VASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS PATIENTS AND THEIR ASSOCIATION WITH HYPERTENSION AND DYSLIPIDEMIA

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By

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LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
NDR	National Diabetic Registry
NHMS	National Health Morbidity Survey
NCD	Non communicable Disease
OHA	Oral Hypoglycemic Agent
CPG	Clinical Practice Guideline
WHO	World Health Organization
IDF	International Diabetes Federation
CSME	Clinically Significant Macular Edema
DR	Diabetic Retinopathy
DME	Diabetic Macular Edema
ACE inhibitors	Angiotensin converting enzyme inhibitors
ARB's	Angiotensin Receptor Blockers

LIST OF SYMBOLS

>	More than
<	Less than
≥	More than and equal to
≤	Less than and equal to
%	Percentage
α	Alpha

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ABSTRAK

KOMPLIKASI VASKULAR DI KALANGAN PESAKIT DIABETIS MELLITUS JENIS 2 DAN HUBUNGKAIT DENGAN TEKANAN DARAH TINGGI DAN KADAR KOLESTROL TINGGI

Latar belakang: Penyakit diabetis mellitus jenis 2 adalah penyakit tidak berjangkit yang paling utama dikalangan penduduk daerah Marang. Penyakit diabetis mellitus jenis 2 adalah sejenis penyakit kronik yang boleh menyebabkan masalah komplikasi vaskular. Penyakit tekanan darah tinggi dan penyakit dislipidimia adalah merupakan 2 jenis morbiditi bersama dengan penyakit diabetis mellitus jenis 2.

Objektif: Tujuan utama kajian ini dijalankan bagi melihat kehadiran komplikasi vascular dan faktor-faktor berkaitan di kalangan pesakit diabetis mellitus jenis 2 di daerah Marang dari tahun 2010 sehingga 2016.

Metodologi: Kajian ini menggunakan kaedah hirisan lentang melibatkan data sekunder pesakit diabetis mellitus jenis 2 yang berdaftar daripada Januari 2010 sehingga Disember 2016 di dalam pangkalan data Pendaftaran Diabetis Kebangsaan atau "*National Diabetic Registry (NDR)*", unit penyakit tidak berjangkit, Pejabat Kesihatan Daerah Marang, Terengganu. Kesemua pesakit diabetis mellitus jenis 2 yang berdaftar dengan data lengkap variabel akan dimasukkan ke analisa trend, dan 500 sampel telah di pilih secara rawak ringkas bagi menggambarkan kadar bilangan komplikasi vaskular dan menentukan samada terdapat kaitan di antara kehadiran penyakit darah tinggi dan penyakit dislipidimia dengan belakunya komplikasi vaskular.

Keputusan: Seramai enam ribu empat ratus lapan puluh tujuh kes pesakit kencing manis jenis 2 telah berdafatar di dalam NDR Marang daripada 2010 sehingga 2016. Peringkat umur pesakit kencing manis jenis 2 berumur di antara dari 23 sehingga 93 tahun. Kadar pesakit wanita adalah lebih tinggi iaitu seramai 362(72.4%) berbanding dengan bilangan pesakit lelaki iaitu seramai 138(27.6%). Majoriti pesakit diabetis mellitus jenis 2 adalah berbangsa Melayu iaitu seramai 478(95.6%). Majoriti pesakit mempunyai indeks jisim badan kumpulan berat badan berlebihan ("*Body mass index*" BMI $\geq$25kg/m^2) iaitu seramai 185(37%). Kadar purata HbA1c di kalangan pesakit diabetis melltus jenis adalah sebanyak 8.6(2.29). Majoriti pesakit diabetis mellitus jenis 2 seramai 431(86.2%) tidak mencapai kadar gula terkawal iaitu nilai HbA1c kurang daripada 6.3% . Seramai 340(68%) pesakit mengidap penyakit darah tinggi dan seramai 357(71.4%) pesakit mengidap penyakit dislipidimia. Seramai seratus lapas belas(23%) pesakit mengalami komplikasi vaskular, samada nephropati, retinopati, penyakit jantung, penyakit angin ahmar, ulser kaki diabetis dan amputasi anggota badan samada satu atau beberapa komplikasi serentak.

Komplikasi vaskular yang paling utama berlaku adalah nephropati 59(11.8%) di ikuti dengan retinopati 47(9.6%). Kadar nephropati teringgi di kesan adalah sebanyak 116 kes pada tahun 2010 dan kemudiannya berlaku naik turun bilangan kes sebelum menurun pada tahun 2016. Kadar komplikasi retinopati kekal tinggi dari tahun 2010 hingga ke 2016. Kadar tertinggi bilangan kes retinopati dikesan adalah 91 kes pada tahun 2015 dan kadar yang terendah dikesan adalah sebanyak 61 kes pada tahun 2013. Kadar penyakit jantung pada mulanya menurun pada tahun 2010 sehingga 2013 tetapi seterusnya menunjukkan peningkatan yang berterusan daripada tahun 2014. Bilangan kes ulser kaki diabetis, amputasi anggota badan dan penyakit angin ahmar kekal rendah daripada tahun 2010 sehingga 2016. Kehadiran penyakit tekanan

darah tinggi(AdjOR 1.750, 95%CI(1.062, 2.886) p-value 0.028) and penyakit dislipidimia(AdjOR 1.858, 95%CI: 1.092, 3.160; p-value 0.022) didapati ketara dikaitkan dengan berlakunya komplikasi vascular.

Konklusi: Komplikasi vaskular terutamanya nephropati dan retinopati masih lagi merupakan masalah kesihatan awam di kalangan pesakit diabetis jenis 2 di daerah Marang. Kehadiran bersama penyakit darah tinggi dan penyakit kolestrol tinggi menigkatkan lagi risiko untuk berlakunya komplikasi vaskular.

KATA KUNCI: Penyakit diabetis mellitus jenis 2, penyakit tekananan darah tinggi, penyakit dislipidimia, komplikasi vaskular.

ABTRACT

VASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS PATIENTS AND ITS ASSOCIATION WITH HYPERTENSION AND DYSLIPIDEMIA

Background: Type 2 diabetes mellitus (T2DM) is a common non communicable disease among population of Marang district. T2DM is a chronic disease which may progress to vascular complications. Hypertension and dyslipidemia are two common co morbidities in T2DM.

Objective: This study aimed to study the occurence of vascular complications and their asscoiated factors among T2DM patients in Marang from 2010 to 2016.

Methodology: This is a cross sectional design using secondary data of registered T2DM patients from January 2010 to December 2016 in National Diabetic Registry (NDR) database, Non Communicable Disease Unit, District Health Office Marang, Terengganu. All registered T2DM cases with no missing data variable were included For trend analysis, and 500 samples were randomly selected to describe the type of vascular complication and determine the association between hypertension and dyslipidemia with vascular complication.

Result: Six thousand four hundred and eighty seven T2DM cases had been registered in NDR Marang from 2010 to 2016. The T2DM patient's age ranged from 23 to 93 years old. There were more female 362(72.4%) as compared to male patients 138(27.6%). Majority of the T2DM patients were Malay 478(95.6%). Majority of the patients were overweight group (BMI ≥25kg/m²) 185(37%). The mean HbA1c of the T2DM patients was 8.6(2.29). Majority, 431(86.2%) of the

T2DM patients did not achieve good glycaemic control target of HbA1c less than 6.3% . Hypertension present in 340(68%) whereas 357(71.4%) has dyslipidaemia. One hundred and eighteen(23%) had vascular complications,either nephropathy, retinopathy, ischemic heart disease (IHD), cerebrovascular disease, diabetic foot ulcer and amputations as single or multiple complications.

The most common vascular complications was nephropathy 59(11.8%) followed by retinopathy 47(9.6%). The highest detection of nephropathy were 116 in 2010 which then fluctuate before reducing back in 2016. Retinopathy complication remained high since the year 2010 to 2016. The highest case of retinopathy detected were 91 case in 2015 and the lowest detected were 61 case in 2013. IHD reducing from 2010 to 2013 but increase steadily again by 2014. Diabetic foot ulcer, amputation and cerebro vascular disease remain at lower frequency through out 2010 to 2016. Presence of hypertension(AdjOR 1.750, 95%CI(1.062, 2.886) p-value 0.028) and dyslipidemia(AdjOR 1.858, 95%CI: 1.092, 3.160; p-value 0.022) was found to be significantly associated with the presence of vascular complication

Conclusion: Vascular complications especially nephropathy and retinopathy still pose a public health problem among T2DM patients in Marang. Presence of hypertension and dylipidemia increase the risk of vascular complication.

KEYWORDS: Type 2 diabetes mellitus, hypertension, dyslipidemia, vascular complications.

Chapter 1: INTRODUCTION

1.1 Introduction of Diabetes mellitus

Diabetes mellitus (DM) is defined as a state of metabolic diseases with an elevated blood glucose level (hyperglycaemia). Diabetes is the one of the one the most common non communicable disease (NCD) which is currently increasing in trend globally. World Health organization (WHO) has estimated that by the year of 2030, 2.48 million of people in Malaysia will be diagnosed as diabetes mellitus (WHO, 2016).

DM complications are divided into 2 groups known as acute and chronic complications. The acute complications are hypoglycaemia, hyperglycaemic states which include diabetic ketoacidosis and hyperglycaemic hyperosmolar state; and microbial infections. The chronic complications are divided into macrovascular and microvascular. Macrovascular complication comprises the cardiovascular, cerebrovascular and peripheral vascular diseases. Microvascular complications are retinopathy, nephropathy and neuropathy (Ministry of Health, 2016).

National Diabetic Registry (NDR) was introduced by Ministry of Health in 2009. The objectives of NDR are to strengthen the NCD surveillance in Malaysia in order to monitor quality of care, to keep track of the target achievement and clinical outcomes annually . Data was initially collected manually in 2009, before web based data was introduced in 2011. There were 644 participating health care clinics all over in Malaysia. Patient status is regularly updated. The proportions of active patients are audited annually, before 31st August each year. This audit is done to

obtain clinical and treatment information including clinical investigations result, drug dose, complications and co-morbidities. The NDR 2009-20012 report listed hypertension (70.1%) and dyslipidaemia (55.1%) as the most common comorbidity. The most common complications are nephropathy (7.8%), retinopathy (6.7%), and ischemic heart disease (5.3%). (Ministry of Health, 2013).

1.2 Problem statement & Study rationale

Data from National Health Morbidity Survey (NHMS) I-IV shows that the prevalence of diabetes is increasing in trend from 1986 to 2011. Despite of the clinical practice guideline regular revision, optimal treatment with oral hyperglycaemic agent (OHA), early initiation of insulin and increased percentage of patient with controlled HbA1c < 6.5%, the number of diabetes with complications are still abundant (Ministry of Health, 2013).

The vascular complications in T2DM are preventable. Hypertension and dyslipidemia is risk factors for diabetes complication which can be controlled with lifestyle modification and pharmacotherapy. The burden to patients, their family and hospital management can be reduce by early intervention and comprehensive diabetic care. Information on the occurrence of vascular complications, types of treatment and to the association between hypertension and dyslipidaemia in development of vascular complications are able to facilitate effort in reducing mortality and morbidity among patients with diabetes.

1.3 Research questions

1. What is the prevalence of vascular complications among type 2 diabetes mellitus in Marang Terengganu.

2. What is the incidence trend of newly detected vascular complications in type 2 diabetes mellitus diagnosed by year in Marang Terengganu.

3. Is there any association between hypertension and dyslipidaemia with presence of vascular complications.

1.4 Objectives

General:

To study the occurrence of vascular complications among type 2 diabetes mellitus patient in Marang for the year of 2010-2016

Specific:

1. To describe the percentage of types vascular complications among type 2 diabetes mellitus patient in Marang for the year 2010-2016.
2. To describe trend of newly detected vascular complications by year from 2010 to 2016 in Marang.
3. To determine the association between the presence of hypertension and dyslipidemia in type 2 diabetes mellitus with occurence of vascular complications.

1.5 Hypothesis

The occurence of vascular complications in type 2 diabetes mellitus is associated with presence of hypertension and dyslipidaemia.

Chapter 2: LITERATURE REVIEW

2.1 Epidemiology of Diabetes mellitus

In 2017, the global prevalence of DM were 425 million people , and is estimated to keep on rising to 629 million people by 2045. This figure is estimated by using the International Diabetes Federation (IDF) diabetes atlas prevalance estimation and including the people aged 20-79 provided by the United Nations Population Division. The estimate includes both diagnosed and undiagnosed diabetes. The number of DM cases in South East Asia is expected to increase by 2 times by the year of 2025(Ogurtsova *et al.*, 2017).

National Health Morbidity Survey (NHMS) has reported that the prevalence of DM in Malaysia are increasing in trend. The NHMS reported the prevalance of DM according to two age groups which is above 18 years old and above 30 years old group. For the age group above 18 years old, the prevalence of DM were showing an increasing trend from 6.3% in 1986 to 8.3% in 1996 to 11.6 % in 2006 and keep on increasing upto 15.2% in 2011 and further rised to 17.5% in 2015 (Institute of Public Health, 2015). For the age group of above 30 years old, the prevalance of DM had shown a faster increasing in trend which is, 8.3% in 1996 to 14.9% in 2006, and further increase to 20.8% in 2011 and keep on increasing to 22.5% in 2015 (Institute of Public Health, 2015). The DM prevalence was different significantly statistically between sex where higher prevalence were noted in females at 9.1% (95% CI: 8.4, 9.8) compared to males at 7.6% (95% CI: 7.0, 8.3). By etchnicity, the highest prevalence were among Indians 16.0% (95% CI: 13.7, 18.6), followed by Malays at 9.0% (95% CI: 8.4, 9.7), Chinese at 7.7% (95% CI: 6.7, 8.9) and other Bumiputras at

6.8% (95% CI: 5.3, 8.8). The prevalence was significantly different between urban areas at 8.7% (95% CI: 8.0, 9.3) compared to rural at 7.2% (95% CI: 6.6, 7.9). The highest prevalence by states is in Perak at 11.9% (95% CI: 9.9, 14.3), followed by Perlis at 10.9% (95% CI: 9.3, 12.7) and Negeri Sembilan at 10.5% (95% CI: 8.5,12.9); while the lowest is WP Putrajaya at 5.3% (95% CI: 3.3, 8.5)(Institute of Public Health, 2015).

2.2 Screening Of Types 2 Diabetes Mellitus (T2DM)

Screening is defined as the process of identifying asymptomatic individuals who are at high risk of a specific disorder and require further investigation or action. It is initiated by health care provider and not by a patient's request for help on account of a specific complaint. The screening will gives benefit to the individuals who are being screened. (WHO, 2003).

Screening in asymptomatic populations is done when the disease imposed a significant health problem and brought a significant burden on the population. Screening will be useful when the natural history of the disease is understood and the preclinical asymptomatic stage can be diagnosed with the available, acceptable and reliable test. Early detection lead to early treatment that benefits and cost effective compared to those delayed treatment. Screening should be a continous effort and not merely a single one-time effort with available facilities and resources to treat newly diagnosed cases (WHO, 2003)

It is important to screen and diagnose the disease when an individual transitions from being disease free to the asymptomatic state is able to reduce the long term sequelae. Implementation of lifestyle modification and pharmacological

interventions will be able to reduce health-care expenditures ultimately (Abid et al., 2016). Diabetes can lead to long term effects of blindness, renal disease, and amputations more than any other preventable diseases. The estimated burden on the health-care system in Malaysia is around 245 billion ringgit (National Diabetes Statistics Report 2017).

In United State Of America, the screening is done by taking fasting blood glucose, oral glucose tolerance test and A1c. The level of fasting blood glucose $\geq$ 126 mg/ dL is diagnostic for diabetes and required for retesting. A 75-g oral glucose tolerance test will be done and screening is positive if a 2-hour postload value of $\geq$200 mg/dL. Values $\geq$200 mg/dL are repeated on a different day to confirm diagnosis of diabetes. The A1c test is also a valuable tool for diagnosis of diabetes. The level of A1c > 5.6 indicates impaired glucose tolerance. (ADA, 2002). In Tunisia, a study reported that Hba1c is a reliable tool for screening DM and pre-diabetes in a high risk population (Oueslati *et al.*, 2017).

In Malaysia, the guideline of T2DM management 2015 recommended venous or capillary blood using glucometer, followed by fasting blood glucose or random blood glucose, oral glucose tolerance test (OGTT) and A1c as the screening method (Ministry of Health, 2016). In general population screening should includes individuals at risk and the specific high-risk population. These include the symptomatic individuals which has symptoms suggestive of diabetes (tiredness, lethargy, polyuria, polydipsia, polyphagia, weight loss, pruritus vulvae, balanitis) as well as the asymptomatic individuals. Other high risk group are adults who are overweight or obese (BMI $\geq$23 kg/m^2 or have a waist circumference of $\geq$80 cm for

women and ≥90 cm for men), and have one or more of the following additional risk factors for diabetes:

i. First-degree relative with diabetes
ii. History of cardiovascular diseases
iii. Hypertension (BP ≥140/90 mm Hg or on therapy for hypertension)
iv. Impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing
v. High density lipoprotein (HDL), total cholesterol <0.9 mmol/L or triglycerides (TG) >2.8 mmol/L
vi. Other clinical conditions associated with insulin resistance (e.g. severe obesity and acanthosis nigricans)
vii. Women who delivered a baby weighing ≥4 kg or were diagnosed with gestational diabetes mellitus (GDM)
viii. Women with polycystic ovarian syndrome (PCOS)
ix. Physical inactivity
x. Special populations (those who are receiving antiretroviral therapy or atypical antipsychotic drugs. (Ministry of Health, 2016)

2.3 Diagnosis Of Types 2 Diabetes Mellitus

T2DM may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) or A1C criteria (Table 2.3.1). Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic testing. The

similar tests may also be used to screen for and diagnose prediabetes and diabetes individuals (ADA, 2018).

Table 2.3.1 Criteria for diagnosis of diabetes

FPG ≥ 7.0 mmol/L (126mg/dL). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥ 11.1 mmol/L (200 mg/dL) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
Random plasma glucose ≥11.1 mmol/L (200 mg/dL). In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

Source:(ADA, 2018)

In 2011 the WHO Consultation had concluded that HbA1c can be used as a diagnostic test for diabetes. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. In an asymptomatic person, the diagnosis of diabetes should not be made from a single abnormal plasma glucose or HbA1c value. The HbA1c or plasma glucose test should be repeated and the result with a diabetic range value is required, either fasting, from a random (casual) sample, or from the oral glucose tolerance test (OGTT). It is advisable to use one test or the other but if both glucose and HbA1c are measured and both are “diagnostic” then the diagnosis is confirmed. If only one of the test is abnormal, a repeat test is necessary to confirm the diagnosis (WHO, 2011)

The Malaysian Clininal Practice Guidelines of management T2DM 5th edition 2015 stated that the diagnosis of T2DM should be confirmed by the measurement of fasting or random venous plasma glucose or A1c level. Prior to therapy initiation, the venous sample for plasma glucose and A1c should be taken first. The diagnostic value for type 2 diabetes mellitus based on fasting venous plasma glucose are ≥7.0 mmol/L, and for the random venous plasma glucose ≥11.1 mmol/L. In symptomatic individual, one abnormal glucose value is diagnostic however, in asymptomatic individual, 2 abnormal glucose values are required prior to the diagnosis of T2DM (Table 2.3.2).

Table 2.3.2 Diagnostic Values for Glucose Intolerance and T2DM Based on OGTT.

OGTT Plasma Glucose Values (mmol/L)		
Category	0-hour	2-hour
Normal	<6.1	<7.8
IFG	6.1–6.9	
IGT	-	7.8–11.0
DM	≥7.0	≥11.1

• IFG = impaired fasting glucose; IGT = impaired glucose tolerance; DM = diabetes mellitus
• In adolescents, the glucose load in OGTT is based on body weight (1.75 g/kg body weight maximum of 75 g).

Source:(Ministry of Health, 2016)

Once the first fasting venous plasma glucose ≥7.0 mmol/L or random venous plasma glucose ≥11.1 mmol/L, the patient is advise to perform oral glucose tolerance test (OGTT) where patient will be given 75g of glucose load prior to the blood taking.The normal value of OGTT 0-hour <6.1mmol/L and 2-hour <7.8mmol/L. The OGTT value for impaired fasting glucose (IFG) value of 6.1 to 6.9mmol/L and impaired glucose tolerance 2-hour post pandrial value of 7.8-11.0 mmol/L. The diagnostic value for type 2 diabetes mellitus based on OGTT are 0-hour ≥7.0 mmol/L, and 2-hour ≥11.1 mmol/L (Table 2.3).

Table 2.3.3 Dianostic Value for T2DM Based on Venous Plasma Glucose.

	Fasting	Random
Venous Plasma Glucose	≥7.0 mmol/L	≥11.1 mmol/L

• In symptomatic individual, one abnormal glucose value is diagnostic.
• In asymptomatic individual, 2 abnormal glucose values are required.
Source:(Ministry of Health, 2016)

The diagnosis of diabetes can be confirmed by taking the A1C. The normal A1c value are <5.6% (38 mmol/mol) .The diagnostic value for pre diabetes range from 5.6-6.2% (38-44mmol/mol) and for the diabetes ≥6.3% (45 mmol/mol). If the first positive test for asymptomatic patients, then the A1c should be repeated after 4 weeks. In symptomatic patients, a single positive test is sufficient for the diagnosis of diabetes.(Table 2.4)

Table 2.3 4 Diagnostic Values for Pre-diabetes and T2DM Based on A1c

	Normal	Pre-diabetes	Diabetes
A1c	<5.6% (38 mmol/mol)	5.6-6.2% (38-44mmol/mol)	≥6.3% (45 mmol/mol)

• A repeat A1c should be done 4 weeks after the first positive test for asymptomatic patients.
• For symptomatic patients, a single positive test is sufficient.
Source (Ministry of Health, 2016).

2.4 Vascular complications in type 2 diabetes mellitus

Type 2 diabetes mellitus patients have insulin resistance and usually relative, rather than absolute, insulin deficiency. Prolonged period of hyperglycemia is associated with long-term damage and multiple organ systems failure mainly affecting the eyes, nerves, kidneys, and the heart. (DiabetesCare, 2016)

2.4.1 Pathohysiology of Macrovascular and Microvascular complications

The function macrovessels is to supply blood to organs, otherwise microvessels play important roles in maintaining blood pressure and delivery of

nutrient by regulating systems that control the vascular permeability and myogenic responses that can adapt blood flow according to local metabolic needs. The pathognomonic changes in the microvasculature induces by diabetes, affect the capillary basement membrane by increasing thickness of the glomerular arterioles, retina, myocardium, skin, and muscle, then will leads to the development of diabetic microangiopathy. This thickening will alter the vessel function, and later it will cause multiple clinical problems such as hypertension, wound healing delay, and tissue hypoxia. Neovascularization in the vasa vasorum may interconnect macro-and microangiopathy, causing platelet rupture and atherosclerosis. (Orasanu and Plutzky, 2009).

Atherosclerosis is one of the underlying cause for development of cardiovascular disease. It involves a pathologic process initiated at endothelial dysfunction, by retention, accumulation, and oxidative modification of lipoprotiens in arterial wall (Chapman, 2007). Thomaseth study stated that micro and macrovascular complications has strong association with level of systolic and diastolic blood pressure (Thomaseth *et al.*, 2008). The main pathology effects of uncontrolled DM involves the vasculature which involving both microvascular and macrovascular complications (Orasanu and Plutzky, 2009). The underlying pathogenic mechanisms for the development of diabetic nephropathy involve the generation of reactive oxygen, accumulation of advanced glycation end product, and activation of intracellular signaling molecules such as protein kinase C (Trevisan *et al.*, 2006).

2.4.2 Prevalence of vascular complications

The prevalence of diabetic nephropathy was higher in African Americans, Asians, and Native Americans as compared to the Caucasians(Gross *et al.*, 2005). A study done at Hospital Putrajaya Malaysia showed the prevalence of microvascular complications are 75% which is much higher when compared to macrovascular complications which is 29% (Hussein *et al.*, 2015). The most common complications in Malaysia are nephropathy (7.8%), retinopathy (6.7%), and ischemic heart disease (5.3%) (Ministry of Health, 2013). This showed an almost similar pattern in Bangladesh where the most common microvascular complications are nephropathy (21.3%), neuropathy (16.8%), and retinopathy (12.3%) (Khanam *et al.*, 2017).

2.4.3 The associated factors to the development of vascular complications

Age, body mass index (BMI) and triglyceride are the associated factors to the development of vascular complications (Abougalambou *et al.*, 2010). A London study stated that obesity, hypertension and lipid abnormalities are the risk factor for the development of cardiovascular diseases (Jonathan Valabhji *et al*. 2002). The risk of diabetic complications was strongly associated with raised blood pressure in T2DM patients, thus a reduction in systolic blood pressure by 10 mm Hg was reported to be able to reduce the risk of any end point related to diabetes upto 12% (Adler *et al.*, 2000). Retinopathy or nephropathy is associated with an increased in risk for cardiovascular events in type 2 diabetes mellitus patients in New York, USA (Rosenson *et al.*, 2011).

Another study in Italy among type 2 diabetes mellitus with micoalbuminuria and hypertension, stated that the glomerular filtration rate (GFR) is determined by

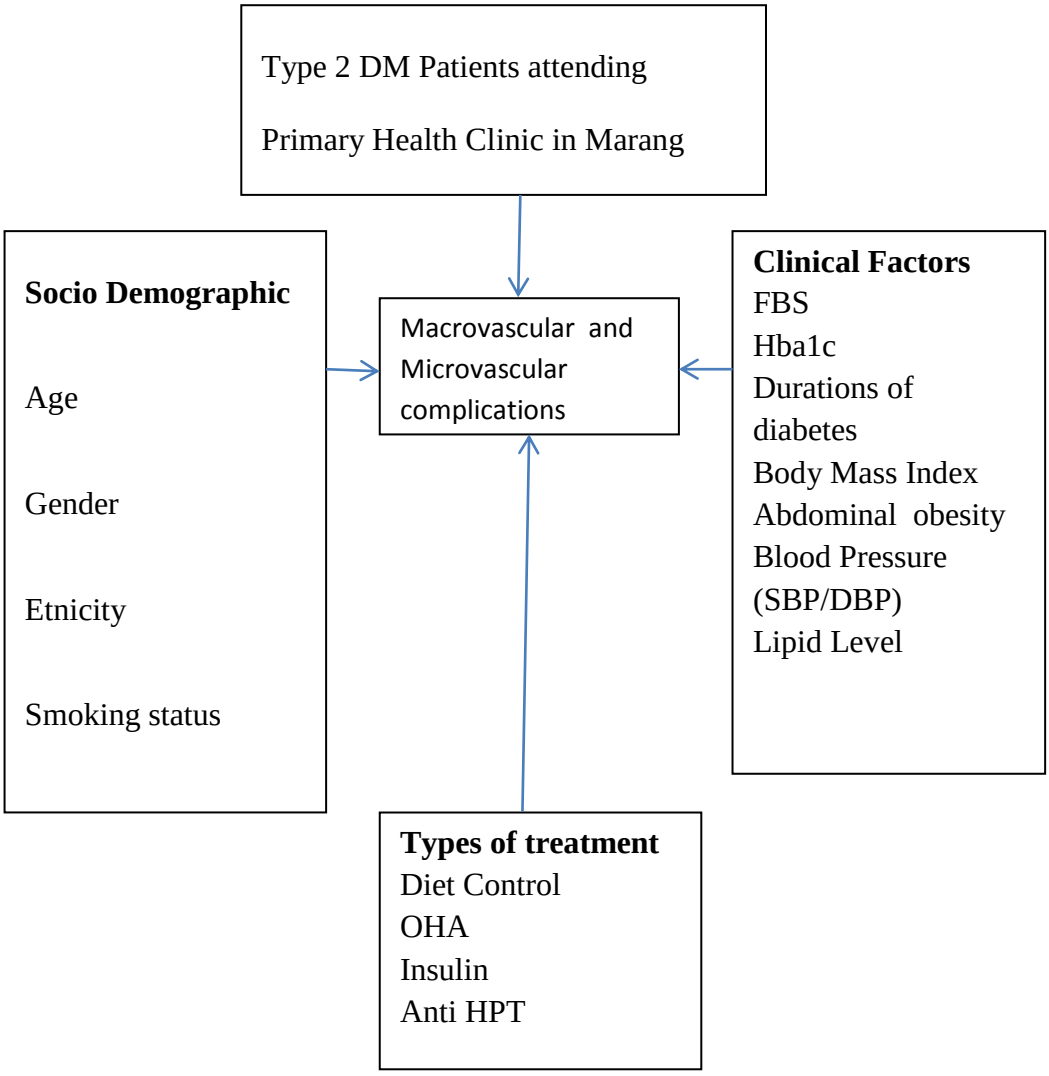
glycemic control and blood pressure control (Thomaseth *et al.*, 2008). Ravid *et al.* (1998) shows that the combination of high blood pressure with moderately elevated levels of total cholesterol and hemoglobin A_{1c} will leads to the progression of diabetic nephropathy and arteriosclerotic cardiovascular disease.

Another study conducted in Hong Kong stated that coronary artery disease, cerebrovascular disease and nephropathy in T2DM patients is related to plasma lipid alteration (Chan *et al.*, 2011). In the World Health Organization Multinational Study of Vascular Disease in Diabetes, the incidence of myocardial infarction (MI) and death from cardiovascular disease (CVD) are associated with retinopathy (Fuller *et al.*, 2001). In the Atherosclerosis Risk in Communities study, retinal microvascular abnormalities and generalized arteriolar narrowing was associated with increased incidence of clinical stroke (Yatsuya *et al.*, 2010). A study done in Faisalabad, Pakistan stated that the prevalance of T2DM are more in age group of 50-59 years old (Muhammad Hassan *et al.*, 2010). This has also been explored in prior studies by prevalance and incidence of diabetes is directly related to increasing age (Doria *et al.*, 1999)

Previous studies have shown that the development of diabetic retinopathy are significantly associated with HbA1c, BMI, duration of diabetes and microalbuminuria (Chawla *et al.*, 2016). Mohd Ali *et al.*, 2016, reported that age, duration of DM, presence of nephropathy and peripheral neuropathy are the predictors of proliferative diabetic retinopathy in T2DM. A study done in Tehran, Iran states that increased in development of retinopathy with hypertension, since hypertension coexisted in 33.5% of patients with retinopathy (Heydari *et al.*, 2010).

Early initiation of insulin is recommended as one of the prevention of vascular complications in T2DM patients especially for patients who have poor glycaemic control at diagnosis(Ministry of Health, 2009).

2.5 Conceptual framework



Chapter 3: METHODOLOGY

3.1 Research design

This study is cross sectional study using surveillance data

3.2 Reference population

Type 2 Diabetes Mellitus patients in Marang, Terengganu

3.3 Source population

Type 2 Diabetes Mellitus patient registered in NDR from January 2010 till December 2016.

3.4 Inclusion Criteria

Data of Type 2 Diabetes Mellitus patients registered in NDR from January 2010 till December 2016.

3.5 Exclusion Criteria

Data with any missing variable from NDR.

3.6 Sample size calculation

Objective 1 : To determine the proportion of vascular complications, the sample size will be calculated using the single proportion formula.

$$n = \left(\frac{Z_{\alpha}}{d} \right)^2 * P(1 - P)$$

Zα = 1.96 . ***α***=0.05 (95% Condfidence Interval)
The ***d*** = precision 0.05
The ***P*** = prevalance of vascular complications in Malaysia
(Ministry of Health, 2013)

Table 3.6 1 The value of proportion of vascular proportions

Variable	P	n	n +20% missing data
Nephropathy	0.78	263	315
Retinopathy	0.67	339	406
IHD	0.53	382	458
CeVD	0.13	173	207
Diabetic Foot Ulcer	0.12	162	194
Amputation	0.09	125	150

Objective 2: To describe trend of newly detected vascular complications by year.

All data NDR from January 2010 till December 2016 were used to plot the trend.

Objective 3: To describe association between presence of hypertension and dyslipidemia in type 2 diabetes mellitus with development of vascular complications. The sample size will be calculated using PS Sofware for dichotomous 2 proportion. The value of proportion of vascular complication in group with no event variable of interest (Po) is taken from previous study (Table 3.6)

Table 3.6 2 The value of proportion of vascular complications in relation to hypertension and dyslipidemia

Variable	Po	P1	m	n	n = nx2+20%	Study
HPT only	0.36	0.63	1	53	123	M.Hassan et al. 2010
Dyslipidemia only	0.5	0.20	1	38	91	Tseng L.N. et al. 2012
HPT and Dyslipidemia	0.5	0.21	1	42	98	Tseng L.N. et al. 2012

P1= estimated proportion of vascular compliations in expose group
Po= proportion of vascular complications in non expose group
This study is a cross sectional study, m=P1:P0 = 1, α=0.05, power=80%

Therefore 500 data was extracted from NDR considering the biggest sample size estimation for objective 1.

3.7 Sampling Method

Simple random sampling is done using Microsoft excel program NajibMY4.0. The data from NDR with the selected number will be used for this study to answer objective 1 and 3.

3.8 Study area, Time & Duration

Study Location: Marang, Terengganu

Study duration: March 2018- April 2018

3.9 Research tool & materials

All data of registered T2DM cases from January 2010 till December 2016 was obtained from the Ministry of Health, Malaysia through National Diabetic Registry; an online database system for reporting Diabetic cases from Non Communicable Disease Control(NCD) Unit.The data was formated in Microsoft Excel later extracted into the data collection form (Appendix 1). Variables collected were:

a) sex

b) Ethnicity

c) Age

d) BMI

e) SBP

f) DBP

g) HbA1c

h) Types of vascular complications and

j) Co morbidity – Hypertension and dyslipidaemia

3.10 Operational definition

i. Vascular complications:

Any NDR variable such as retinopathy nephropathy, Ischaemic heart disease, cererobvascular disease, diabetic foot ulcer, amputation labelled as 'yes'.

ii. Retinopathy:

In NDR the variable retinopathy is labelled as 'yes'. It indicate the presence of retinal haemorrhages, exudates and macular edema. A non-mydriatic fundus camera was used as a screening tool for diabetic retinopathy based on two field fundus photo (central and peripheral) assessment. The initial assessment should be conducted at the time of diagnosis of T2DM and annually.

iii. Nephropathy:

In NDR the variable nephropathy is labelled as 'yes'. The diagnosis of diabetic nephropathy was made clinically by the presence of proteinuria (either microalbuminuria or overt proteinuria) at least three consecutive readings per year and or serum creatinine>130mmol/L and/or GFR<60mil/min.The serum creatinine was used to estimate GFR and stage the level of chronic kidney disease(CKD).

iv. Ischaemic heart disease (IHD):

In NDR the variable the ischemic heart disease is labelled as ‘yes’. It was diagnosed by documented angina symptoms and confirmed by electrocardigraph(ECG).

v. Cererobvascular disaease :

In NDR the variable cerebrovascular disease is labelled as ‘yes’. It was the presence of any sign and symptoms of body weakness or any history of hospital admission for cerebrovascular disease.

vi. Diabetic foot ulcer:

In NDR the variable diabetic foot ulcer and amputation is labelled as ‘yes’. Diabetic foot ulcerations are define as any wound or ulcer noted at diabetic patients’ foot.

vii. Amputation:

In NDR the variable amputations is labelled as ‘yes’. It is define as any surgical amputation done on patients limbs secondary to diabetes.

viii. Hypertension :

Variable comorbidity HPT ‘yes’.

ix. Dyslipidaemia :

Variable comorbidity Dyslipidaemia ‘yes’.

x. HbA1c:

The latest HbA1c data entered for each patient.

3.11 Data collection method:

This study involved secondary data collection from National Diabetic Registry. The required information was extracted anonymously and recorded in data collection form (Appendix 1).

3.12 Statistical analysis

Data were entered and analysed using the Statistical Program for Social Sciences (SPSS version 24). Descriptive statistics will be used to summarise the socio-demographic characteristics of subjects. Numerical data will be presented as mean and standard deviation. Categorical data will be presented as frequency and percentage.

The percentage of type vascular complications was computed by dividing the total number of cases for each complication by the total number of data multiplied by 100. Trend of newly detected vascular complications by year was illustrated was presented using line graph with percentage of patients with vascular complications as the Y axis, and number of newly diagnosed as X axis.

The association between the presence of hypertension and dyslipidaemia in with the presence of vascular complications were tested using simple and multiple logistic regression. The dependent variable was the presence or absence of vascular complications. The independent variable was the presence of hypertension and

dyslipidemia. The multivariable regression model was performed by adjusting for other possible confounders which were age, sex, ethnicity, HbA1c and body mass index. Significant variables or variables with p value less than 0.25 in simple logistic regression were used in variable selection for the multiple logistic regression. Preliminary main model was obtained from forward LR and backward LR method. Correlation matrix showed that there are weak correlation between variable, hence it indicate no multicolinearity was present in the model. All plausible two-way interaction were checked betweeen independent variables. Model fitness was tested by Hosmer-Lemeshow test, classification table and reciever operation characteristic (ROC) curve. The Hosmer Lemeshow test of p-value > 0.005 was taken as not significant, which indicate that the model was fit. The findings of final model were presented with adjusted odds ratio(OR), its 95% confidence interval(CI) and corresponding P-value. The level of significance was set at 0.05. The recommended area under ROC curve is at least 0.70.

3.13 Ethical consideration

This study was approved by the National Medical Research Register (NMMR) of MOH Malaysia with ethical approval number: NMRR-17-3277-39113, and approved by the Human Research Ethics Committee of USM (JEPeM), JEpem Code: USM/JEpem/17120696.

1. **Privacy and confidentiality**

All data was extracted and entered in SPSS software as anonymous data. Only research team members can access the data. Data will be presented as grouped data

and will not identify the responders individually. Permission for access into database will be obtained from the State Health Director of Terengganu.

2. **Declaration of absence of conflict of interest**

The authors have no conflict of interest on the collection and applicability of the data.

3. **Community sensitivities and benefits**

This study preserved confidentiality of collected data surveillance and may facilitates the health care plan in reducing morbidity and mortality related to T2DM.

3.14 Flow chart of study

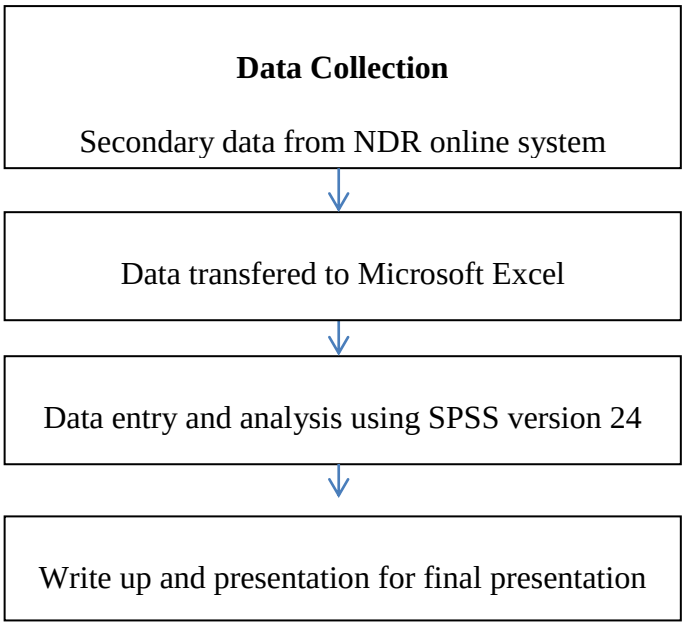


Figure 3.14: Flow chart of study