IMPACT OF PHARMACIST INTERVENTION ON CLINICAL OUTCOMES, QUALITY OF LIFE, COST OF TREATMENT AND COMPLICATIONS AMONG DIABETIC PATIENTS IN DMTAC, KEDAH, MALAYSIA

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by

MUHAMMAD ZAHID IQBAL

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DEDICATION

To

MY FATHER

For the Uncompromising Principles that Guided His Life

MY MOTHER

For Leading Her Children into Intellectual Pursuits

MY BROTHERS

For Making Everything Worthwhile

MY WIFE

For Her Insight, Patience and Unfailing devotion

MY DAUGHTERS

For Their continuous Encouragements and Patience

To

MY TEACHERS

For Showing Me the Excitement and Joy of indulging in the field of Pharmacy

MY FRIENDS

For Their Abundant Support, Patience, Understanding and Help.

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LIST OF ABBREVIATIONS

mmol/L	Millimoles per liter
mmHg	Millimeter of mercury
%	Percentage
APM	Airborne particulate matter
BBB	blood-brain barrier
BMU	Best Matching Unit
CMB	Chemical Mass Balance
CPCA	Consensus PCA
CSI	Class Separation Indices
CSM	Class Sample Matrix
CSV	Class Sample Vector
CWM	Class Weight Matrix
CWV	Class Weight Vector
EDC	Euclidean Distance to Centriods
IPS	Institut Pengajian Siswazah
USM	Universiti Sains Malaysia

LIST OF APPENDICES

IMPAK INTERVENSI AHLI FARMASI TERHADAP DAPATAN KLINIKAL, KUALITI KEHIDUPAN, KOS PERUBATAN DAN KOMPLIKASI DALAM KALANGAN PESAKIT DIABETES DI DMTAC, KEDAH, MALAYSIA

ABSTRAK

Prevalens diabetes mellitus menunjukkan peningkatan yang berterusan di Malaysia dan prevalens terkini adalah 19%. Impak ahli farmasi sudah terbukti untuk terapi ubat pesakit, kesesuaian, keberkesanan, dan pematuhan pesakit terhadap plan rawatan. Oleh kerana diabetes mellitus adalah penyakit yang berkaitan dengan gaya hidup bagi mendapatkan kawalan glisemik yang ketat, bukan hanya kepatuhan dan kepatuhan doktor terhadap garispanduan yang diberikan adalah penting, tetapi kepatuhan pesakit terhadap rejimen ubat juga memainkan peranan penting. Untuk meningkatkan kualiti hidup dan hasil klinikal yang lebih baik pada pesakit diabetes, ia memerlukan intervensi yang sesuai dari ahli professional kesihatan. Merujuk kepada sistem penjagaan kesihatan di Malaysia, ahli farmasi memberikan perkhidmatan di klinik DMTAC (Diabetes Medication Therapy Adherence Clinic) hospital. Kajian semasa dilakukan untuk menilai kesan intervensi ahli farmasi di klinik DMTAC terhadap hasil klinikal, kualiti hidup, kos rawatan dan komplikasi dalam kalangan pesakit diabetes di dua hospital awam Kedah Malaysia. Reka bentuk kajian adalah ujian klinikal rawak dan telah mendapat kelulusan dari MREC (Jawatankuasa Kajian dan Etika Malaysia). Pengumpulan data kajian diambil dari fail pesakit.Seramai 400 pesakit dipilih secara rawak dan dibahagikan kepada dua kumpulan. Kumpulan kawalan mengandungi 200 pesakit yang mendapat rawatan biasa dari hospital manakala kumpulan intervensi mengandungi 200 pesakit yang menerima rawatan

biasa dari hospital di samping sesi kaunseling ahli farmasi dari klinik DMTAC. Antara 400 pesakit yang terpilih , hanya 299 pesakit mengambil bahagian secara lengkap dalam kajian prospektif selama satu tahun yang merangkumi 4 lawatan untuk kedua-dua kumpulan kajian. Daripada 299 pesakit, 143 adalah dari kumpulan kawalan dan 156 adalah dari kumpulan intervensi. Pada akhir kajian, hasil klinikal, kualiti hidup (QoL), kos rawatan dan komplikasi diabetes dinilai pada kedua-dua kumpulan kajian. Analisis data dijalankan dengan menggunakan SPSS versi 24. Data deskriptif dinyatakan sebagai min ± sisihan piawai (SD). Normalisasi data dilakukan oleh SPSS dengan menggunakan ujian skewness dan kurtosis. Sekiranya data menunjukkan taburan normal, maka statistik ujian-t bebas / ANOVA dua hala digunakan untuk menilai hipotesis null. Untuk data kategori, ujian Chi Square dan Fisher tepat digunakan untuk mencari nilai p di mana untuk mengetahui ukuran kesan Phi (φ) dan Cramer digunakan. Nilai P <0.05 dianggap signifikan secara statistik. Pada akhir kajian, dalam kumpulan intervensi terdapat penurunan kadar HbA1c yang lebih ketara berbanding dengan pesakit kumpulan kawalan (3.59% berbanding 2.17%; p <0.001). Pengurangan yang signifikan secara statistik juga diperhatikan pada tekanan darah sistolik (9.29mmHg) dan tekanan darah diastolik (7.58mmHg) pesakit (p <0.005). Di samping itu, peningkatan yang signifikan secara statistik juga diperhatikan pada tahap kolesterol (0.13mmol / L) untuk kumpulan intervensi (p <0.001) pada akhir kajian. Semua domain soal selidik EQ-5D 5L mengenai kualiti hidup bertambah baik (p <0.05) dalam kumpulan intervensi kajian. Skor min pesakit yang melaporkan kualiti hidup pada Skala Analog Visual (skala VAS) bertambah dari 55.62 ± 7.64 hingga 65.48 ± 4.60 pada kumpulan kawalan manakala 54.64 ± 8.80 hingga 74.00 ± 6.10 pada kumpulan intervensi ketika rawatan susulan yang terakhir. Penurunan kos rawatan yang signifikan (p <0.001) berlaku pada kumpulan intervensi ahli farmasi. Pada

rawatan susulan keempat, jumlah penambahan kos rawatan adalah sebanyak RM 236.07 untuk setiap pesakit berbanding dengan permulaan. Sebaliknya, dengan intervensi ahli farmasi, jumlah penambahan kos rawatan adalah RM 47.33 bagi setiap pesakit. Tanda dan gejala untuk semua komplikasi diabetes menunjukkan penurunan yang ketara pada kumpulan intervensi berbanding dengan pesakit kumpulan kawalan. Dengan intervensi ahli farmasi bukan sahaja HbA1c bertambah baik tetapi semua domain yang berkaitan dengan kesihatan juga bertambah baik dalam kalangan pesakit.

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ABSTRACT

The prevalence of diabetes mellitus is continuously increasing in Malaysia and currently its prevalence is about 19%. The impact of pharmacists is well established for patient drug therapy, appropriateness, effectiveness, and the patient compliance towards the treatment plan. As diabetes mellitus is a lifestyle associated disease thus for achieving rigorous glycaemic control, not only the physician adherence and compliance to the given guideline are important, but patient adherence to medication regimens also plays a vital role. To improve the quality of life and better clinical outcomes in diabetic patients need the appropriate interventions from health care providers. In the health care system of Malaysia, pharmacists are delivering services in DMTAC (Diabetes Medication Therapy Adherence Clinic) in hospitals. The present study was conducted to evaluate the impact of pharmacist intervention in DMTAC clinics on clinical outcomes, quality of life, cost of treatment and complications among diabetic patients in two public hospitals of Kedah Malaysia. The current study design was randomized controlled trial and was ethically approved from the Medical Research and Ethics Committee (MREC) Malaysia. Data in the form of information was collected from the patient files in hospitals. A total of 400 patients were randomly selected and divided into two groups. The control group contained 200 patients who were receiving usual treatment from hospitals whereas intervention group contained those 200 patients who were receiving usual treatment from hospitals together with

separate counselling sessions with pharmacists from DMTAC clinics. Among these 400 selected patients only 299 patients completed the study for one year and 4 visits prospectively for both study groups. In control group 143 and in intervention group 156 patients had completed the study. At the end of the study, clinical outcomes, QoL, cost of treatment and diabetic complications were evaluated in both study group. The data analysis was done using SPSS version 24. Descriptive data are expressed as mean ± standard deviation (SD). The normality of the data was determined by SPSS using skewness and kurtosis testing. If data showed normal distribution, then independent t-test statistic/Two-way ANOVA was used to evaluate the null hypothesis. In categorical data, Chi square and Fisher exact test was used to find the p-value whereas to find the effect size Phi (φ) and Cramer's was used. A value of $P < 0.05$ was considered statistically significant. At the end of the study, in intervention group a greater reduction in HbA1c level was observed as compared to the control group patients (3.59% vs. 2.17%; $p < 0.001$). Statistically significant reduction was also observed in Systolic (9.29mmHg) and Diastolic (7.58mmHg) BP of the patients ($p < 0.005$). Similarly, statistically significant improvement was also observed in cholesterol level (0.13mmol/L) of intervention groups ($p < 0.001$) at the end. All domains of EQ-5D 5L questionnaire on quality of life was significantly improved ($p < 0.05$) in intervention group of the study. The mean score of patients reported quality of life on Visual Analogue Scale (VAS scale) were improved from 55.62±7.64 to 65.48±4.60 in control group whereas 54.64±8.80 to 74.00±6.10 in intervention group at last follow up since baseline. A statistically significant ($p < 0.001$) decrease in cost of treatment was observed in pharmacist intervention group. At fourth follow up, additional RM 236.07 amount per patient was added since baseline. In contrast, with the involvement of pharmacist the added amount was only RM 47.33 per patient. The sign and symptoms

in all diabetic complications were significantly improved in the intervention group than the control group patients. With the intervention of pharmacist not only the HbA1c improves but all other health-related domains also improved in patients.

CHAPTER 1

INTRODUCTION

Pharmacists' impact is well established for patient drug therapy, appropriateness, effectiveness, and the patient compliant towards the treatment plan (American Pharmacists Association, 2016). As diabetes mellitus is a lifestyle-associated disease, achieving rigorous glycaemic control, not only the physician adherence and compliance to the given guideline are essential, but patient adherence to medication regimens also plays a vital role (Polonsky & Henry, 2016). Patient adherences toward the medication, dosage regimens, proper use, and storage of insulin devices are the key factors in patient compliance. Patient compliance can be increased with proper counselling and patient education about the consequences of uncontrolled disease by healthcare providers (Polonsky & Henry, 2016). Studies throughout the globe have proven that healthcare providers' involvement in patient education will result in better outcomes of diabetes mellitus (Jeong et al., 2018). However, there is a need to appraise the particular effect of pharmacist intervention by patient counselling on all aspects of diabetes mellitus.

Diabetes mellitus became a prolonged upsetting public health issue throughout the world for the last few decades (Tabish, 2007). Diabetes mellitus (DM) is one of the oldest diseases known to the human population. It initially appeared in the Egyptian manuscript about 3000 years ago in history (Ahmed, 2002). The difference among type 1 and type 2 DM was made in 1936 (Olokoba et al., 2012). According to the World Health Organization (WHO) type 2 diabetes mellitus (T2DM) results from the ineffective use of the body's insulin (WHO, 2016). T2DM is primarily because of insulin deficiency and resistance in the body of patients. The insulin resistance will result in an augmented hepatic output of glucose, reducing glucose utilization by

different body organs (CPG Malaysia, 2015). Generally, T2DM is a vital risk factor development of cardiovascular disorders along with various diabetic complications such as diabetic nephropathy, retinopathy, and neuropathy (Chawla et al., 2016).

At present, T2DM does not have any known cure; however, the disease can be controlled to decrease the progression of its complications and to improve the quality of life of patients (Marín-Peñalver et al., 2016). Proper glycaemic control plays a vital role in decreasing the chances of developing microvascular and macrovascular complications in patients (Iqbal et al., 2019). The core purpose of management for T2DM is directly associated with a reduction in acute and chronic microvascular and macrovascular complications (CPG Malaysia, 2015).

The prevalence of type 2 diabetes is continuously increasing throughout the globe (Sugawara & Nikaido, 2014). The risk of developing diabetes in adults is more in developing countries (Paz-Pacheco, 2011).

1.1   Prevalence of T2DM globally

According to WHO statistics, it's a major public health issue with a global prevalence of 415 million in 2014. Furthermore, in adults age 18 years and above, its prevalence increased from 4.7% in 1980 to 8.5% in 2014, which is anticipated to be increased by up to 642 million by the year 2040 (Y. Zheng et al., 2018). In adults, DM is one of the top ten causes for death and was assessed to have instigated four million deaths worldwide in 2017 (WHO 2019). International Diabetes Federation (IDF) estimated that 463 million people had diabetes in 2019. Furthermore, in the absence of any urgent and adequate actions, it is projected to 578 million people in 2030 with diabetes, and the quantity will rise to 700 million people with diabetes in 2045 (Saeedi et al., 2019). In the United States, the prevalence of T2DM intensifying abruptly with

diabetic acute and chronic complications (Kharroubi, 2015). Diabetes was one of the most important causes of death in the United States (Carrillo-Larco et al., 2019).

1.2   Prevalence of T2DM in Malaysia

The risk of developing diabetes in adults is more in developing countries such as in Malaysia (Chan et al., 2019). According to the Malaysian National Health and Morbidity Survey 2018 by the Ministry of Health Malaysia (Elderly Health), the total prevalence of diabetes mellitus was 18.8% (National Health and Morbidity Survey, 2018). The prevalence of DM in continuously increasing and many of them are still undiagnosed. The highest prevalence is in Kedah (25.4%), Perlis (20.6%) and Johor (19.8%) states of Malaysia (Malaysia Diabetes Care Performance Report 2016). In the age of 30 years about 90%, and at 18 years almost 52% of the population are still undiagnosed in Malaysia (National Health and Morbidity Survey, 2018) due to lack of disease awareness among the general population (Ismail et al. 2016). According to the WHO data published in 2018, diabetes mellitus deaths in Malaysia reached 4,635 or 3.29% of total deaths (WHO 2018). Furthermore, at age 18, 52% have undiagnosed diabetes. The overall percentage of undiagnosed diabetes is more in Malays race, which is 53%, followed by the Chinese, about 49%, then in Indians bout 42% (CPG Malaysia, 2015). Concerning the control of diabetes, only 23.8% of total diabetic patients in primary care, whereas in tertiary institutions, about 12.7% able to achieve glycaemic targets (CPG Malaysia, 2015).

This intensification in the prevalence of diabetes mellitus will result in a remarkable increase in the economic burden on the health care systems of the country (Chongsuvivatwong et al., 2011). Similarly, this increase in prevalence will ultimately result in diabetic complications as uncontrolled or poorly controlled diabetes can lead

to various microvascular and macrovascular complications; thus, rigorous glycaemic control is required for the reduction of diabetic microvascular and macrovascular complications (Chawla et al., 2016).

1.3   Impact of uncontrol T2DM on outcomes of co-morbidities

Diabetes mellitus is associated with many risk factors, such as obesity, dyslipidemia, hypertension, cardiovascular complications (Petrie et al., 2018), and end-stage renal disease (Ghaderian et al., 2015).

The results of different epidemiological studies had proven that hypertension and T2DM are normally connected conditions, and their co-occurrence is increasing in patients (Krentz, 2016; Long & Dagogo-Jack, 2011). Diabetes and hypertension have considerable overlap between their mechanisms and etiology (Krentz, 2016). Lack of physical activity and obesity are the two basic and foremost reasons that influence both diseases (Cheung, 2010). High blood pressure is a common outcome in T2DM patients and is believed to reflect the effect of the basic insulin resistance (Ferrannini & Cushman, 2012). About 75% of adult people with diabetes have hypertension in comorbidity also, and patients with hypertension alone usually show evidence of insulin resistance (Long & Dagogo-Jack, 2011). Contradictory pieces of evidence suggested that instabilities in carbohydrates' metabolism are directly associated with uncontrolled hypertension in individuals (Perreault et al., 2017; Wei et al., 2011). A cardiovascular risk factor prevalence study reported that only 42% diabetics had normal blood pressure, and only 56% of hypertension patients had normal glucose tolerance (Cheung, 2010); thus, it indicates that the relationship of T2DM with hypertension is bidirectional in nature. Hypertension with T2DM co-morbidities in patients is not only complicated for treatment management and raises

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the cost of treatment but also increases the risk of development of macrovascular and microvascular complications (Aroda et al., 2017; Wei et al., 2011).

Dyslipidemia is the second more important co-morbidity after hypertension in T2DM patients (Bozkurt et al., 2016; Halpern et al., 2010; Petrie et al., 2018). T2DM in co-morbidity of dyslipidemia is directly associated with a significantly increased risk of atherosclerosis, mainly coronary heart disease and peripheral arterial disease (Leon, 2015; Martín-Timón, 2014). The abnormalities of lipoprotein generally present in T2DM include an increased level of triglycerides and LDL-Cholesterol, whereas a decreased HDL-Cholesterol level (Iqbal et al., 2019).

Although control of blood pressure will result in a significant reduction in microvascular complications but still a large portion of diabetic patients have poorly controlled hypertension (Rodondi et al., 2006; Volpe et al., 2015). The most probable reason reported by various studies is the patient's knowledge or understanding about the complications and consequences of the disease (Karaoui et al., 2018; Obirikorang et al., 2016; Waghachavare et al., 2015). Thus, to increase the control of diabetes with hypertension or dyslipidemia, there is a need to increase the patient understanding of the disease.

1.4 Impact of uncontrol T2DM on diabetic complications

T2DM is the important endocrine and metabolic disorders affecting different body organs of diabetic patients when their glycaemic control is poor (Ekoru et al., 2019). The uncontrolled T2DM will result in short and long-term complications, including hypoglycaemia, heart problems, neuropathy, nephropathy, retinopathy, and diabetic foot (Chawla et al., 2016; Goel et al., 2019; Huang et al., 2020). Poor control of diabetes is a major public health problem and a considerable hazard aspect for the

progression of its complications. Thus, glycaemic control remains the key therapeutic goal for the stoppage of these organ damages and any other problems due to diabetes (Haghighatpanah et al., 2018). The HbA1c has become a benchmark for determining the control of diabetes and is helping in predicting short or long-term diabetic complications (Bennett et al., 2007; Rohlfing et al., 2000; The UK Prospective Diabetes Study, 1998). Since the control of HbA1c is complex in clinical practice thus both patient and health care provider related factors are equally important in good control of HbA1c (Greenapple, 2011; Rhee et al., 2005). The health care providers should give individual attention to patients, and the patients should comply with the prescribed treatment regimens (Greenapple, 2011).

1.5   Impact of T2DM on Quality of life

It is generally believed that a basic objective for early diagnosis and treatment of diabetes is the quality of life (QoL) of patients (Trikkalinou et al., 2017). Diabetes is directly affecting all domains of health-related quality of life (Trikkalinou et al., 2017). Thus, if the blood glucose level is not controlled properly, it will decrease the quality of life in patients (Ginsberg, 2009). The significant decrease in HbA1c is directly related to the increase in health-related quality of life of diabetic patients and vice versa (Sherwani et al., 2016).

Once proper treatment given to patients, the outcomes of that given therapy can be measure by various methods. Health-related quality of life (HRQoL) measurement is one of the methods to measure the treatment outcomes for the given therapy, which is usually based on patient self-assessment about his/her health (Jing et al., 2018). It is usually influenced by a patient's expectations, beliefs, observations, and understandings about the disease (Megari, 2013). There are several domains

available to assess the patient-reported quality of life. The most important domains for patient self-reported quality of life are Physical Health, Psychological, Level of Independence, Social Relations, Environment and Spirituality/Religion/Personal beliefs (Cheung & Li, 2012). Various studies reported that diabetes mellitus could directly decrease the patient-reported quality of life. However, many other demographic factors are still not reported yet (Cheung & Li, 2012). Moreover, the type of diabetes, duration of disease, use of insulin, and various type of diabetic complications are directly affecting the patient-reported quality of life (Jing et al., 2018).

Many research tools have been developed and validated throughout the world to evaluate the patient-reported quality of life in various chronic diseases to date. Most importantly, the WHOQOL tool, SF-36 tool, and EQ-5D. The EQ-5D is one of the most achievable and easiest tools to evaluate the patient-reported quality of life in all the diseases that can easily evaluate the physical, mental and social and mobility performance of the patients (Whalley et al., 2018). It is already validated and has been used in numerous studies to evaluate the patient-reported quality of life in many chronic diseases such as diabetes, asthma, cardiac diseases, and many chronic mental complications (W. J. Lee et al., 2012; Pinto et al., 2011). The latest version available for EQ-5D is version (EQ-5D-5 L), which is tested as a better instrument as compared with the previously available versions of EQ-5D (E.R. Foundation, 2019).

1.6   Impact of T2DM on the cost of treatment

The prevalence of diabetes is continuously increasing every year worldwide and is anticipated to be increased by up to 642 million by the year 2040 (Zheng et al., 2018). Approximately 90% of the total population of diabetes belong to T2DM

(Korean Diabetes Association, 2016), which results in an increasing economic burden on global healthcare systems. Even though prevention of T2DM is the ultimate resolution and has been proven to be cost-effective in studies (Andreas Liebl et al., 2015), but providing cost-effective treatment for T2DM is required for all patients (Andreas Liebl et al., 2015; Massi-Benedetti, 2002). Poor glycaemic control will result in various microvascular diabetic complications and will ultimately result in macrovascular complications (Boehme et al., 2015; Long & Dagogo-Jack, 2011). These diabetic complications have a negative impact on the quality of life (QoL) of patients, and management of these complications is the main expenditure in the cost of treatment required for T2DM (Liebl et al., 2002; Williams et al., 2002). In 2010, global healthcare expenditure for treatment and prevention of diabetes and its complications was USD376 billion, and the expenditure was predicted to be USD490 billion in 2030 (Zhang et al., 2010).

In Malaysia, several studies have estimated the cost of different aspects of diabetes treatment. A study by Sharifa Ezat and colleagues stated that inpatient costs for diabetes in MOH facilities without specialists were around RM1,951.00 per year. In contrast, with specialists, it is about RM 1,974.44 per year (Sharifa Ezat WP et al., 2009). Another study conducted by Mustapha et al. found that the annual costs of outpatient care for each patient follow-up was estimated at RM459 per year other than any diabetic complication, but in the presence of diabetic complications, the cost is more than RM4000 per year per patient (Mustapha et al., 2017).

The study conducted by Stratton and colleagues had proven that every decrease of 1% in mean HbA1c is directly related with 21% decrease in risk for micro vascular complications (Stratton et al., 2000). Thus, tight glycaemic control is needed to avoid

or slow down the progression of diabetic complications, which will ultimately result in decreased costs of treatment in T2DM.

1.7 Management of T2DM at the global health care system

The management of T2DM was initially done with diet and lifestyle modifications, afterwards use of oral antidiabetic agents (Marín-Peñalver et al., 2016). Historically, insulin therapy was used as the 'last option' in patients with T2DM (Rotella et al., 2013) still, the benefits of earlier starts of insulin are now well documented with improved glycaemic control and decrease the progression of diabetes complications (Hanefeld & Bramlage, 2013; Owens, 2013; Ramsdell et al., 2003).

Studies have proven that good and tight glycaemic control can be achieved by the collaboration of healthcare providers, patient and physician adherence to given guidelines, and proper health care system (Munshi et al., 2013; Nixon et al., 2019; Zgibor & Songer, 2001). For good glycaemic control in all over the world, the role (function or part played) of physician, patient, pharmacist, and pharmaceutical care process is as follows:

1.7.1 Role of Physician

It is proven that the majority of diabetic patients receive their treatment from family physicians all over the world (Brown et al., 2002; Davidson, 2010). Teamwork is required between physicians and patients for good glycaemic control in diabetic patients (Heisler et al., 2003). The most important responsibilities for physicians are collecting a medical history, establishing a diagnosis and disease progression, and providing clear and brief instructions about the treatment regimens (Duffy et al., 2004). Furthermore, physicians must have interactive and relationship skills to create a

trustable relationship with patients (Ritholz et al., 2014). Both physician and the patient consensus is required for trustable treatment and honest self-care communication (Duffy et al., 2004).

Many factors are responsible for poor glycemic control, including lack of personalized care in health care systems, poor patient adherence towards self-care recommendations, and clinical inertia of health care providers which will increase the risk of diabetic complications (Peyrot et al., 2005). Thus, the patients must feel comfortable with their physicians in discussing their problems and difficulties due to T2DM, and ultimately their physician can personalize treatment prescriptions for successful management of the disease (Duffy et al., 2004). Despite all efforts done by the physicians still, it is required that the patients should have proper knowledge about the consequences of the disease, and compliance to the recommended therapy is still important in the proper management of T2DM (Nam et al., 2011).

1.7.2   Role of Patient

T2DM is a chronic illness and requires proper medical care along with patient education about self-management to avoid its long-term complications (American Diabetes Association, 2003). Over the previous decade, the curiosity of health professionals towards patient education about self-management of T2DM has been abruptly increased (Khazrai et al., 2014). The ultimate goal of patient education about T2DM is to achieve the changes in human behavior by providing knowledge, understanding, and consequences of the disease (Kirkman et al., 2002; Lin et al., 2007).

The patient self-care in diabetes is directly related with the increase of awareness about the complex nature of the diabetes (Cooper et al., 2003). Because the

day-to-day care in diabetes is ultimately handled by patients themselves or their families (Paterson, 2000). Therefore, there is an essential need for reliable and valid actions for the self-management of diabetes in patients (Shrivastava et al., 2013). There are some essential self-care behaviours in diabetic patients which estimate good outcomes in glycemic control of diabetes. These can include healthy eating, regularly monitoring of blood glucose levels and compliant with prescribed medications (Roxas & Nemencio Nicodemus, 2014). Participant behaviour is a major barrier contributing to the less control of diabetes. Lack of patient acceptance about diabetes as a chronic illness is an example of negative patient behaviour, which requires significant lifestyle modifications (Shrivastava et al., 2013).

The patient education about T2DM is not able to attain metabolic regulation if the patient does not aware of the basic principles of the daily diet, physical activity, care of the body parts, along with specific skills needed for subcutaneous administration of insulin injection, daily control of blood sugar levels, and some other compulsory parameters (Puder & Keller, 2003; Swiątoniowska et al., 2019). The patient education program contains many parts. The most important part of the patient education program is learning the technique of insulin subcutaneous injection by the patient and his/her family members (Polonsky et al., 2017). In the patient education program, the technique of injection, the adjustment of insulin units, the selection of injection sites, and the way of handling the equipment with the aim of stop infection and injuries. Thereafter, basic principles regarding daily diet, maintenance of body weight, resting, and prevention of hypoglycemia are taught by the health care providers globally (Hansen & Drivsholm, 2002; Rutten, 2005; Tessier & Lassmann-Vague, 2007; F. Zheng et al., 2019).

1.7.3   Role of Pharmacist

After Physicians and Nurses, Pharmacists are the third largest health care providers in the world (International Pharmaceutical Federation, 2016). Pharmacists are working in the community pharmacies, hospital pharmacies, academia, industries, and in research all over the world. In pharmacies, they provide services to diabetic patients with prescription and non-prescription medication, blood glucose meters, and testing strips, dietary supplements, and some other services like medication review, needle exchange, and disposal of unwanted medicines, etc. (Health at a Glance, 2019). Community pharmacists are believed to be the utmost reachable health care providers, because usually, no appointments are needed to meet them, and they have a good level of patient interactions. Ultimately, they are available to provide significant role in the care of diabetic patients (Hughes et al., 2017).

The awareness and compliance of patients toward the treatment of diabetes can be increased by giving proper counseling to the patient with the help of pharmacists (Maxwell et al., 2014; Nascimentoa et al., 2015; Eikenhorst et al., 2017). Looking into the past, numerous studies have proven that the contribution of pharmacists in achieving better control of diabetes is significant (Hassali et al., 2015; Nascimentoa et al., 2015; Eikenhorst et al., 2017). These studies focused on many types of pharmacist interventions, including; self-care related interventions, or on counseling, but always resulted in a significant effect on the outcomes of diabetes mellitus. Therefore, to achieve the targeted glycaemic control, patient awareness and compliance towards the treatment are important (Handelsman et al., 2015). Thus, it is proven that pharmacist intervention will result in better control of diabetes all over the world (Ayadurai et al., 2016).

1.7.4 Concept of personalized medicine

The prevalence of diabetes mellitus is increasing all over the world, and if not managed properly, many complications will develop in patients. Thus, diabetes is directly or indirectly decreasing the quality of life of patients resulting in increasing the economic burden on patients or the healthcare system. Research proved that diabetes is directly related to lifestyle and dietary habits, so the patient himself/herself can play a significant role in controlling the disease and improve his/her quality of life. Despite this fact, many are still not adhered to their medication and lifestyle modification plan resulting in poor control of disease and the development of many diabetic complications. These non-adherence related problems can be avoided up-to much extent by increasing the individual patient adherence to the prescribed treatment and implementing appropriate non-pharmacological measures. A well-structured personalized medicine program can make this improvement with the help of pharmacists (Machado-Alba et al., 2011). Personalized medicine contains recognizing, determining, and preventing all drug-related problems in individualized patients.

The personalized medicine can be done by pharmaceutical care program which is a program by pharmacy practice where the pharmacist evaluates the drug regimen by his/her expertise and provides patient counselling on medication, modification of lifestyle and diet plan for better outcome of the disease, and to improve the quality of life in individualized diabetic patients. Hepler and Strand developed the actual pharmaceutical care model in 1990, which elaborates on the involvement of pharmacists in the healthcare system to attain better therapeutic outcomes (Hepler & Strand, 1990). According to this model, 'pharmaceutical care includes direct interaction of the patient with a pharmacist, with the drug therapy for achieving definitive outcomes that will result in improvement in the quality of life of diabetic

patients and help disease management. These outcomes in this model were the cure of disease, decrease symptomatology of the disease, slowing the disease progression, and ultimately preventing the disease (Hepler & Strand, 1990). Later this Hepler and Strand's philosophy was refined by Cipolle et al., and according to them, 'it is a patient-centred practice (Cipolle et al., 2004). In both these models, the focus was on the responsibilities of the patient and the pharmacist to improve the quality of care of the patient and to attain better outcomes of the disease.

Pharmaceutical care provided by a team of healthcare professionals, including the pharmacist, doctors, nurses, and technicians, but usually pharmacists are regarded worldwide because they are product-focused, preparing, and dispensing drugs to the patients. Pharmaceutical care involves instruction on receiving and using medications, responsibilities, medication surveillance, counseling, and outcomes of care. Pharmaceutical care also facilitates good communication among the different members of the healthcare system (Hepler & Strand, 1990; Mehuys et al., 2011; Nascimentoa et al., 2015; Taveira et al., 2010)

Nevertheless, the idea of pharmaceutical care program/ medication therapy management is a distinct facility that improves drug therapy with the intention of better therapeutic outcomes of the disease for individualized patients (Almarsdóttir et al., 2019). This program comprises five major components, which include medication therapy review, patient individual medication records, the action plan for medication, lifestyle intervention education, and documenting each and follow-up of the patients (Zachariah et al., 2019). During the sessions in these programs, the pharmacist recognizes medication-related problems (DRPs) and suggests appropriate intervention

as a solution. The pharmacist usually collaborates with other health care providers to solve the identified problems (American Pharmacists Association, 2008)

1.8   Management of T2DM in Malaysian health care system

Malaysia is situated in a geographic region and consists of 13 states and three federal territories with a complete landmass of 329,847 square kilometers. For the foremost part, health care in Malaysia is the responsibility of the Ministry of Health under the government (Ministry of Health Malaysia, 2017). Just like many other developing nations, the Malaysian health care system consists of a government health care system with a coexisting of private health care system (Hussein et al., 2015). Diabetes may be the main public un-healthiness in Malaysia that's thoroughly associated with augmented macro-and microvascular complications, together with premature and preventable mortality (Hussein et al., 2015)

Diabetes care is often accessible at all major public hospitals in every state of Malaysia. Patients on an individual basis are referred for sessions with dietitians, diabetes nurse educators, and pharmacists. Complete care available in hospital-based diabetes clinics comprises of normal screening for diabetic complications as recommended by current clinical practice guidelines provided by the Ministry of Health Malaysia (CPG Malaysia, 2015). Diabetic patients with poor glycaemic control or with multiple co-morbidities and complications are referred to endocrinologists for further consultation of care.

Diabetes Resource Centres are available in most of the hospitals within which trained diabetes nurse educators to deliver patient-centered diabetes education to all diabetic inpatients and outpatients. Group-based diabetes education is still not well established within the public hospital of Malaysia. In recent years, group-based

diabetes education using the Diabetes Conversation Maps endorsed by the International Diabetes Federation has been promoted all over the world. Thus in Malaysia, the whole set was translated into Bahasa Malaysia (BM), the national language of Malaysia. The Ministry of Health has conducted training courses for diabetes nurse educators since 2004, and an estimated 900 diabetes nurse educators are trained and practice in both primary care tertiary diabetes care (Hussein et al., 2015).

1.9   Diabetes Medication Therapy Adherence Clinic (DMTAC) in Malaysia

In Malaysia, including hospital pharmacists in diabetes education simplifies medication use, the effect, promotes better disease-related education and enhanced medication adherence. This strategy was introduced in 2004 from the Ministry of Health to establish Diabetes Mellitus Treatment Adherence Clinics (DMTAC) as a part of the clinical pharmacy services in the Ambulatory Clinic System, which emphasizes medication management improve on quality, safety and cost-effectiveness of diabetic patients. The first-ever DMTAC service was initiated in Penang General Hospital. Presently, all major public hospitals of Malaysia have this service, and recently it has been extended to primary care clinics also. The Ministry of health provides DMTAC protocols to all the health care centers in the country. The latest edition is the second edition, and it was published in 2014 (DMTAC protocol, Ministry of Health Malaysia, 2014).

The Malaysian DMTAC protocol includes plans, procedures, and documentation during DMTAC sessions. It assists as a guide for pharmacists while managing diabetic patients in DMTAC sessions. The availability of this protocol will

maintain the standardization of practice and accessibility of DMTAC services throughout MOH diabetes clinics and care centers all over the country.

Diabetes Medication Therapy Adherence Clinic (DMTAC) is ambulatory care and value-added service provided by pharmacists in collaboration with physicians to help diabetic patients to accomplish better medication adherence and good glycaemic control. Patients enrolled under DMTAC followed-up for a minimum of 8 visits, where they receive medication adherence evaluation, identification and solving of drug-related problems, counseling for prescribed medication, evaluating the clinical outcomes, and diabetes education by the pharmacist. In total patients registered in DMTAC services receive further counseling sessions from the pharmacist, other than the usual consultation from physicians (Ministry of Health Malaysia, 2014)

1.10   Problem statement

Due to the lack of knowledge of patients about the disease, the required outcomes are not achieving (Shu Hui Ng, 2012). The subsequent significant factor for not getting the required outcome of diabetes mellitus is the dietary habit, which is equally responsible for the poor control of diabetes in Malaysia. The poor control of fasting or random blood glucose level will ultimately result in an increased HbA1c level, which is the main risk factor for developing microvascular and macrovascular diabetic complications. Patient knowledge can increase with the help of pharmacist education interventions. Hence, looking at these facets, the study has decided the following major problems:

Past literature recommends a lack of awareness and knowledge about diabetes in Malaysian diabetic patients resulted in poor control of disease in the country. Health care providers need to give proper education to diabetic patients about the disease and

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lifestyle modification. There is a lack of research and scientific data that can measure the effect of educational intervention on clinical outcome in diabetic patients at different public hospitals in Malaysia. There has been a lack of data and research to assess the effect of educational intervention on health-related quality of life (HRQoL), direct medical cost of treatment bearing by the Ministry of Health Malaysia, and effect of educational intervention on diabetic complications.

Furthermore, pharmacist involvement in individual patient care and the effect of educational intervention on disease outcomes are still not studied in public hospitals of Malaysia. Although some studies with limited sample size investigate the impact of pharmacist intervention on limited diabetes outcomes in Malaysia (Butt et al., 2016; X. Y. Lee et al., 2015; Lim et al., 2016; Lim & Lim, 2010), but many limitations were present in these studies. These limitations included information biasness as the data were analyzed by the same pharmacist involved in the intervention, single-centre or retrospective nature of the study. Besides, the effect of pharmacist education intervention from DMTAC services (Government program) on quality of life of patients, the direct medical cost of treatment bearing by Ministry of Health Malaysia and effect of educational intervention on the progression in sign and symptoms of its complications was not yet studied in Public hospitals of Malaysia. These comprehensive observations establish the necessity of an in-depth study that evaluates the effect of pharmacist intervention on all relevant domains of diabetes.

1.11   The rationale of the study

The concept of pharmaceutical care and the role of the pharmacist in patient care is mainly established in developed countries, and numerous studies have conducted in different areas (Abrahamsen et al., 2020; Correr et al., 2009; Krass &

Hoti, 2019; Krzyżaniak et al., 2019; Lum et al., 2019; Obreli-Neto et al., 2011; Presley et al., 2019). The total number of registered pharmacists with the Malaysian Pharmacy Council until the year 2020 was 14000 among the country's 33 million population, with the pharmacist-to-public ratio of 1:2367 and Malaysia had already achieved the WHO target of 1:2000 ration (Malaysian Pharmacy Council, 2020). But the pharmacist participation in patient care is not well documented yet in Malaysia.

No prospective follow up study has been conducted so far in multicentre public hospitals that focused on the pharmacist's role in diabetic patient care through DMTAC concept in the public healthcare system of Malaysia. Similarly, no study conducted so to measure the effect of DMTAC services in Malaysia on quality of life, hospital bearing cost of treatment, and the effect of these services on progression and development of diabetic complications. Due to limited knowledge of patients about disease status and the related risk factors, the public health problems like cardiovascular diseases, hypertension, and diabetes have dramatically increased, which will ultimately lead to long- and short-term diabetic complications and untimely result in more mortality and morbidity in the country.

Poor knowledge of patients combined with unhealthy eating and lifestyle habits in patients leads to poor therapeutic outcomes, resulting in more hospital services requirement (Puder & Keller, 2003; Świątoniowska et al., 2019; Waghachavare et al., 2015). As a result, this produces a more economic burden on the healthcare system of the country as the Ministry is providing all cost of treatment in Malaysia. Therefore, this situation needs a bidirectional approach. First and of all, the diabetes educational program about the methods to prevent the disease and lifestyle modification need for the disease should be taught to all diabetic patients. Secondly,

all diabetic patients should receive proper treatment counseling and advice for lifestyle modification as per their disease condition. Early detection of T2DM can help in handling the disease by exercise and proper controlled diet, which will directly affect the Pharmacoeconomic burden on the healthcare system of Malaysia. Educational intervention by counselling would help the diabetic patient sustain and control their blood glucose level, which is directly affecting the quality of life of patients. Very little work has been done in Malaysia so far to evaluate the effectiveness of DMTAC services on some limited outcomes of diabetes mellitus.

Therefore, by conducting this study, we will establish a relationship between the effectiveness of pharmacist intervention by DMTAC services in public hospitals of Malaysia on the clinical outcomes of diabetes mellitus, on quality of life of patients, on the progression of diabetic complications and with emphasis the effect of pharmacist intervention on direct costs of treatment that the government is bearing for treating the patients of diabetes mellitus.

1.12   The study hypothesis

The present study was performed to evaluate the effect of pharmacist intervention by DMTAC services in public hospitals of Malaysia on the clinical outcomes, quality of life of patients, the progression of diabetic complications, and direct costs of treatment that the government is bearing for treating the patients of diabetes mellitus. The study hypothesis was as follows:

1.12.1 Null Hypothesis:

H0: DMTAC services in public hospitals of Malaysia do not have any significant effect on the clinical outcomes, quality of life of patients, the progression

of diabetic complications, and direct costs of treatment (hospital bearing) on diabetic patients.

1.12.2 Alternative Hypothesis:

H1: DMTAC services in public hospitals of Malaysia have a significant effect on the clinical outcomes, quality of life of patients, the progression of diabetic complications, and direct costs of treatment (hospital bearing) on diabetic patients.

Different statistical analysis by using SPSS version 24 was used to evaluate this null hypothesis of the study.

1.13   Significance of the study

It was predicted to receive significant contributions during the commencement of this study. Those anticipated results of this study will help establish the importance of the pharmacist intervention from DMTAC services in public hospitals and on the healthcare system of Malaysia where earlier no studies have addressed the present concept. It was also expected from the present study that the study would be beneficial for the diabetic patients to improve their knowledge and awareness about the disease, modification in their daily food habits and lifestyle which will help them to improve their practice regarding the preventive measure of the disease complications and ultimately, they can improve their quality of life.

The study will also provide an effective method to improve the therapeutic outcome and decrease the chances and progression of diabetic complications with the passage of time. The study will provide the effectiveness of DMTAC services in public hospitals of Malaysia, and later the pharmacist services can be implemented to all health care centers in Malaysia, including in all "*Klinik Kesihatan*" Malaysia.

This study can also convey the message to other healthcare providers that the pharmacist is also an important member of the healthcare system and can play a major role in patient care and can improve the healthcare system of the country. Moreover, this study was anticipated to contribute to an improved understanding of future pharmacists for their role and place in the healthcare system of Malaysia, and it might distract their thinking from becoming further patient oriented.

In addition to that, this study is an effort to explain to the government and policymakers about the pharmacist's place in the healthcare system and their role in patient care, which will ultimately result in an improved healthcare system of the country. The findings of the current study will be the part of literature in Malaysia that can also set up a good platform for future researchers and will provide a well-established module and primary data for further research on a large scale throughout the country.

1.14   Study objectives

The study objective of the current study was as follows:

1.14.1 General objectives

The present study's general objective is to evaluate the impact of pharmacist intervention in DMTAC services in the public hospitals of Kedah state of Malaysia on clinical outcomes, health-related quality of life of patients, and diabetic complication progression in patients of diabetes mellitus.

1.14.2 Specific objectives

The various specific objectives are as below:

1. To evaluate the impact of pharmacist intervention on clinical outcomes of diabetes mellitus in diabetic patients.

2. To evaluate the impact of pharmacist intervention on patient-reported quality of life in diabetic patients.

3. To evaluate the impact of pharmacist intervention on the direct cost of treatment (hospital bearing) in diabetic patients.

4. To evaluate the impact of pharmacist intervention on the progression of signs and symptoms of diabetic complications in diabetic patients.

1.15 Thesis overview

This thesis contains seven chapters together with **chapter 1** (Introduction).

Chapter 2 is associated with the literature review and the conceptual framework of this study. This chapter briefly explains information related to diabetes and the impact of pharmacist intervention on different aspects of diabetes, followed by in-depth reviews of literature related to individual study objectives of the current study. This chapter will conclude with the conceptual framework of the current study, research questions, expected outcomes of the current study, and provide significant research gaps in pharmacist intervention on diabetes mellitus.

Chapter 3 will be briefing about the methodology used in the present study. This chapter will elaborate on the methodology used in the present research study with the explanation of the study tools used in the current study and data collection form formulation. This chapter also talks about how the type of intervention used in DMTAC services for educating diabetic patients with a brief note on a tools' validation and the statistical analysis used in the present study to test the hypothesis of this study.

Chapter 4 is all about the current study results; furthermore, it will provide details about the impact of pharmacist intervention by DMTAC services in different public hospitals (Ministry of Health) of Kedah Malaysia. This chapter comprises a detailed analysis of the impact of the pharmacist educational intervention on clinical outcomes of diabetes mellitus, impact of pharmacist intervention on the patient-reported quality of life, impact of pharmacist intervention on the direct cost of treatment (hospital bearing) and also the impact of DMTAC services on the progression of the sign and symptoms of diabetic complications.