should include aggressive efforts to lower blood glucose levels as close to normal as possible. Diabcare Malaysia 2013 which recruited 1667 patients from public hospitals showed only a small improvement in glycaemic control with a mean HbA1c of 8.52 ± 2.01% as compared to DiabCare 2008 with a mean of 8.66 ± 2.09% (Mafauzy et al., 2011; Mohamed,

Hussein, Nazeri, & Pheng Chan, 2016). Therefore, more awareness needs to be created on diabetes, lifestyle modification and self-testing.

However, it is worth noting that the The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group (2008) found that aggressively lowering blood glucose levels in patients with cardiovascular disease or with presence of risk factors was not necessarily beneficial. In the ACCORD study, 10,251 T2DM patients who had either established cardiovascular disease or additional cardiovascular risk factors with a median Hba1c of 8.1% were designated to receive intensive therapy with a target of HbA1c level of below 6% or standard therapy with a target HbA1c of 7.0 to 7.9%. Unexpectedly, the use of intensive therapy increased mortality and did not significantly reduce major cardiovascular events. The intensive-therapy group had a relative increase in mortality of 22% and an absolute increase of 1.0% during the follow-up period of 3.5 years as compared with the standard-therapy group, with similar differences in death from cardiovascular causes. This increase in mortality was found to be equivalent to one extra death for every 95 patients who were treated for 3.5 years. The findings of this study suggest that individualising treatment in high-risk patients with T2DM is necessary. However, intensive and quick lowering of blood glucose level is not always the right approach.

Litwak et al. (2013) conducted a study called $A_1$chieve which was an observational study over four months of 66,726 T2DM patients who had begun using biphasic insulin aspart 30, insulin aspart, or insulin detemir. The participants included patients from 28 countries in Asia, Africa, Europe and South America. Malaysia was one of the countries which were included in this study. Litwak and colleagues found poor

glycaemic control with mean baseline HbA1c values of ≥ 9.1% in patients with macrovascular complications and ≥ 9.4% in patients with microvascular complications in all regions in this study. At the time the analogue insulin therapy was started, vascular complication rates were generally high and preventive therapy was not at optimal level. They concluded that poor glycaemic control and sub-optimal diabetes management in the regions studied may be due to poor adherence to treatment regimens, lack of access to therapy, poor diet, and delay in initiating, or failure to adequately optimise insulin therapy. Litwak and colleagues also drew attention to the fact that significant numbers of people with diabetes have poor psychological well-being and these psychological problems can adversely affect adherence to treatment, as found by another study (Peyrot et al., 2005).

### 2.1.3 Pharmacologic Therapy in Diabetes

Although psychological management in diabetes is important, pharmacological therapy is the mainstay of treatment in diabetes in addition to lifestyle changes such as diet control, physical activity and weight reduction. Pharmacologic management is important in controlling blood glucose levels and has been shown to be of benefit in reducing microvascular complications (Huri, Lim, & Lim, 2015; Kahn, Cooper, & Del Prato, 2014). Pharmacologic therapy of diabetes consists of oral anti-diabetic agents and injectable agents, namely insulin and Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA) (Ministry of Health Malaysia, 2015).

These are the groups of oral diabetic agents (OAD) and injectable agents that are currently recommended for use in the CPG (Ministry of Health Malaysia, 2015):

OAD

- Biguanides: Metformin
- Sulphonylureas: Glibenclamide, Gliclazide, Glipizide and Glimepiride
- Meglitinides: Repaglinide and Nateglinide
- α-Glucosidase inhibitors: Acarbose
- Thiazolidinediones: Rosiglitazone and Pioglitazone
- Dipeptidyl Peptidase-4 inhibitors:

  Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin and Alogliptin
- Sodium-glucose Co-transporter 2 inhibitors:

  Dapagliflozin, Canagliflozin and Empagliflozin

Injectable Medication

- Glucagon-like Peptide-1 Receptor Agonists: Exenatide, Liraglutide and Lixisenatide
- Insulin: Prandial, Basal and Pre-mixed

According to the CPG, an OAD can be used on its own as monotherapy or as combined therapy with other OADs and insulin and/or GLP-1 RA. Based on the Malaysian CPG and American Diabetes Association (ADA) guidelines, metformin is recommended as the initial medication for the treatment of T2DM and can be used either as monotherapy or in combination with other OADs if the patient is not able to achieve glycaemic control after 3 months of intensive monotherapy (Chamberlain et al., 2017; Ministry of Health Malaysia, 2015). According to both guidelines, insulin should be started in patients who are unable to achieve good glycaemic control despite being on optimal combination therapy and newly diagnosed patients who are symptomatic or poorly controlled (HbA1c >10%).

### 2.1.4 Chronic Kidney Disease (CKD) in Diabetes

CKD is defined as abnormalities of kidney structure or function, present for 3 months, with implications for health and CKD is classified based on cause, GFR category and albuminuria category (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013). Diabetic nephropathy progresses from microalbuminuria to macroalbuminuria and finally End Stage Renal Disease (ESRD) (Soldatos & Cooper, 2008). As mentioned by the KDIGO CKD Work Group (2013), diabetic nephropathy occurs in 25-40% of patients with type 1 or type 2 diabetes within 20-25 years of disease onset and is also an independent risk factor for early death due to cardiovascular disease.

In the USA, a study was carried out by Bailey, Wang, Zhu and Rupnow (2014) with the aim of providing current national estimates of the prevalence of CKD in the overall T2DM population, and in the subpopulation aged above 65 years using the new KDIGO classification. 2915 adults diagnosed with T2DM were identified using data from the National Health and Nutrition Examination Survey (NHANES) in the USA, with 1466 being 65 years and above. Prevalence of CKD was 43.5% in the Type 2 Diabetes Mellitus population overall, and 61.0% in those above 65 years of age. The prevalence of mildly decreased renal function or worse was 22.0% overall and 43.1% in those 65 years and above. Prevalence of more severe renal impairment was 9.0% overall and 18.6% in those above 65 years of age. Thus, Bailey et al. were able to confirm the high prevalence of CKD in T2DM, especially in the age group of 65 years and above (Bailey, Wang, Zhu, & Rupnow, 2014).

Wu et al. (2005) conducted a cross-sectional epidemiological study aimed to assess the prevalence of microalbuminuria and macroalbuminuria among consecutively screened hypertensive type 2 diabetic adult patients in 103 centres in China, Hong Kong, Indonesia, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan and Thailand. A population of 5549 patients was used for analysis. It was found that the prevalence of microalbuminuria, which represents the earliest clinical evidence of diabetic nephropathy and is a marker of increased cardiovascular morbidity was 39.8% (39.2-40.5; 95% Confidence interval (CI)) and the prevalence of macroalbuminuria was 18.8 % (18.2-19.3; 95% CI). This high prevalence is disturbing as it reflects the high risk the Asian diabetic population is at of developing renal disease. In the multivariate analyses, the predictive factors for the presence of microalbuminuria were age greater than 59 years, elevated BMI, systolic blood pressure level greater than 139 mm Hg, and ethnic origin. In this study, it is important to note that 18.8% of patients had macroalbuminuria despite patients with previously known macroalbuminuria or diabetic nephropathy having been excluded. This is worrisome as the high rate of macroalbuminuria had not been expected and had not been previously detected, therefore it was questioned whether screening was adequate. Among the Malaysian population of 733 patients in this study, it was found that 40% of patients had microalbuminuria, whereas 15% of patients had macroalbuminuria. Wu et al. recommended the implementation of screening programmes for microalbuminuria in type 2 diabetic patients.

There was a study carried out in 19 public hospitals in Malaysia with 1099 patients as part of the Diab-care Asia project, which was an initiative started in 1997 to document and provide a baseline for the status of diabetes care as well as to assess prevalence of

diabetes complications (Mafauzy, 2006). The majority of patients, precisely 94.8% had T2DM with a gender distribution of 46.5% males and 53.5% females. The mean age was 55.8 ± 11.4. The diabetes control was unsatisfactory, as 59% of the patients had a HbA1c level of more than 7% which reflects poor control with 6.6% of the patients having microalbuminuria and 15.7% of the patients having macroalbuminuria. Mafauzy concluded that control was not satisfactory with a high prevalence of complications.

A study with 1077 patients was carried out at Hospital Universiti Sains Malaysia (USM) with the purpose of identifying the diabetic status of T2DM outpatients in a tertiary center and to estimate the prevalence of vascular complications (Abougalambou et al., 2010). They found that nephropathy was the most common vascular complication at 91.0% followed by neuropathy 54.4%, retinopathy 39.3%, and macrovascular complications 17.5%. The mean age of patients in this study was 58.3 years with a mean duration of diabetes of 11 years, with only 23.4% of the patients managing to achieve a HbA1c of below 7%, again reinforcing the poor glycaemic control and high rate of complications as also found by Mafauzy (2006). However, as this analysis was based on the T2DM patients in USM, which is a tertiary hospital, the authors recommended that data from other centres are necessary to determine whether the findings can be utilised for the diabetes care setting in general.

Diabetic nephropathy as the primary aetiology of renal failure has the highest mortality when compared to other causes of end stage renal failure and diabetes has consistently remained as the leading cause of CKD contributing to all new patients requiring dialysis in Malaysia increasing from 53% in 2004 to 61% in 2013 (Goh, Ong, & Lim,

2013). In the 22nd Report of the Malaysian Dialysis and Transplant 2014, it was reported that the number of patients receiving dialysis had increased from 13, 356 patients in 2005 to 34, 767 patients in 2014, which is a staggering increase of 160% (Goh & Ong, 2015). Demographic changes were noted too in this report as patients above 55 years old constituted 58% of all new dialysis patients as opposed to 52% in 2005.

It has been documented that dialysis acceptance and prevalence rates in Malaysia have almost doubled in recent years with the dialysis acceptance of 1733 per million population (PMP) in 2004 increasing to 3156 PMP in 2013 (Begum, Khan, & Ming, 2016). Begum et al. also attributed this increase in kidney failure to the increasing incidence of diabetic kidney disease. In a series of six papers about global kidney disease, it was noted that although CKD is an important cause of death and loss of disability-adjusted life-years worldwide, awareness is still low among patients and health-care providers (Jha et al., 2013). Jha et al. also commented that integration of screening and management strategies for chronic kidney disease into national programmes for non-communicable diseases can reduce the burden and cost of care of CKD.