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ORIGINAL ARTICLE

Risk factors analysis of peripheral arterial disease in type 2 diabetes: A cross-sectional study

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ABSTRACT

Background: Peripheral Arterial Disease (PAD) is characterized by the narrowing of the arteries in the upper and lower extremities as a consequence of the atherosclerotic process. The incidence and mortality rates of PAD are increasing, particularly among patients with Type 2 Diabetes (T2D). The impact of T2D on PAD is associated with several risk factors. This study aims to evaluate the relationship between risk factors and PAD in patients with T2D.

Materials and methods: A Cross-sectional analytic study with total sampling was conducted at Dr. Wahidin Sudirohusodo Hospital. The study samples were T2D patients who performed Ankle Brachial Index (ABI) to determine PAD. Risk factors included age, gender, PAD, nutritional status, hypertension, dyslipidemia, smoking, duration of T2D and glycemic control. Data analysis was conducted using Chi-square and multiple logistic regression test.

Results: This study involved 170 patients with T2D who fulfilled the study's eligibility criteria. In this study, there was a significant association between T2D and PAD in males ($p = 0.029$), age >60 years ($p = <0.001$), had hypertension ($p = 0.009$), smoking ($P = 0.001$), duration of T2D >

10 years (p = <0.001). Multivariate analysis demonstrated that age >60 years (OR 3.3, 95%CI: 1.64-6.59, p=0.001), T2D duration >10 years (OR 3.3, 95%CI: 1.63-6.83. p=0.001) and smoking (OR 2.9, 95%CI: 1.41-6.09, p=0.004) were independently associated with the incidence of PAD.

Conclusions: Risk factors associated with PAD in T2D are age, gender, hypertension, duration of T2D, and smoking. Age, duration of T2D and smoking significantly increased the incidence of PAD. The risk factors of dyslipidemia, BMI, and glycemic control have not been proven to play a role in the incidence of PAD in T2D.

Keywords: type 2 diabetes, peripheral arterial disease, risk factors

INTRODUCTION

Type 2 diabetes (T2D) and cardiovascular complications have become a global health problem that is predicted in 2035 to have a prevalence of 591 million (1 in 10 individuals) based on the Federation of International Diabetes. Cardiovascular complications, including coronary heart disease (CHD), peripheral arterial disease (PAD), and heart failure (HF), increase mortality rates by 50% in people with T2D.[1,2]

Peripheral arterial disease is an important landmark of cardiovascular risk and an indicator of extensive atherosclerosis in other vascular sites such as coronary, carotid, and cerebrovascular arteries. In several studies with large populations, T2D is associated with a 2-4-fold increase in the incidence of PAD compared to non-T2D patients, and the mortality rate in T2D patients with PAD is 3-4-fold higher than in healthy populations.[3,4]

The morbidity effects of T2D with PAD may lead to increased perioperative complications, amputation, and disability. The American Heart Association/American College of Cardiology (AHA/ACC) recent guidelines recommend that people diagnosed with T2D should be screened for PAD in order to manage the disease, but recommendations on specific approaches have not been specified. Some studies have investigated T2D and PAD separately, and few studies have investigated the relationship between both diseases as a unit. The increased incidence of PAD in T2D is associated with the involvement of several risk factors, including age, gender,

hypertension, dyslipidemia, and smoking.[5,6] This study aims to determine the role of risk factors in T2D patients on the incidence of PAD.

METHODS

Patient Population

This study worked with an analytic observational study using a cross-sectional design at Dr. Wahidin Sudirohusodo Hospital from March to June 2024. A total of 170 samples were collected met the inclusion and exclusion criteria.

Inclusion and Exclusion criteria

The study sample criteria are patients T2D with the following criteria: (1) Patients agreed to undergo a series of examinations, (2) not consuming drugs that affect vascular function such as antiplatelet and vasodilator groups (e.g., phosphodiesterase type III inhibitors), and (3) no history of previous PAD.

Clinical Data and sample collection

Sampling was carried out by total sampling, all the patients with T2D who met the criteria included in the study. The diagnosis of PAD is based on the Ankle Brachial Index (ABI) measurement, which is performed by comparing the systolic pressure of the dorsalis pedis artery/posterior tibial artery with the highest brachial artery. The interpretation of ABI values can be divided into two subgroups, <0.9 as Peripheral Arterial Disease and >0.9 as non-Peripheral Arterial Disease. The duration of diabetes mellitus will be categorized into ≥10 years and <10 years. Nutritional status is determined by weight (kg) divided by the square of height (m). Interpretation of BMI ≥25 kg/m² was declared obese, and <25 kg/m² was declared not obese. Glycemic control was based on the value of hemoglobin A1c (HbA1c) measured in the study sample with the condition that there was no anemia (Hb <10 g/dl). It is said to be controlled if HbA1c ≤7 and an uncontrolled if HbA1c >7. Dyslipidemia will be defined as total cholesterol >200 mg/dl, and/or triglycerides >150, and/or HDL-C <40 mg/dl.

Statistical Analysis

Data analysis was carried out using SPSS version 25. The analysis method consists of calculating descriptive statistics and frequency distribution. Descriptive methods aimed to obtain general information about the study sample. The statistical test used was Chi Square Test and multivariate analysis using Multiple logistic Regression Test to determine the most influential and independent risk factors. Statistical test results were considered significant if the test p value was <0.05. The results obtained will be displayed in the form of a narrative supplemented by tables.

RESULTS

This study involved 170 subjects with T2D to evaluate the contribution of risk factors for PAD. There were 92 male subjects (54.1%) and 78 female subjects (45.9%). Subjects aged <60 years were 104 subjects (61.2%). The distribution of PAD events in the study population was found to be almost balanced where 83 subjects (48.8%) had PAD and 87 subjects (51.2%) did not have PAD. Obese risk factors were found in 57 subjects (33.5%), hypertension in 106 subjects (62.4%), dyslipidemia in 130 subjects (93.5%), and smoking in 55 subjects (32.5%). The study subjects suffered from T2D <10 years in 111 subjects (65.3%). HbA1c examination was performed on 144/170 research subjects to assess glycemic control and the majority of research samples were 103 subjects (71.5%) with uncontrolled glycemic state. Table 1 shows the characteristics of the subjects.

Table 1. Study Characteristics

Variable	Category	N	%
Gender	Male	92	54,1

Variable	Category	N	%
	Female	78	45,9
Age	≥60 years old	66	38,8
	<60 years old	104	61,2
Nutrition Status (BMI)	Obese	57	33,5
	Non-Obese	113	66,5
Hypertension	Yes	106	62,4
	No	64	37,6
Dyslipidemia	Yes	130	93,5
	No	9	6,5
Smoking	Yes	55	32,4
	No	115	67,6
Duration of T2D	≥10 years	59	34,7
	<10 years	111	65,3
Glycemic Control	Controlled	41	28,5
	Not-Controlled	103	71,5
PAD	PAD	83	48,8
	Non-PAD	87	51,2

BMI: Body Mass Index; T2D: Type 2 Diabetes; PAD: Peripheral Arterial Disease. Source: Primary data, 2024

Table 2 shows the relationship between risk factors and the incidence of PAD in T2D. In this study, it was found that male gender significantly (P 0.029) had a higher proportion of PAD in T2D (56.5%). Age group >60 years was a significant risk factor ($p < 0.001$) for PAD (66.7%). Hypertension was more likely (P 0.009) to have PAD in T2D compared to those without hypertension (56.6%: 35.9%). Significant results also showed differences in smoking habits ($P < 0.001$) on the incidence of PAD, where smoking habits had a higher proportion of PAD incidence compared to the non-smoking subjects (69.1%: 39.1%). Longer duration of T2D showed a significant association ($p < 0.001$) with a higher incidence of PAD, in this study, the T2D duration group of ≥10 years was more at risk of PAD (67.8%). In this study, there was no significant relationship between the risk factors of nutritional status, dyslipidemia, and glycemic control ($p>0.05$).

Table 2. Association of T2D Risk Factors with the Incidence of PAD

Variable	Category	Ankle Brachial Index (ABI)	Total	p*

		PAD (83)		Non-PAD (87)			
		N	%	N	%		
Gender	Male	52	56,5	40	43,5	92	**0,029**
	Female	31	39,7	47	60,3	78	
Age	≥60 years old	44	66,7	22	33,3	66	**<0,001**
	<60 years old	39	37,5	65	62,5	104	
Nutrition Status (BMI)	Obese	27	47,4	30	52,6	57	0,787
	Non-Obese	56	49,6	57	50,4	113	
Hypertension	Yes	60	56,6	46	43,4	106	**0,009**
	No	23	35,9	41	64,1	64	
Dyslipidemia	Yes	59	45,4	71	54,6	130	0,956
	No	4	44,4	5	55,6	9	
Smoking	Yes	38	69,1	17	30,9	55	**<0,001**
	No	45	39,1	70	60,9	115	
Duration of T2D	≥10 years	40	67,8	19	32,2	59	**<0,001**
	<10 years	43	38,7	68	61,3	111	
Glycemic Control	Controlled	21	51,2	20	48,8	41	0,302
	Not-Controlled	43	41,7	60	58,3	103	

*Chi Square test
BMI: Body Mass Index; T2D: Type 2 Diabetes; PAD: Peripheral Artery Disease

Table 3 shows the multivariate analysis of risk factors for PAD in patients with T2D. In this study, it was shown that among gender, age, duration of T2D, hypertension and smoking, the risk factors most significantly associated with the incidence of PAD in T2D were age, duration of T2D and smoking. Based on the OR value, subjects aged >60 years or T2D duration group >10 years had a 3.3 times greater risk of suffering from PAD than subjects aged <60 years or T2D duration <10 years. Whereas subjects who had a smoke behavior had a greater risk of 2.9 times to suffer PAD than subjects who did not smoke.

Table 3. Multivariate Analysis of T2D Risk Factors with the Incidence of PAD

Step	Variable	B	S.E.	Wald	p*	OR	95% C.I	
							Lower	Upper
Step 1	Gender	-0,173	0,445	0,150	0,698	0,8	0,35	2,01
	Age	1,228	0,361	11,557	0,001	3,4	1,68	6,93
	Duration of T2D	1,127	0,371	9,248	0,002	3,1	1,49	6,38
	Hypertension	0,616	0,365	2,843	0,092	1,9	0,90	3,79
	Smoking	1,114	0,482	5,350	0,021	3,0	1,19	7,83
Step 2	Age	1,218	0,360	11,448	0,001	3,4	1,67	6,84
	Duration of T2D	1,120	0,370	9,157	0,002	3,1	1,48	6,33
	Hypertension	0,617	0,365	2,855	0,091	1,9	0,91	3,79
	Smoking	0,998	0,377	7,023	0,008	2,7	1,30	5,68
Step 3	Age	1,189	0,356	**11,177**	**0,001**	**3,3**	1,64	6,59
	Duration of T2D	1,205	0,366	**10,829**	**0,001**	**3,3**	1,63	6,83
	Smoking	1,077	0,373	**8,355**	**0,004**	**2,9**	1,41	6,09

*Multiple Logistic Regression – Backward Wald Method
T2D: Type 2 Diabetes

DISCUSSION

Peripheral arterial disease is one of the major cardiovascular complications in T2D patients. The prevalence of PAD is 3-4-fold greater in T2D patients compared to non- T2D patients with an approximate prevalence of 202 million people globally. The results of studies on the prevalence of PAD in T2D in several countries are quite varied, in studies conducted in Nigeria found a prevalence rate of 22%, Uganda found a 24% incidence of PAD, 28.7% in Korea, and the prevalence of PAD in the Indian population reached 36%.[7,8] In this study, the prevalence of PAD in the T2D population was found to be higher than the previous study with a rate of 48.8%. The difference in prevalence in various studies on the incidence of PAD can be caused by the role of risk factors that are associated with the T2D, which contributes in the process of atherosclerosis leading to PAD.

Male (56.5%) had more PAD when compared to female gender (39.7%), but overall, it did not increase the risk of PAD in T2D patients. Similar results were obtained in Sudiagene's study with a total sample of 1468 subjects that found the prevalence of men with T2D had more PAD compared to women (58%: 42%). [9] In a cohort study involving 150,000 subjects, the prevalence of men was higher when compared to women (58.4%: 41.6%).[10] However, contrary results were reported by Hiramoto, et al where women tended to have lower ABI values

when compared to men (ABI 1.05: 1.10, P<0.001) [11]and this is in line with the IDON-PAD study which found a higher proportion of women than men (59%: 41%) for the incidence of PAD.[12] The inconsistent results in several studies on the involvement of gender as a risk factor for PAD in T2D may be due to the multifactorial role including age, smoking habits, and hormones on the incidence of atherosclerosis.[13,14] In this study, the involvement of gender could not be proven as an independent risk factor (P =0.029) for PAD in T2D due to the role of other factors such as smoking habits found in the male population but not in the female population.

A study of risk factors for PAD in T2D by Althouse et al in 1,479 subjects found that the risk of PAD increased with age especially in those aged >60 (OR: 1.32; 95% CI: 1.17-1.54; p<0.001).[15] A similar result by Ostchega et al suggested that the prevalence of PAD increases with age and associated with an increased risk of cardiovascular disease, where the prevalence of PAD was 7.0% (95% CI 5.6-8.4%) for those aged 60 to 69 years, 12.5% (95% CI 10.4-14.6%), and 23.2% (95% CI 19.8-26.7%) for 70 to 79 years and 80 years and older, respectively. An increase in age each year in T2D increases the risk of incident PAD by 9%.[7] In this study, age was categorized into <60 years and >60 years. Patients with age >60 years (66.7%) had a higher prevalence of PAD compared to those with age <60 years (37.5%) and significantly increased the risk of PAD (OR 3.3, 95%CI 1.64-6.59). The risk of PAD is consistent with ageing due to changes in the structure of blood vessels that become more rigid and stiff. Aging-induced thickening of the tunica intima impairs endothelial integrity and decreases the availability of nitric oxide, known as a vasodilator. Arterial wall stiffness disrupts normal blood flow which facilitates the accumulation of calcium and fat in the arteries further narrowing the blood vessels resulting in PAD.[7,15,16]

Obesity is one of the major risk factors for the growth and progressivity of atherosclerosis and cardiovascular disease, but the role of obesity in the incidence of PAD in several studies has inconsistent results. In this study, obesity assessed based on IMT measurements found that the percentage of incidence of PAD in obese patients (47.4%) was almost equivalent to non-obese patients (49.6%), and statistically obesity did not increase the risk of PAD in T2D (p= 0.787). The PERART study found that BMI ≥ 25kg/m2 (OR 0.57, 95% CI 0.38-0.87) was a protective

factor for PAD events[17] but in contrast, a study by Agboghoroma involving 200 T2D patients in Nigeria found that obesity was an independent risk factor that increased the incidence of PAD was 2-fold when compared to non-obese.[18] The inconsistent results are due to the role of other factors such as age, gender, genetics, ethnicity, sarcopenia in parents, and other underlying metabolic conditions that make obesity unable to prove its significance to the incidence of PAD in this study.[19,17,20]

The role of hypertension on the incidence of PAD is due to increased pressure on the arterial wall resulting in endothelial injury and impaired vasodilation, which causes reduced blood flow that can accelerate the process of atherosclerosis in the peripheral arteries, which contributes to the development and progression of PAD.[8,21] A study in Ethiopia found a 40% percentage of hypertension in the T2D population with PAD but based on statistical tests hypertension was not a significant risk factor for the incidence of PAD.[7] Similar results were obtained in this study where the incidence of PAD in T2D who experienced hypertension (56.6%) was more when compared to the non-hypertensive population (35.6%), but hypertension was not an independent factor for the incidence of PAD in T2D. The insignificant role of hypertension could be due to the contribution of other independent risk factors in this study.

Dyslipidemia is a risk factor for PAD by inducing the progression of atherosclerosis through vascular inflammation and endothelial cell dysfunction, disruption of various types of cells such as platelets in the blood vessel wall, coagulation, and inhibition of fibrinolysis.[7,22] The majority of T2D patients (93.5%) in this study suffered from dyslipidemia, which was found in PAD 45.4% of subjects ($p = 0.959$). This result is consistent with a study conducted in Uganda on patients with T2D where there was no significant role of dyslipidemia on the incidence of PAD [22] and a study in Saudi Arabia which found a high prevalence of dyslipidemia in T2D but was not associated with an increased prevalence of PAD.[23] The inconsistent results in this study may be due to the limitations of cross-sectional study methods in assessing the causal relationship of dyslipidemia to the incidence of PAD, as well as further assessment of each lipid component's role.

Smoking is a major risk factor for PAD. This is mediated by the effect of nicotine on plaque formation and free radicals in the components of cigarettes which cause oxidative stress to promote the process of atherosclerosis as the underlying cause of PAD.[7,24] In this study, 69.1% of PAD subjects had a smoking habit ($p<0.001$) and increased the incidence of PAD to 2.9-fold when compared to the non-smoking population. A meta-analysis by Lu et al found that smoking was associated with the incidence of PAD (OR 3.08, 95% CI 2.56 - 3.69), even in patients who previously had a history of smoking (OR 1.67, 95% CI 1.54-1.81).[24] Similar results were obtained by Akalu et al's study which mentioned a history of smoking had a risk of PAD (OR = 4.68, 95% CI (1.93-11.30)) and higher in the active smoking population (AOR = 5.84, 95% CI (1.79-19.04)).[7]

The duration of T2D is associated with an increase of the incidence of PAD because long-term exposure to metabolic disorders can increase and accelerate the process of atherosclerosis.[8,23] In line with this theory, another study by Alzahrani et al. stated that the duration of T2D ≥ 20 years had a risk of increasing the incidence of PAD up to 3.08 times (95%CI 1.63-5.83).[23] In this study, PAD (67.8%) was found more frequently in patients with T2D > 10 years and significantly increased the risk of PAD (OR 3.3, 95% CI 1.63-6.83). In addition, a study by Weragoda et al showed that an increase in the duration of T2D was significantly in line with the percentage of PAD incidence, with T2D duration ≤5 years there were 5.1% PAD cases, 5-10 years the incidence rate increased by 15.2%, and at a duration of ≥ 10 years, 56.9% of T2D experienced PAD.[25]

Glycemic control based on HbA1c has an important role in the development of PAD. based on research by Akalu et al. stated that every 1% increase in HbA1c correlates with a PAD incidence of 1.9 fold (AR 1.97, 95% CI 1.03-3.40).[7] The BARI 2D study showed an increase in PAD risk of up to 21% for every 1% (11 mmol/mol) increase in HbA1c.[15] In the study, poor glycemic control was found in 71.5% of T2D patients, but this did not show significance to the increased risk of PAD. Similar results were obtained in Alzahrani et al's study, where the mean HbA1c value in the T2D population with PAD was 9.1%, but this did not significantly increase the incidence of PAD.[18,23] HbA1c is a description of glycemic control in a 3-month period, this may not be able to describe glycemic control of the atherosclerosis process which is a long-term

process. Therefore, in this study, glycemic control cannot be proven to play a role in the risk of PAD in T2D.

CONCLUSIONS

This study found association between risk factor age, gender, hypertension, duration of T2D, and smoking with the incidence of PAD in T2D. Age, duration of T2D and smoking significantly increased the incidence of PAD. The risk factors of dyslipidemia, BMI, and glycemic control have not been proven to play a role in the incidence of PAD in T2D.

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Conflict of interest: All authors declare that they have no commercial relationships (e.g. consultancy, shareholding, equity interests, patent/licensing arrangements, etc.) that could create a conflict of interest in connection with the submitted article

Authors' contributions:

NF (Concept, Design, Sources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Manuscript Writing). AMA (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). IM (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). SB (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). HR (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). AS (Concept, Design, Analysis and Interpretation, Critical Review). The manuscript was written by all authors, who also contributed to its revisions and content assessment. They have all read and given their approval to the paper, verifying to the accuracy and validity of the study findings.

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