ASYMPTOMATIC PERIPHERAL ARTERIAL DISEASES AND ITS ASSOCIATED RISK FACTORS AMONG TYPE 2 DIABETES MELLITUS PATIENTS IN HOSPITAL USM

DR MOHD FARHAN SHARAFUDDIN BIN MOHD

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR MASTER OF MEDICINE

(INTERNAL MEDICINE)

UNIVERSITI SAINS MALAYSIA

2022

ACKNOWLEDGMENT

In the name of Allah, Most Gracious and Most Merciful.

Praise upon Allah for His blessing and grace; I have completed this dissertation. I am deeply thankful to my lecturers from the Department of Internal Medicine Hospital Universiti Sains Malaysia for their teaching, guidance, encouragement, and motivation throughout the Master of Medicine journey.

Special thanks to my dear and superb supervisor, Associate Prof Dr Wan Mohd Izani Wan Mohamed for his continuous encouragement, support, and patience throughout my journey to complete this dissertation. Without his support and guidance, I do not dare to think I would complete this journey smoothly and timely.

Besides my advisors, I would like to express my appreciation to my family, especially my lovely parents, Mohd bin Jusoh and Salamah binti Mohammed. They raised, supported, taught, and loved me wholeheartedly. They had sacrificed all their endless efforts to endure my future and provide me with the opportunity to pursue my dream of becoming a better person. Thank you for your support to my one and only soul partner, Mas Suria binti Mat Daud and my princess Hawa Ibtisam.

Finally, I would like to say my sincerest gratitude to my fellow friends and everyone who has contributed, supported and encouraged me directly and indirectly throughout this colorful period. May Allah bless every single one of you with the best rewards.

Mohd Farhan Sharafuddin bin Mohd

TABLE OF CONTENTS

LIST OF ABBREVIATION

ABI	Ankle brachial index
PAD	Peripheral arterial disease
T2DM	Type II Diabetes mellitus
HbA1c	Glycated haemoglobin test
HUSM	Hospital Universiti Sains Malaysia
BMI	Body mass index
HPT	Hypertension
HLP	Hyperlipidaemia
CKD	Chronic Kidney Disease
EGFR	Estimated glomerular filtration rate
IHD	Ischemic heart disease
CVA	Cerebrovascular accident

ABSTRAK

Pengenalan

Penyakit arteri periferal [PAD] adalah manifestasi penyakit aterosklerosis secara sistemik dan dikaitkan dengan peningkatan risiko kematian dan komplikasi iskemia. PAD adalah punca utama morbiditi dan kematian dalam kalangan penduduk diabetes. Pengesanan PAD di kalangan pesakit T2DM memberikan peluang untuk memulakan pencegahan sekunder dengan memulakan pengubahsuaian faktor risiko aterosklerosis, dan dengan itu mengurangkan risiko komplikasi kardiovaskular. Bacaan Ankle Brachial Index [ABI] dengan ultrasound Doppler ialah kaedah pemeriksaan piawai untuk pengesanan aterosklerosis dalam pesakit PAD. Kajian ini menentukan penilaian kadar PAD asimptomatik dan faktor risiko yang berkaitan untuk pesakit di bawah Klinik Diabetik HUSM.

Kaedah

Ini adalah kajian keratan rentas prospektif dan deskriptif 159 pesakit yang mejalani rawatan di klinik Diabetes HUSM antara Jun 2021-November 2021. Ujian ABI dilakukan dalam semua subjek untuk mengesan PAD yang tidak mempunyai gejala PAD. Nilai ABI <0.90 menunjukkan kehadiran PAD. Analisis regresi logistik berganda dibuat antara pembolehubah bebas dan kehadiran ABI<0.90.

Keputusan

Sampel akhir adalah 159 pesakit yang pengukuran ABI dilakukan. Purata umur 62.79 tahun, terdiri daripada 105 (66.0%) lelaki dan 54 (34.0%) perempuan di mana 30 (18.9%) memperoleh ABI<0.90. Regresi Logistik Berbilang telah dilakukan untuk kesemua 5 pembolehubah tidak bersandar, iaitu umur, IHD, HLP, CVA dan LDL. Hanya 2 pembolehubah

yang signifikan iaitu IHD (OR 4.56 95% CI 1.41, 13.77 p=0.007)) dan HLP (OR 6.71 95% CI 2.47, 18.25 p=<0.001)

Konklusi

Prevalens PAD tanpa gejala di kalangan pesakit diabetes adalah 18.9%. (ABI <0.90). Kehadiran penyakit jantung iskemia dan hiperlipidemia yang dikaitkan dengan PAD. Ujian ABI sepatutnya menjadi amalan biasa di klinik diabetes, terutamanya pada pesakit yang mengidap penyakit jantung iskemik dan hiperlipidemia

Kata kunci: *ABI, PAD, T2DM, penyakit jantung iskemia, hiperlipidemia*

ABSTRACT

Background

Peripheral arterial disease [PAD] is a common manifestation of systemic atherosclerosis and is associated with an increased risk of death and ischemic events. PAD is a significant cause of morbidity and mortality the among diabetic population. Detection of PAD among T2DM patients presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, thus reducing the risk of cardiovascular complications. Ankle brachial index [ABI] by ultrasound Doppler is the standard screening method for detecting atherosclerosis in PAD patients. This study is determined to evaluate the proportion of asymptomatic PAD and associated risk factors for patients under Diabetic Clinic HUSM.

Methodology

This prospective and descriptive cross-sectional study included 159 diabetic patients who were regularly followed up in the Diabetic clinic HUSM between June 2021-November 2021. An ABI test was performed in all subjects for detection of PAD who did not have symptoms of PAD. An ABI value <0.90 indicates presence of PAD. A multiple logistic regression analysis was made between independent variables and the presence of an ABI<0.90.

Results

The final sample was 159 patients for whom ABI measurement was performed. The average age of 62.79 years, comprising 105 (66.0%) males and 54 (34.0%) females from which 30 (18.9%) obtained an ABI<0.90. Multiple Logistic Regression was done for 5 independent variables which are age, IHD, HLP, CVA and LDL. 2 variables were significant which were

the IHD (OR 4.56 95% CI 1.41, 13.77 p=0.007)) and HLP (OR 6.71 95% CI 2.47, 18.25 p=<0.001)

Conclusion

The proportion of asymptomatic PAD among diabetes patients was 18.9%. (ABI <0.90). The presence of ischemic heart disease and hyperlipidaemia is significantly associated with PAD. The ABI test should be a regular routine in the diabetic clinic, especially on patients with ischemic heart disease and hyperlipidaemia.

Keywords: *ABI, PAD, T2DM, ischemic heart disease, hyperlipidemia*

CHAPTER 1: INTRODUCTION

Peripheral arterial disease [PAD] is a common manifestation of systemic atherosclerosis and is associated with an increased risk of death and ischemic events. PAD may be underdiagnosed as it is frequently asymptomatic or accompanied by exertional leg symptoms other than claudication. A diagnosis of PAD holds important prognostic value as a marker of increased mortality and vascular event risk. Still, methods to identify PAD at an early stage are not widely used. (1)

PAD is a major cause of morbidity and mortality among the diabetic population. As PAD becomes symptomatic, there is a decrease in quality of life associated with functional impairment. The development of intermittent claudication can significantly reduce walking speed and distance, resulting in a progressive loss of function and long-term disability. (2). Detection of PAD among T2DM patients presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, and thus reducing the risk of cardiovascular complications. (3). A failure to diagnose PAD misses this opportunity. Estimation of ankle brachial index [ABI] by ultrasound Doppler is the standard screening method for detecting atherosclerosis in PAD patients.

Screening for asymptomatic PAD among high-risk groups has been recommended by major PAD authorities to increase early diagnosis. Screening for PAD using the ankle-brachial index can detect asymptomatic patients. A diagnosis of PAD holds important prognostic value as a marker of increased mortality and vascular event risk (4).

A diagnosis of PAD is made by using Doppler ultrasound with sensitivity of 97%, specificity of 81%, and diagnostic accuracy of 85% (5) An ABI < 0.9 is diagnostic of PAD even in asymptomatic patients and can predict morbidity and mortality from cardiovascular diseases (6). Diagnosis of PAD using ABI in an individual has been identified as indirect evidence of having subclinical IHD, CVA, or both. (7) Screening for asymptomatic PAD presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, and thus reducing the risk of cardiovascular complications. A failure to diagnose PAD misses this opportunity. (8)

The proportion of diabetics with PAD has been challenging to determine because of its asymptomatic nature and presence of neuropathy. Early diagnosis of PAD can help patients effectively manage the condition and prevent its long-term sequelae. Higher prevalence of PAD is observed among diabetics who have a predilection for lower limbs (9). It has been hypothesized that the metabolic abnormality in the prediabetic phase predisposes to a more distal and aggressive atherosclerosis. Once diabetes has developed, this process is sped up because of chronic hyperglycaemia, endothelial damage, non-enzymatic glycosylation and polyneuropathy which could lead to impaired vascular remodelling and collateral formation. The risk of lower extremity amputation has been estimated to be 15 times greater in diabetics than in non-diabetics (10).

Literature review on the prevalence rate of PAD among T2DM patients varies from 5–32%. (11). In a local study done at the primary care clinic of a teaching hospital in Kuala Lumpur, Malaysia revealed the overall proportion of PAD was 16% in the diabetic population. (12). A similar study done in India also showed a similar proportion of PAD at 15% among

type 2 diabetics. (13). Another study was done in Northern Ethiopia, the proportion of PAD among type 2 diabetes was higher at 30.7% (9,10).

The risk factors associated with PAD among T2DM, HbA1c, and duration of T2DM were significantly associated with PAD where each 1% increase in HbA1c was associated with 1.9 times (AOR = 1:97, 95% CI (1.03-3.40)) higher odds of developing PAD. A 1-year increase in the age of DM patients was associated with 9% higher odds (AOR = 1:09, 95% CI (1.03-1.16)) of PAD. (10) Meanwhile, a study in Arab reported smoking, hypertension, hyperlipidaemia, as well as advancing age as the risk factors for PAD (14). Besides that, a longer duration of diabetes is also significantly associated with PAD (15). However, previous study in Malaysia found no significant association between age, gender, smoking status, duration of diabetes mellitus, hypertension and dyslipidaemia with PAD (12).

A review study had reported diabetes mellitus (DM) as a major risk factor for PAD, with diabetic patients had two-times odds of having PAD compared to the general population (10). Detection of PAD among T2DM patients presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, and thus reducing the risk of cardiovascular complications. Failure to diagnose PAD misses this opportunity. To our knowledge, there are only limited studies done in Malaysia regarding factors associated with asymptomatic PAD in T2DM patients.

Hopefully, by doing this study in our local centre, more patients with asymptomatic PAD can be identified and necessary action could be taken. Studies have revealed that early detection and intervention of PAD can improve morbidity and mortality from devastating clinical outcomes in patients with T2DM. Hopefully, by doing this study in our local centre,

more patients with asymptomatic PAD can be identified and necessary action could be taken. This is because early identification of risk factors for PAD can help in reducing the prevalence of PAD among T2DM patients, which will prevent life-threatening complications (2, 6).

CHAPTER 2: OBJECTIVES OF STUDY

Main Objective

To evaluate patients with T2DM attending Diabetes clinic in Hospital USM for the presence of asymptomatic PAD

Specific Objectives

1. To determine the proportion of asymptomatic PAD among T2DM patients attending Diabetes Clinic Hospital USM

2. To determine the associated risk factors of asymptomatic PAD among T2DM patients attending Diabetes Clinic Hospital USM

CHAPTER 3: MANUSCRIPT

TITLE: Proportion of asymptomatic Peripheral Arterial Diseases in Type 2 diabetes mellitus and its associated risk factors.

Author:

Mohd Farhan Sharafuddin MOHD[1,2]

[1]School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[2]Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Corresponding author:

Wan Mohd Izani WAN MOHAMED[1,2]

Department of Internal Medicine, School of Medical Sciences Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

e-mail:

Disclosure of finding: none of the authors received any financial support for this study.

ABSTRACT

Background

Peripheral arterial disease [PAD] is a common manifestation of systemic atherosclerosis and is associated with an increased risk of death and ischemic events. PAD is a significant cause of morbidity and mortality the among diabetic population. Detection of PAD among T2DM patients presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification thus reducing the risk of cardiovascular complications. Ankle brachial index [ABI] by ultrasound Doppler is the standard screening method for detecting atherosclerosis in PAD patients. This study is determined to evaluate the proportion of asymptomatic PAD and associated risk factors for patients under Diabetic Clinic HUSM

Methodology

This prospective and descriptive cross-sectional study included 159 diabetic patients who were regularly followed up in the Diabetic clinic HUSM between June 2021-November 2021. An ABI test was performed in all subjects for detection of PAD who did not have symptoms of PAD. An ABI value <0.90 indicates presence of PAD. A multiple logistic regression analysis was made between independent variables and the presence of an ABI<0.90.

Results

The final sample was 159 patients for whom ABI measurement was performed. The average age of 62.79 years, consisting of 105 (66.0%) males and 54 (34.0%) females from which 30 (18.9%) obtained an ABI<0.90. Multiple Logistic Regression was done for those all 5 independent variables which are age, IHD, HLP, CVA and LDL. 2 variables were significant

which were the IHD (OR 4.56 95% CI 1.41, 13.77 p=0.007)) and HLP (OR 6.71 95% CI 2.47, 18.25 p=<0.001)

Conclusion

The proportion of asymptomatic PAD among diabetes patients was 18.9%. (ABI <0.90). The presence of ischemic heart disease and hyperlipidaemia is significantly associated with PAD. The ABI test should be a regular routine the in diabetic clinic, especially on patients with ischemic heart disease and hyperlipidaemia.

Keywords: *ABI, PAD,T2DM, ischemic heart disease, hyperlipidaemia*

INTRODUCTION

Peripheral arterial disease [PAD] is a common manifestation of systemic atherosclerosis and is associated with an increased risk of death and ischemic events. PAD may be underdiagnosed as it is frequently asymptomatic or accompanied by exertional leg symptoms other than claudication. A diagnosis of PAD holds important prognostic value as a marker of increased mortality and vascular event risk. Still, methods to identify PAD at an early stage are not widely used. (1)

PAD is a major cause of morbidity and mortality among the diabetic population. As PAD becomes symptomatic, there is a decrease in quality of life associated with functional impairment. The development of intermittent claudication can significantly reduce walking speed and distance, resulting in a progressive loss of function and long-term disability. (2). Detection of PAD among T2DM patients presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, and thus reducing the risk of cardiovascular complications. (3). A failure to diagnose PAD misses this opportunity. Estimation of ankle brachial index [ABI] by ultrasound Doppler is a standard screening method for detecting atherosclerosis in PAD patients.

Screening for asymptomatic PAD among high-risk groups has been recommended by major PAD authorities to increase early diagnosis. Screening for PAD using the ankle-brachial index can detect asymptomatic patients. A diagnosis of PAD holds important prognostic value as a marker of increased mortality and vascular event risk (4).

A diagnosis of PAD is made by using Doppler ultrasound with sensitivity of 97%, specificity of 81%, and diagnostic accuracy of 85% (5) An ABI < 0.9 is diagnostic of PAD even in asymptomatic patients and can predict morbidity and mortality from cardiovascular diseases (6). Diagnosis of PAD using ABI in an individual has been identified as indirect evidence of having subclinical IHD, CVA, or both. (7) Screening for asymptomatic PAD presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, and thus reducing the risk of cardiovascular complications. A failure to diagnose PAD misses this opportunity. (8)

The proportion of diabetics with PAD has been challenging to determine because of its asymptomatic nature and presence of neuropathy. Early diagnosis of PAD can help patients effectively manage the condition and prevent its long-term sequelae. Higher prevalence of PAD is observed among diabetics who have a predilection for lower limbs (9). It has been hypothesized that the metabolic abnormality in the prediabetic phase predisposes to a more distal and aggressive atherosclerosis. Once diabetes has developed, this process is sped up because of chronic hyperglycaemia, endothelial damage, non-enzymatic glycosylation and polyneuropathy which could lead to impaired vascular remodelling and collateral formation. The risk of lower extremity amputation has been estimated to be 15 times greater in diabetics than in non-diabetics (10).

Literature review on the prevalence rate of PAD among T2DM patients varies from 5–32%. (11). In a local study done at the primary care clinic of a teaching hospital in Kuala Lumpur, Malaysia revealed the overall proportion of PAD was 16% in the diabetic population. (12). A similar study done in India also showed a similar proportion of PAD at 15% among

type 2 diabetics. (13). Another study was done in Northern Ethiopia. The proportion of PAD among type 2 diabetes was higher at 30.7% (9,10).

The risk factors associated with PAD among T2DM, HbA1c, and duration of T2DM were significantly associated with PAD where each 1% increase in HbA1c was associated with 1.9 times (AOR = 1:97, 95% CI (1.03-3.40)) higher odds of developing PAD. A 1-year increase in the age of DM patients was associated with 9% higher odds (AOR = 1:09, 95% CI (1.03-1.16)) of PAD. (10) Meanwhile, a study in Arab reported smoking, hypertension, hyperlipidaemia, as well as advancing age as the risk factors for PAD (14). Besides that, a longer duration of diabetes is also significantly associated with PAD (15). However, previous study in Malaysia found no significant association between age, gender, smoking status, duration of diabetes mellitus, hypertension and dyslipidaemia with PAD (12).

A review study had reported diabetes mellitus (DM) as a major risk factor for PAD, with diabetic patients had two-times odds of having PAD compared to the general population (10). Detection of PAD among T2DM patients presents the opportunity to initiate secondary prevention by instituting atherosclerosis risk factor modification, and thus reducing the risk of cardiovascular complications. Failure to diagnose PAD misses this opportunity. To our knowledge, there are only limited studies done in Malaysia regarding factors associated with asymptomatic PAD in T2DM patients.

Hopefully, by doing this study in our local centre, more patients with asymptomatic PAD can be identified and necessary action could be taken. Studies have revealed that early detection and intervention of PAD can improve morbidity and mortality from devastating clinical outcomes in patients with T2DM. Hopefully, by doing this study in our local centre,

more patients with asymptomatic PAD can be identified and necessary action could be taken. This is because early identification of risk factors for PAD can help in reducing the prevalence of PAD among T2DM patients, which will prevent life-threatening complications (2, 6).

METHODOLOGY

Study design

This study was a prospective design, descriptive and cross-sectional study. Demography data and clinical parameters were taken from eligible participants who consented to join this study. The study was conducted according to the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia.

Participants

A total of 159 consented and eligible participants above 18 years old T2DM patients with asymptomatic PAD were recruited for this study up to November 2021. Participants with symptoms of PAD and/or lower limb deformity/injury/trauma were excluded from this study. The pool of participants was recruited from the Diabetic clinic, Hospital Universiti Sains Malaysia. Demographic and clinical data were collected as below:

1. Demographic data: Age, gender, ethnicity.
2. Clinical parameters: Duration of T2DM, HbA1c, BMI, HPT, HLP, LDL, IHD, CVA, CKD, EGFR.

Study Outcome

The primary outcome was to determine the proportion of asymptomatic PAD in T2DM patients in Diabetic Clinic HUSM. Any associated risk factors with the diagnosis of asymptomatic PAD will be demonstrated in this study.

Study procedure

For ABI measurement procedure, patients were asked to lie down for 10 minutes. The patient's ankle and brachial systolic blood pressures were measured in supine position using a handheld Doppler ultrasound and a sphygmomanometer.

First, the blood pressure cuff is placed on the arm, with the limb at the level of the heart. Ultrasound gel then applied on to the antecubital fossa over the patient's brachial pulse. The transducer of the handheld Doppler is then put on the gel and positioned to maximize the intensity of the signal. Blood pressure cuff is then inflated to about 20 mmHg above the expected systolic blood pressure of the patient.

Once the Doppler signal disappears, the cuff is slowly deflated. When the Doppler signal re-appears, the pressure of the cuff is equal to the brachial systolic pressure. Brachial systolic pressure is then recorded for each arm. The process is repeated on both legs for systolic pressure measurement of the posterior tibialis artery (PTA) and dorsalis pedis artery (DPA).

The ABI value is determined by taking the higher pressure of the 2 arteries at the ankle, divided by the brachial arterial systolic pressure, and the lowest value was recorded as ABI. The calculated ABI values are recorded in 2 decimal places. ABI reading will be measured by the principal investigator, PI who was trained to do the ABI measurement using Huntleigh Dopplex ABI Ankle Brachial Index Kit. The result of ABI is immediately informed to participants.

$$\text{ABI} = \frac{\text{Highest systolic pressure (PTA/DPA}}{\text{Highest brachial systolic pressure}}$$

Huntleigh Dopplex ABI Ankle Brachial Index Kit

Statistical Analysis

All statistical analyses were performed using SPSS version 24. Descriptive analysis was used to characterise the socio–demographic characteristic of subjects. The significant clinical factors associated with PAD were obtained by comparing specific patient characteristics between those with PAD and those without. The strength of association of individual factors for PAD is evaluated by multiple logistic regression analysis with forward stepwise strategy by finding the odds ratio confidence interval (CI) 95% with ABI <0.9 as positive outcome and ABI ≥0.9 as negative outcome. A p-value < 0.05 will be used as the level of significance.

Ethical approval

This study was approved by the Research Ethics Committee (Human) School of Medical Sciences (PPSP) University Sains Malaysia JEPeM Code: USM/JEPeM/22010001

RESULTS

Demographic Characteristics of Patients

The socio-demographic characteristics that were considered in this study were age, age group, sex, ethnicity, smoking status and BMI amongst T2DM patients who undergo treatment under diabetic clinic in Hospital USM, Kelantan. The overall mean age of the patients was 62.79 years, with the standard deviation (SD) of 10.63. Of all the age categories, the highest category was the age ≥ 61 years with 101 (63.6%) patients followed by the age group between 41–60 years and 21–40 years with 53 (33.3%) and 5 (3.1%) patients, respectively. According to the gender, males contributed to the highest number with 105 (66.0%) of the patients whereas 54 (34.0%) female patients.

Besides, the highest number of patients was Malay with 118 (74.2%) followed by Chinese 25 (15.7), and Siamese with 16 (10.1%) of the patients. The mean BMI of the patients was 25.99, with the SD of 4.04. Most of the patients, 80 (50.3%) were pre-obese followed by obesity class 1 with 42 (26.4%) and normal weight of 31 (19.5%) of the total number of patients. Out of all the number of the patients, only 7 (4.4%) were smokers while 9 (5.7%) of them were ex-smokers. The distributions of these variables were shown in Table 1.

Patients' Comorbidities

Patients' comorbidities that were included in this study were hypertension (HPT), ischemic heart disease (IHD), hyperlipidaemia (HLP), and cerebrovascular accident (CVA) diseases. Based on data collected, 105 (66.0%) patients were present with hypertension, while 54 (34.0%) patients were not. For ischemic heart disease, 30 (18.9%) patients were having this disease while 129 (81.1%) patients were not. Hyperlipidaemia was presented in 66 (41.5%) patients, while the rest 93 (58.5%) patients were free from this medical condition. Meanwhile, out of 159 patients, only 10 (6.3%) patients were cerebrovascular accident, while the rest 149 (93.7%) patients were free from CVA on presentation. The distribution of patients' comorbidities was described in Table 2.

Patient's Laboratory Reports

The distribution of patient's lab report is shown in Table 4.3 below. The mean and SD for the duration of T2DM was 15.12 (5.60). Most of the patients had more than 10 years of T2DM with 122 (76.7%) of the total patients while 37 (23.3%) of them were experience T2DM within 1- 10 years. The mean and SD for LDL and HbA1c level was 2.67 (0.84) and 8.59 (1.67) respectively. Besides, it was observed that 145 (91.2%) of the patients were having ≥ 7.0% of the HbA1c level whereas only 14 (8.8%) of them with < 7.0% HbA1c level as described in Table 3.

Patient's Clinical Outcomes

The distribution of patient's clinical outcomes is shown in Table 4 and Table 5. The mean and SD for systolic pressure ankle for right and left side was 141.92 (20.76) and 143.36 (21.11) respectively. The reported mean and SD for systolic pressure brachial of right and left side was 144.15 (15.49) and 145.03 (16.51) respectively. Besides, it was noted that the mean and SD for ABI ratio of right and left side was 0.98 (0.12) and 0.99 (0.12) respectively. The mean for overall ABI was reported as 0.95 with the SD of 0.09.

Most of the patients, 129 (81.1%) were having a normal value of ABI while 30 (18.9%) of the patients were having overall ABI below 0.9. Additionally, 129 (81.1%) of the patients were absence of PAD while 21 (13.2%) of them were having mild PAD and about 9 (5.7%) of the patients was observed with moderate PAD while none of them were having severe PAD., as described in Table 4,5.

The Risk Factors That Associated With Asymptomatic PAD In T2DM

Multiple Logistic Regression was used to predict the risk factors that associated with the asymptomatic PAD amongst T2DM patients in the diabetic clinic of Hospital USM, Kelantan. The risk factors that were included in the analysis were the age of patients, gender, ethnicity, smoking status, BMI, HbA1c, HPT, IHD, HLP, CVA, T2DM duration, HbA1c, LDL, creatinine and eGFR. The data exploration and cleaning were done to check for all numerical and categorical variables involved and to screen for any missing values. Descriptive statistic was done for all independent variables and the result was summarised in the Table 6 and 7.

Simple Logistic Regression

Univariable analysis was done for all predictor factors to screen for important independent variables. The factors with p-value < 0.25 or clinically or biologically important were selected as a potential candidate in Multiple Logistic Regression step. Out of all independent variables, only 5 independent variables were significant with p-value < 0.25 and were eligible for the next analysis, which was the variable selections. They were age, IHD, HLP, CVA and LDL. The result was showed in the Table 8.

Multiple Logistic Regression

Multiple Logistic Regression was done for those all 5 independent variables. P-value of 0.05 was the cut-off point for the selection criteria. Out of 5 independent variables, only 2 variables were significant, which were the IHD (Odds ratio 4.56 (1.51, 13.77), p-value 0.007 and HLP (Odds ratio 6.71 (2.47, 18.25), p-value <0.001. The result was showed in the Table 9.

Multicollinearity & Interaction

Multicollinearity between the independent variable was checked by comparing correlation matrix of regression coefficient, standard error, p-value and 95% confident interval. No multicollinearity was found, as there was a poor correlation between those variables. Moreover, small standard error, p-value which closed to zero and a bit narrow confidence interval observed in all independent variables.

The significant independent variables also were tested for all possible two-way interaction term one at a time to check if there were significant interactions between those variables. The result showed that no interaction was found among the significant predictor factors in preliminary main effect model. The interaction term with Wald test p-value was 0.318 which was greater than 0.05. Therefore, no interaction term was needed to be included in the model. The preliminary final model was obtained. The results of biologically plausible two-way interaction term and multicollinearity are presented in Table 10.

Interpretation

Risk factors that associated with PAD in asymptomatic peripheral arterial diseases study amongst T2DM patients in a diabetic clinic of Hospital USM, Kelantan by Simple & Multiple Logistic Regression (n=342) were IHD with crude odds ratio 2.20 (0.89. 5.48), p-value 0.089, adjusted odds ratio 4.56 (1.51, 13.77), p -value 0.007 and HLP with crude odds ratio 4.36 (1.82, 10.30), p-value 0.001, adjusted odds ratio 6.71 (2.47, 18.25), p-value <0.001 as described in Table 11

DISCUSSION

PAD is a common macrovascular complication in T2DM patients in which it contributes to initiation and aggravation of diabetic foot ulcer. The detection and diagnosis of PAD are difficult as a large proportion of patients remain asymptomatic in diabetic patients. (1,2).

For the first objective, this cross-sectional descriptive study aimed to estimate the proportion of asymptomatic PAD among T2DM patients having PAD where ABI<0.9. A total of 159 diabetic patients were included in the study. Doppler ultrasound-proven proportion of asymptomatic PAD among T2DM patients was 18.9%. where ABI value <0.9. The proportion is higher than another study done in primary care setting Universiti Malaya, Malaysia in which the proportion of PAD was 16% in the diabetic population. (12) The findings are similar to the study conducted at Tertiary Care Center in 2011 in Kulasekharam, Tamil Nadu, India, which showed the proportion of PAD in the asymptomatic diabetics to be 19%, (17). In this study, among the PAD diagnosed patients, 21 (70%) of them had mild PAD and 9 (30%) of the patients were observed with moderate PAD while none of them had severe PAD. This high prevalence of mild PAD could probably be explained by the very low rate of smoking (0.6%) and less prevalence of obesity (5%) among patients with PAD.

The second objective was to determine associated risk factors of asymptomatic PAD in T2DM in which the risk factors that were included in the analysis were the age of patients, gender, ethnicity, smoking status, BMI, HbA1c, HPT, IHD, HLP, CVA, T2DM duration, HbA1c, LDL, creatinine and eGFR. Univariable analysis was done for all predictor factors to screen for important independent variables and multiple Logistic Regression was used to

predict the risk factors that associated with the asymptomatic PAD amongst T2DM patients. Out of all independent variables, only 5 independent variables were significant with p-value < 0.25 which are age, IHD, HLP, CVA and LDL.

In this current study, the age of patients was not statistically significant in association with asymptomatic although 30 patients (18.9%) from 142 patients with age ≥ 50 years had PAD, its odd risk was 1.03 (0.99, 1.07), with p-value 0. 128. This is contrary to other studies whereby the proportion of PAD is increased due age (18,19). The reason is due thickening and stiffening of blood vessels with age, which then disturbs the normal blood flow and leads to fatty built up and narrowing of vessels resulting in PAD. The expected finding was not found in this study probably because of non-probability sampling.

In this study, only 5 (2.5%) patients with CVA had ABI<0.90. Presence of CVA posed crude odds risk of 1.15, p-value 0.091 of having asymptomatic PAD. In other studies, higher proportion of PAD in CVA patients as high as 13%. (20). This is because PAD is a major complication of atherosclerosis as well as a manifestation of atherosclerosis in major blood vessels like cerebral arteries.

PAD in this study was not significantly associated with smoking status in which ex-smoker crude odds risk 1.23, p-value 0.805 while active smoker crude odds risk 0.72, p-value 0.762 compared to non-smokers. Contrarily, many studies revealed that current smokers have higher risk, odds risk of 4 to 7 of PAD than non-smokers (21). Smokers are more prone to PAD is because of the toxic effect of nicotine as it impairs endothelium-dependent vasodilation and increases platelet aggregability and thrombosis. (22)

Multiple Logistic Regression was done for those all 5 independents but only 2 variables were significant, which were the IHD and HLP.

In this study, T2DM patients with IHD had 4.56 times higher odds of having peripheral arterial diseases (PAD) than those without IHD (95% CI: 1.51, 13.77, p = 0.007) as the association between PAD and IHD are well known. (23) This finding is like a study done in Korea where they analysed the factors associated with PAD among T2DM patients. The odds ratio in that study was 4.19 CI: 2.22, 7.87, p <0.001) for T2DM patients with IHD to develop PAD (24).

Hyperlipidaemia was presented in 66 (41.5%) patients, while the rest 93 (58.5%) patients were free from this medical condition. Patients who have HLP, will have 6.71 times higher odds of having peripheral arterial diseases (PAD) compared to those without HLP (95% CI: 2.47, 18.25, p < 0.001). This finding is higher than found in another study where hyperlipidaemia has an odds ratio of 1.76 of having PAD (95% CI: 1.10, 2.81, p 0.017). (25). This finding suggests that these factors may be particularly important in the development of PAD in diabetic populations.

In this study, duration of T2DM, smoking, HPT, HbA1c and BMI were not significantly associated with PAD. This is contrary to other studies that showed that duration of T2DM, HPT, HbA1c, smoking, and BMI are significantly associated with PAD. (27,28) This disagreement might be because of a difference in sample size, study population, and study design characteristics.