# The Prevalence Rate of Peripheral Arterial Disease in Type 2 Diabetes Mellitus and Associated Risk Factors

*Arnadi,* Imam Subekti,** R.Miftah Surjadipradja,*** Abdul Muthalib,**** Sarwono Waspadji***


## ABSTRACT

*Aim: To determine the prevalence of peripheral arterial disease and to its risk factors in patients with type 2 diabetes mellitus.*

*Subjects and Methods: A cross sectional study was conducted on 110 subjects with type 2 diabetes mellitus. Subjects underwent comprehensive medical examinations, including lipid profile, body mass index, Hemoglobin A1c and Ankle Brachial Index.*

*Results: The prevalence of PAD in diabetic subjects was 35.5%. In multivariate analysis: cholesterol levels of ≥ 200 mg/dL, history of smoking, a duration of diabetes of ≥ 5 years, hypertension, triglyceride levels of ≥ 150 mg/dL, and body mass index of ≥ 150 mg/dL are significant risk factors for PAD in diabetic subjects. Gender, age of ≥ 50 years old, LDL levels of ≥ 100 mg/dL, HDL levels of < 40 mg/dL, and HbA1c levels of ≥ 7% were not significant risk factors for PAD in diabetic subjects.*

*Conclusion: In this study, the prevalence rate of PAD in diabetic subjects was approximately 35.5%. Total cholesterol levels, history of smoking, duration of diabetes, hypertension, triglyceride, and body mass index were significant risk factors for PAD in diabetic subjects.*


## INTRODUCTION

The prevalence rate of diabetes mellitus has increased along with the lifestyle changes of the community. Data from Jakarta demonstrate an increased prevalence of diabetes mellitus from 1.7% in 1982 to 5.6% in 1993. Complications of diabetes mellitus should start early. Other wise, chronic complications of diabetes mellitus will be a heavy burden to deal with.[1] In the long term, diabetes mellitus could cause macrovascular and microvascular complications as well as neuropathy. Macrovascular complications are mostly caused by the process of atherosclerosis, consisting of coronary heart disease, cerebrovascular disease, as well as peripheral arterial disease. Peripheral arterial disease (PAD) is a vascular disease in the form of blockages of medium-size and small arteries and often inflicts the lower limbs. PAD increases the prevalence of foot gangrene and disturbs healing of diabetic ulcer. Inadequate management of foot gangrene increases the prevalence of amputation.[2] Amputation causes patients to lose their jobs, their incomes, causes dependency, depression, and reduces their quality of life.[2]

Risk factors for PAD in type 2 diabetes mellitus are genetic factors, age, sex, duration of diabetes mellitus, smoking, obesity, hypertension, total cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL), hyperglycemia, drugs, homocysteinemia, coagulation disturbance and fibrinolytics. The prevalence of these risk factors in patients with diabetes mellitus is quite high.[3,4]

This study aims to determine the frequency and risk factors associated with increased PAD in type 2 diabetes mellitus patients at Cipto Mangunkusumo Hospital, Jakarta.


* *Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/Dr.Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia*

** *Division of Metabolic-endocrine,Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/ Dr.Cipto Mangunkusumo National General Hospital. Jakarta, Indonesia*

*** *Division of Cardiology. Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/Dr.Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia*

**** *Division of Hematology and Medical Oncology,Department of Internal Medicine. Faculty of Medicine of The University of Indonesia/ Dr.Cipto Mangunkusumo National General Hospital. Jakarta, Indonesia*

## MATERIALS AND METHODS

The study was a cross-sectional study conducted from January to May 2002 at the Subdivision of Metabolic Endocrinology of the Department of Internal Medicine of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta. Study subjects were selected by consecutive random sampling with the following inclusive criteria: type 2 diabetes mellitus patients who were willing to be involved in the study. The exclusion criteria were as follows: an ankle brachial index (ABI) of over 1.3, use of peripheral vasodilatation agents (pentoxiphillin, silostazole, and naftydrofuril), use of alpha receptor blocker anti-hypertensive agents such as carvedilole, Buerger disease, venous thrombosis, arterial thrombosis, and loss of one of four extremities. The independent variables studied were age, sex, duration of diabetes, history of smoking, blood pressure, body mass index, total cholesterol levels, triglyceride, LDL cholesterol, HDL cholesterol, and HbA1c. The dependent variable was the prevalence of PAD. Lipid profile (total cholesterol, triglyceride, and HDL levels) was determined using the enzymatic method, LDL was calculated using the Friedewald formula, and HbA1c was measured using the Elisa method. Blood pressure was taken in a seated position with a mercury sphygmomanometer on both arms after staying seated for 5 minutes. Ankle brachial index (ABI) was determined by measuring the systolic pressure of both upper arms followed by the systolic pressure of both dorsal foot arteries using the Doppler vasoflow instrument (Pneumo-Dop HD-2200 Vascular Testing System Hodeco, Hayashi Denki Co.Ltd) while the patient is lying down, by placing a cuff on the patient's ankle. The ankle brachial index is a comparison of the highest systolic pressure of the dorsal foot artery and the highest systolic pressure of the upper arms. PAD is established when the ankle brachial index is equal to or less than 0.90. All patients with an ankle brachial index of over 1.30 were excluded from the study, since this reflects the presence of vascular calcification. In this study, subjects were classified as follows: based on the duration of diabetes mellitus, subjects were classified into two groups, those who have had diabetes mellitus for ≥ 5 years and those who have had it for less than 5 years; based on age, subjects were classified into 2 groups, those ≥ 50 years and < 50 years; based on BMI subjects were classified into 2 groups, those with a BMI > 25 kg/m$^2$ and ≤ 25 kg/m$^2$; based on total cholesterol levels, subjects were classified into 2 groups, those with total cholesterol levels ≥ 200 mg/dL and < 200 mg/dL; based on triglyceride levels, subjects were classified into 2 groups, those with triglyceride levels of ≥ 150 mg/dL and < 150 mg/dL; based on LDL Cholesterol levels, subjects were classified into 2 groups, those with LDL levels of ≥ 100 mg/dL and < 100 mg/dL; based on HDL cholesterol levels, subjects were classified into 2 groups, those with HDL levels of < 40 mg/dL and ≥ 40 mg/dL; based on HbA1c subjects were classified into 2 groups, those with HbA1c of ≥ 7% and < 7%; based on smoking, subjects were classified into smokers, ex-smokers, and non-smokers. Hypertension was established from blood pressures of ≥ 140/90 mmHg.

The data obtained were computer-processed using SPSS 10.0. The following analysis was performed: univariate analysis, bivariate analysis, and logistic regression with a significance level of <0.05 and a confidence interval of 95%.

## RESULTS

From January to May 2002, there were 110 patients with type 2 diabetes mellitus at the Metabolic-endocrinology outpatient clinic of Cipto Mangunkusumo Hospital, 44 (40%) being males and 66 (60%) females. Out of the 110 patients with type 2 diabetes mellitus, there was a prevalence rate of PAD of 39 (35.5%). The age range was 35-85 years, with the average age being 59.5 years. The subject's ABI ranged from 0.38 to 1.25 with an average of 0.91. Ninety-nine (90%) respondents received treatment with oral hypoglycemic agents. In this study, no respondents were current smokers. They were either ex-smokers or non-smokers.

**Table 1. Demographical Characteristics of Subjects**

| Variable | Type 2 diabetes mellitus | | Number |
|---|---|---|---|
| | PAD | Without PAD | |
| Number (n) | 39 (35.5%) | 71 (64.5%) | 110 |
| Sex | | | |
| Male | 17 (43.6%) | 27 (38%) | 44 (40%) |
| Female | 22 (56.4%) | 44 (66%) | 66 (62%) |
| Average age (years) | 61.8 (SD 8.1) | 58.1 (SD 7.9) | 59.5(SD 8.1) |
| Range | 45-85 | 35-72 | 35-85 |
| Average ABI | 0.73 (SD 0.15) | 1.01 (SD 0.07) | 0.91 (SD 0.2) |
| Range | 0.38-0.90 | 0.91-1.25 | 0.38-1.25 |

**Table 2. Type of Treatment in Subjects**

| Variable | Type 2 diabetes mellitus | | Total |
|---|---|---|---|
| | PAD | Without PAD | |
| Diet | 0 | 5 | 5 |
| Oral hypoglycemic agents | 36 (92.3%) | 63 (88.7%) | 99 (90%) |
| Insulin | 0 | 0 | 0 |
| Diet + oral hypoglycemic agents + Insulin | 3 | 3 | 6 |
| Total | 39 (35.5%) | 71 (74.5%) | 110 (100%) |

Table 3. Independent Variable: Subject Characteristics

| Variable | Type 2 diabetes mellitus | | Number |
|---|---|---|---|
| | PAD | Without PAD | |
| Average duration of DM (year) | 10.4 (SD 7.4) | 8.1 (SD 6.9) | 8.9 (SD 7.2) |
| Range | 0-32 | 0-30 | 0-32 |
| Hypertension | 28 (71.8%) | 30 (42.3%) | 58 (52.7%) |
| History of smoking | 15 (38.5%) | 16 (22.5%) | 31 (28.2%) |
| Total cholesterol level (mg/dL) | 229.9 (SD 65.1) | 184.7 (SD 40.9) | 200.7 (SD 55.0) |
| Range | 101-416 | 79-275 | 79-418 |
| Triglyceride (mg/dL) | 151.4 (SD 83.4) | 116.3 (SD 53.9) | 130.1 (SD 67.4) |
| Range | 28-350 | 46-342 | 28-350 |
| LDL cholesterol level (mg/dL) | 154.8 (SD 55.9) | 122.5 (SD 31.9) | 133.9 (SD 44.5) |
| Range | 43-337 | 41-188 | 41-337 |
| HDL cholesterol level (mg/dL) | 46.6 (SD 9.3) | 44.0 (SD 11.2) | 44.9 (SD 10.6) |
| Range | 23-70 | 12-70 | 12-70 |
| BMI (kg/m2) | 23.8 (SD 4.3) | 23.9 (SD 3.3) | 23.9 (SD 3.7) |
| Range | 16.3-32.9 | 17.8-35.7 | 16.3-35.7 |
| HbA1c (%) | 6.6 (SD 1.2) | 6.5 (1.2) | 6.5 (SD 1.2) |

Note: B = regression coefficient, SE = standard error, P = Significance, OR = Odds Ratio, CI = confidence interval

Based on Chi square analysis, the independent variables that demonstrated a significant correlation with the incidence of PAD in type 2 diabetes mellitus were: ages of ≥ 50 years, duration of diabetes mellitus of ≥ 5 years, hypertension, total cholesterol levels of ≥ 200 mg/dL, LDL cholesterol levels of ≥ 100 mg/dL, and triglyceride levels of ≥ 150 mg/dL. Sex, history of smoking, HDL cholesterol, BMI, and HbA1c did not demonstrate a significant correlation with the prevalence of PAD in type 2 diabetes mellitus (see Table 4).

Table 4. The Correlation Between Independent Variables and the Prevalence of PAD in Subjects

| Variable | Type 2 diabetes mellitus | | P | OR | 95% CI |
|---|---|---|---|---|---|
| | PAD | Without PAD | | | |
| Sex | | | | | |
| male | 17 | 27 | 0.569 | 1.259 | 0.569-2.785 |
| Female | 22 | 44 | | | |
| Age (years) | | | | | |
| ≥ 50 years | 38 | 60 | 0.037 | 6.964 | 0.864-56.159 |
| < 50 years | 1 | 11 | | | |
| Duration of DM (years) | | | | | |
| ≥ 5 years | 30 | 41 | 0.044 | 2.439 | 1.010-5.888 |
| < 5 years | 9 | 30 | | | |
| Hypertension | | | | | |
| Yes | 28 | 30 | 0.003 | 3.479 | 1.500-8.070 |
| No | 11 | 41 | | | |
| Smoking | | | | | |
| History of smoking | 15 | 16 | 0.076 | 2.148 | 0.916-4.037 |
| Non-smoker | 24 | 55 | | | |
| Total cholesterol level (mg/dL) | | | | | |
| ≥ 200 | 29 | 28 | < 0.001 | 4.454 | 1.881-10.546 |
| < 200 | 10 | 43 | | | |
| LDL cholesterol level (mg/dL) | | | | | |
| ≥ 100 | 37 | 54 | 0.013 | 5.824 | 1.269-26.728 |
| < 100 | 2 | 17 | | | |
| HDL cholesterol level (mg/dL) | | | | | |
| < 40 | 7 | 25 | 0.057 | 0.403 | 0.155-1.043 |
| ≥ 40 | 32 | 46 | | | |
| Triglyceride (mg/dL) | | | | | |
| ≥ 150 | 17 | 22 | 0.021 | 2.656 | 1.143-6.171 |
| < 150 | 26 | 55 | | | |
| BMI (kg/m$^2$) | | | | | |
| > 25 | 19 | 26 | 0.217 | 1.844 | 0.745-3.630 |
| ≤ 25 | 20 | 45 | | | |
| HbA1c (%) | | | | | |
| ≥ 7 | 12 | 18 | 0.542 | 1.309 | 0.55-3.108 |
| < 7 | 27 | 53 | | | |

p= significance < 0.05. OR= Odds Ratio, CI= confidence interval

Table 5. The Results of Logistical Regression Analysis of Various Independent Variables and The Prevalence Of PAD In Subjects

| Independent variables | B | SE | p | OR | 95% CI |
|---|---|---|---|---|---|
| 1. Duration of DM (≥ 5 years) | 1.667 | 0.629 | 0.008 | 5.296 | 1.452-18.186 |
| 2. Hypertension | 1.357 | 0.539 | 0.012 | 3.884 | 1.351-11.163 |
| 3. History of smoking | 2.793 | 0.778 | 0.000 | 16.326 | 3.553-75.019 |
| 4. Total cholesterol level (≥ 200 mg/dL) | 2.857 | 0.724 | 0.000 | 17.578 | 4.256-72.591 |
| 5. Triglyceride (≥ 150 mg/dL) | 2.291 | 0.588 | 0.028 | 3.678 | 1.150-11.660 |
| 6. BMI (> 25 kg/m$^2$) | 1.155 | 0.568 | 0.042 | 3.173 | 1.042-9.660 |

Note: B = regression coefficient, SE = standard error, p =significance < 0.05 , OR = Odds Ratio, CI = confidence interval

All independent variables with a p value of equal to or less than 0.25 were included in the multivariate analysis using logistic regression. Logistic regression is used to determine the most influential factor and discard interfering factors. Based on logistic regression analysis, variables that turned out to be significant risk factors for PAD in type 2 diabetes mellitus were history of smoking, total cholesterol levels of ≥ 200 mg/dL, a duration of diabetes mellitus of ≥ 5 years, hypertension, a triglyceride level of ≥ 150 mg/dL, and a BMI of > 25 kg/m$^2$ (See Table 5).

## DISCUSSION

This is a cross sectional study, where independent variables are only evaluated once, without monitoring their developments. Anoter limitation in this study is that angiography, the gold standard for determining PAD, was not used. However, ABI evaluation may be used as a substitute for angiography in establishing the presence of PAD, since ABI has a sensitivity rate of 95% and a specificity rate of 95% in determining PAD. An additional limitation to this study is that other risk factors for PAD, which are hyperhomocysteinemia, coagulation disturbance, and fibrinolysis were not evaluated.

The prevalence of PAD in type 2 diabetes mellitus greatly varies from 9 to 42%. This is due to various differences, such as in the method of selection, sample size, ethnic and geographic background. In this study, the prevalence of PAD in type 2 diabetes mellitus was 35.5%. This number is not greatly different from that found by Kazunari et al (35%).[5] Other studies, such as that by Asakawa et al,[6] and Katsilambors et al,[7] found prevalence rates of 13.3% and 42% respectively for type 2 diabetes mellitus. Gregor et al conducted a population study and found a prevalence of PAD of 22.4%.[8]

Sex is a risk factor for PAD. In type 2 diabetes mellitus, males supposedly suffer from more PADs compared to females. In this study, there was no significant correlation between the male sex and the prevalence of PAD in type 2 diabetes mellitus. Such results supported studies by Gregor et al,[8] and O'Neal et al,[9] who did not

find a significant correlation between the male sex and the prevalence of PAD in type 2 diabetes mellitus.

The prevalence rate of PAD in males is influenced by their habit and hormonal conditions. Males have a higher tendency to smoke and drink compared to females. In addition, there are very low levels of estrogen in males, increasing their risk of atherosclerosis. Estrogen has a vasculoprotective tendency. It has two effects on the vascular system: the non-genomic (rapid) effect, and the genomic (long-term) effect. Non-genomic effects is due to vasodilatation due to the formation and release of NO and prostacyclin by endothelial cells. The genomic effect reduces smooth muscle tone, endothelial damage, and proliferation of vascular smooth muscle cells while increasing endothelial cell growth. In addition, estrogen also reduces total cholesterol levels, LDL, lipoprotein a (Lp a), and increases levels of HDL and triglyceride. This role of estrogen hormone reduces the incidence of atherosclerosis in pre-menopausal women compared to men. However, after menopause, the incidence rate of cardiovascular disease in women increases.[10]

Increased age increases the process of atherosclerosis. In this study, based on the Chi square test, there was a significant correlation between age and the prevalence of PAD in type 2 diabetes mellitus. Kazunari et al,[5] and Asakawa et al,[6] found a significant correlation between increased age and increased prevalence of PAD in patients with type 2 diabetes mellitus.

Animal studies demonstrate that increased age is associated with more progressive endothelial dysfunction. In humans, increased age is associated with disturbance in endothelium-dependent vasodilatation. The mechanism of increased endothelial disturbance with age is still unclear. The survival rate of human endothelial cells is estimated to be approximately 30 years. Afterwards, endothelial cells have reduced ability to produce NO. NO acts as scavenger of superoxyde radicals, thus maintaining a protective function from oxidative stress. The cause for reduced endothelial capacity to produce relaxation factor may be due to the accumulation of free radicals on the surface membrane of endothelial cells. Free radicals destroy endothelial cells, thus reducing endothelial NO production and increasing NO degradation. This reduction in NO induces endothelial dysfunction. All of these functions accelerate the process of atherosclerosis.

The longer a person has suffered from diabetes mellitus, his/her risks for PAD also increases. In this study, there was a significant correlation between the duration of diabetes mellitus and the prevalence of PAD. Asakawa et al did not find a significant correlation between the duration of diabetes mellitus and the incidence of PAD in type 2 diabetes mellitus.[6] The difference in these results may be due to 2 things, first of all, it is unclear which factor, insulin resistance or insulin deficiency, is the most dominant factor among the subjects, and secondly, there is a difficulty in determining the initial time when the diabetes mellitus began. Prior to the diagnosis of diabetes mellitus, there usually is a pre-diabetic phase that could last approximately 5-10 years. During this phase, there is an increase in blood glucose level, particularly post prandial glucose levels. Atherosclerosis should have occurred before this phase, during the initial development of insulin resistance. Thus it is clear that PAD is sometimes found during the time of diagnosis of type 2 diabetes mellitus.

O'Neal et al and Mehler et al[12] found a significant correlation between hypertension and the incidence of PAD in type 2 diabetes. This study also found a significant correlation between hypertension and the incidence of PAD. Hypertension accelerates the development and progressiveness of atherosclerosis in type 2 diabetes mellitus. Hypertension induces endothelial dysfunction and vascular remodeling. Changes that occur include thickening of the vascular tunica media as a result of vascular smooth muscle cell hyperplasia, as well as accumulation of extra-cellular matrix. Increased blood pressure increases shear stress. Shear stress induces various changes in the vascular wall by activating ion Ca and K channels, tyrosine kinase, and integrin, causing endothelial damage. Such activation causes an interaction between vascular smooth muscle cells and extracellular matrix. Hypertension also stimulates hypertrophy of the tunica media and proliferation of vascular smooth muscle cells. This final process is vascular remodeling. The subsequent process is the accumulation of subendothelial matrix, which increases vascular collagen.[11,13,14]

In addition, hypertension increases the release of angiotensin II and endothelin-1 (ET-1) by blood vessel endothelial cells. Angiotensin II stimulates endothelial cells to release various cytokines. In addition, angiotensin II also increases ET-1 release. ET-1 aggravates atherosclerosis, since ET-1 is a strong vasoconstrictor. ET-1 is a marker for atherosclerosis in type 2 diabetes mellitus, while cytokines such as transforming growth factor-β1 (TGF-β1), epidermal growth factor (EGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF) aggravate atherosclerosis.[15]

Efforts to control hypertension produce satisfactory results in reducing the prevalence of PAD in type 2 diabetes mellitus. UKPDS obtained data that efforts to reduce systolic blood pressure of 10 mmHg could reduce the risk of PAD in type 2 diabetes mellitus as much as 16%. UKPDS recommends that systolic blood pressure is maintained at less than 120 mmHg in patients with type 2 diabetes mellitus.[16]

Smoking is a dominant risk factor for PAD in type 2 diabetes mellitus. Gregor et al,[8] and O'Neal et al[9] found a significant correlation between smoking and the prevalence of PAD in type 2 diabetes mellitus. Smoking increases carboxyhemoglobin, causing tissue hypoxia and endothelial damage. In addition, smoking increases platelet aggregation. Smoking also increases adrenalin release, causing vasoconstriction. Smoking increases total cholesterol levels, LDL cholesterol levels, triglyceride, and reduces HDL.17 All of the above aggravates atherosclerosis in type 2 diabetes mellitus. Smoking is one of the dominant risk factors for PAD, both in patients with or without type 2 diabetes mellitus. In this study, there was no patient with type 2 diabetes mellitus who was still smoking, in other words, only ex-smokers and non-smokers were found. The definition of smoking varies from one study to another. In many studies, smoking includes ex-smokers. Even though through bivariate analysis there was no significant correlation between ex-smokers and the prevalence of PAD in type 2 diabetes mellitus, a significant correlation was found using logistic regression analysis, after risk factors were sorted out to eliminate interfering factors. From the logistic regression analysis in this study, history of smoking was also a dominant risk factor for PAD. This result supports a study by Palumbo et al that found a significant correlation between history of smoking and the prevalence of PAD in type 2 diabetes mellitus.[18] Even after a person has stopped smoking, the influence of smoking on the development of atherosclerosis still continues for a long time. This is influenced by the duration of smoking, the number of cigarettes/day, the type of cigarettes, the way they smoke, and the time lapse since the person stopped smoking. The Framingham study found that the risk of death due to cardiovascular disease drops 50% after 2 years cessation of smoking. The mortality risk continues to drop, and after 20 years after cessation, the risk of death due to cardiovascular disease would be.the same as for non-smokers. Koch found the same findings for PAD in patients who have stopped smoking.[19]

A high total cholesterol level is a risk factor for PAD in type 2 diabetes mellitus. In this study, we found a significant correlation between a total cholesterol level of [3]200 mg/dL and the prevalence of PAD. Based on logistic regression analysis, total cholesterol level is a dominant risk factor for PAD aside from smoking. Asakawa et al found a significant correlation between high total cholesterol levels and PAD in type 2 diabetes mellitus.[6]

In patients with type 2 diabetes mellitus, total cholesterol levels are usually normal or slightly increased. In patients with diabetes and insulin resistance, increased total cholesterol levels may be due to increased lipolysis, causing release of free fatty acids (FFA). Free fatty acids are then used by the liver as a material to produces Very-Low Density Lipoprotein (VLDL). VLDL in turn consists of triglyceride and ester cholesterol.[6,31]

In this study, bivariate analysis found a significant correlation between an LDL cholesterol level of ≥100 mg/dL with the prevalence of PAD. Such findings are in accordance with a Finnish study that reported a correlation between total cholesterol level as well as LDL cholesterol levels with the incidence of atherosclerosis in type 2 diabetes mellitus. On the other hand, Gregor and colleagues did not find a significant correlation between LDL cholesterol levels and PAD in type 2 diabetes mellitus.[8] The study by Asakawa et al,[8] and O'Neal et al,[9] also did not find a significant correlation between the two. After logistic regression analysis was performed, no significant correlation was found between LDL cholesterol level and the prevalence of PAD.

LDL cholesterol levels in type 2 diabetes mellitus patients with PAD are usually not much different than those without PAD. In type 2 diabetes mellitus, there is an increase in small dense LDL. Small dense LDL is a factor that plays a greater role in the process of atherosclerosis compared to LDL cholesterol levels. The increase in LDL cholesterol levels in type 2 diabetes mellitus is not a precisely accurate value, since the measurements cannot separate between LDL and Intermediate Density Lipoprotein (IDL), thus making the value high. If LDL and IDL levels could be distinguished, we would find normal LDL levels and increased IDL levels.[19] Small dense LDL undergoes glycation, reducing the sensitivity of LDL receptors in the liver. Reduced sensitivity to LDL receptors causes reduced LDL elimination. Reduced LDL elimination means increased circulating time of small dense LDLs. Small dense LDLs that undergo glycation are easier to oxydize and would then undergo phagocytosis by macrophages. This process in turn stimulates the release of various cytokines involved in the process of atherosclerosis.[18]

In this study, no significant correlation was found between HDL levels and PAD. This result supports studies by Kazunari et al,[5] Asakawa et al,[6] and Gregor et al,[8] who did not find a significant correlation between HDL levels and PAD in type 2 diabetes mellitus. O'Neal on the other hand, found a significant correlation between the two conditions.[9]

HDL carries cholesterol from peripheral tissues through the plasma to the liver to be converted into fatty acids and then excreted through the bile duct. Thus, HDL has an anti-atherogenic characteristic. Reverse cholesterol transport occurs when cholesterols leave the cell and enters a more dense HDL subclass. In this case, lecithin cholesterol acyl transferase (LCAT) esterifizes the cholesterol particle of HDL by transferring unsaturated fatty acids (linoleats from lesithin) into cholesterol to form cholesterol esters. HDL-derived cholesterol esters are immediately transferred to the liver through 2 mechanisms, LDL receptor uptake in the liver, and by being transferred into VLDL by cholesterol ester transferase proteins (CTEPs). These cholesterol esters would then also be sent to the liver to be excreted. These mechanisms thus inhibit atherogenesis. In this study, there was no significant correlation between HDL cholesterol levels in type 2 diabetes mellitus with or without PAD. The reason for the lack of correlation is that in this study, no analysis was performed on weight reduction, calorie restriction, or activity. Weight reduction, calorie restriction, and increased activity could increase HDL levels. In type 2 diabetes mellitus, administration of insulin and oral anti-diabetic agents do not play much of a role in increasing HDL levels.[20]

Hypertriglyceride is often found in type 2 diabetes mellitus. In this study, there was no significant correlation between triglyceride levels and PAD. This result supports studies conducted by O'Neal et al,[6] Asakawa et al,[8] and Gregor et al.[9] Increased triglyceride levels in type 2 diabetes mellitus through 3 mechanisms. The first mechanism is through the secretion of large particle VLDLs by the liver without increasing the rate of VLDL secretion. In this condition, LDL levels are usually normal. This process could occur acutely, particularly when glucose uptake into the liver is increase, or in patients with a high carbohydrate diet. The second mechanism is through reduced lipoprotein lipase (LPL) activity. LPL hydrolyzes VLDL into IDL, to then form LDL. LPL levels on endothelial surfaces are controlled by insulin. In type 2 diabetes mellitus, LPL activity is reduced, thus reducing the hydrolysis of VLDL and kilomicrons. The third mechanism is through increased rate of VLDL secretion by the liver. The VLDL in this final mechanism has a smaller particle size compared to that of the first. In this mechanism, Apo B production is also increased, thus causing hypertriglyceride hyperapo B. LPL is then hydrolyzed by LPL, increasing IDL levels and small dense LDL levels. In type 2 diabetes mellitus, increased VLDL production by the liver plays a greater role in increasing triglyceride levels compared to reduced LPL activity.[18]

Obesity has a close correlation with insulin resistance and type 2 diabetes mellitus. In insulin resistance, aside from the presence of hyperglycemia and obesity, hypertension and hyperinsulinemia are also found. In this study, the chi square test did not find a significant correlation between a BMI of over 25 kg/m$^2$ and the prevalence of PAD, which is in line with findings by O'Neal et al,[6] Asakawa et al,[8] and Gregor et al.[9] However, after logistic regression analysis was performed in this study, a significant correlation was found between a BMI of over 25 kg/m$^2$ and the prevalence of PAD.

Increased prevalence of type 2 diabetes mellitus is not only associated with increased body weight, but also to ethnic and racial background. The obesity type associated with insulin resistance is central or visceral obesity. Visceral obesity could be measured based on waist-hip ratio. Waist to hip ratio is better in determining visceral obesity compared to BMI. Free fatty acid release from adipose tissue is the connector between obesity and insulin resistance. Visceral fat plays an important role, since it is metabolically more active compared to subcutaneous fat, particularly in releasing free fatty acids. Free fatty acids increases liver glucose production and hyperglycemia during fasting. Increased levels of free fatty acids in the peripheral circulation inhibits insulin action in tissues.[21]

Hyperglycemia could cause atherosclerosis through the polyol pathway, auto-oxidation, or protein glycation. These three processes increases oxidative stress and stimulate the release of free radicals. The latter process causes reduced NO release by endothelial cells and increased inflammatory mediators. A high HbA1c level is a parameter for chronic hyperglycemia. In this study, no significant correlation was found between HbA1c and PAD. This result supports the study by O'Neal et al,[6] Asakawa et al,[8] and Gregor et al.[9] The lack of significant correlation between HbA1c and PAD in type 2 diabetes mellitus is because HbA1c could only detect blood glucose regulation in the last 2-3 months, while atherosclerosis in type 2 diabetes mellitus have occurred since the initial phase of insulin resistance. However, the UKPDS study found data that a reduction of HbA1c of

1% reduces the risk of PAD in type 2 diabetes mellitus of 43%.[22]

Hyperglycemia could cause atherosclerosis by means of glycation of the collagen matrix of the vascular wall. This glycation process increases collagen fibers and LDL trapping into the vascular wall.[23] Chronic hyperglycemia facilitates the process of atherosclerosis. Hyperglycemia is toxic to endothelial cells. This toxic effect reduces NO production, thus decreasing vasodilatation, increasing vasoconstriction, hyperplasia of vascular smooth muscle cell hyperplasia, and vascular remodeling. Hyperglycemia induces the expression of fibronectin and type IV collagen and contributes to the development of endothelial dysfunction. Fibronectin is a glycoprotein that plays an important role in cell matrix interaction.[23]

Hyperglycemia increases AGE production, which in turn causes AGE accumulation within cell protein. AGE accumulation is closely correlated to vascular complications. AGEs then bind with AGE receptors on endothelial cells and macrophages. This linkages then causes macrophages and endothelial cells to release TNF and IL-1. Cytokine would then stimulates cells to synthesize protein and proliferate. Aside from that, chronic hyperglycemia increases the production of extracellular matrix and vascular smooth muscle cell proliferation.[23]

## CONCLUSION

In this study, we found a prevalence rate of 35.5% of PAD in type 2 diabetes mellitus. The risk factors associated with PAD are a total cholesterol level of ³ 200 mg/dL, history of smoking, duration of diabetes mellitus of 5 years or more, hypertension, triglyceride levels of ³ 150 mg/dL, and BMIs of over 25 kg/m².

## REFERENCES


1. Waspadji S. Telaah mengenai hubungan faktor metabolik dan respon imun pada penderita diabetes tipe 2: kaitannya dengan ulkus/gangren diabetes [Disertasi]. Jakarta: Universitas Indonesia; 2000.
2. Levin ME, Sicard GA, Rubin BG. Peripheral vascular disease in the diabetic patient. In: Porte D, Sherwin R.S editors. Diabetes mellitus 5th ed. Connecticut : Appleton & Lange; 1997. p. 1127-58.
3. Suyono S. Peranan lipid pada komplikasi vaskular diabetes melitus. In: Waspadji S, Gani RA, Setiati S, Alwi I, editors. Bunga rampai ilmu penyakit dalam. Kumpulan makalah siang klinik Bagian Ilmu Penyakit Dalam FKUI/RSUPNCM 1994 – 1995. Jakarta: Balai Penerbit FKUI; 1996: 171-85.
4. Perkeni: Konsensus Pengelolaan Dislipidemia pada Diabetes Melitus di Indonesia. Perkeni. Jakarta; 1995. p. 1-11.
5. Matsumoto K, Miyake S, Yano M, Ueki Y, Yamaguchi Y, Akazawa S, et al. Insulin resistance and arteriosclerosis obliterans in patients with NIDDM. Diabetes Care 1997; 20: 1738-43.
6. Asakawa H, Tokunaga K, Kawakami F. Comparison of risk factor of macrovascular complications peripheral arterial disease, cerebral disease, and coronary heart disease in Japanese type 2 diabetes mellitus patients. J Diabetes Complication 2000; 14: 307-13.
7. Meijer WT, Groobee DE, Hunink M, Hofman A, Hoes AW. Determinant of peripheral arterial disease in elderly. The Rotterdam study. Arch Intern Med 2000; 60: 2934-8
8. Gregor AS, Price JF, Hau CM, Lee JA, Carson MN, Fowkes FGR. Role of systolic blood pressure and plasma triglyserides in diabetic peripheral arterial disease: Edinburg Artery Study. Diabetes Care 2000; 22: 453-8.
9. O'Neal DN, Lewicki J, Ansari MZ, MatthewsPG, Best JD. Lipid levels and peripheral vascular disease in diabetic and non diabetic subjects. Atherosclerosis 1998; 136: 1-8.
10. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and action of estrogens. N Engl J Med 2002; 46: 340-52.
11. S. Dinko. Hypertension, aging, and atherosclerosis. Med Clin North Am 1997; 81: 1231-40.
12. Mehler PS, Jeffers BW, Estacio R, Schier RW. Association of hypertension and complication in non insulin dependent diabetes mellitus. Am J Hypertens 1997; 10: 152-61.
13. Daugharty, Henecke JW. Epidemiology and risk factors. In: Callow AD, Ernst CB editors. Vacular Surgery: Theory and Practice. Connecticut: Appleton & Lange; 1999. p. 81-9.
14. Coopper ME, Bonnet F, Oldfield M, Dahm K. Mechanism of diabetic vasculopahty: an overview. AJH 2001; 14: 475-86
15. Lehoux S, Tedgui A. Signal transduction of mechanical stresses in vascular wall. Hypertension 1998; 32: 338-45.
16. Adler IA, Stratton IM, Neil AH, Yudkin JS, Mathews RD, Cull AC et al . Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321: 412-9.
17. Dierkx RIJ, Hoek W, Hoekstra JBL, Erkelens DW. Smoking and diabetes mellitus. Neth J Med 1996; 48: 150-62.
18. Palumbo PJ, O'Fallon WM, Osmundson PJ, Zimmerman BR, Langworthy AL, Kazmier FJ. Progression of peripheral occlusive arterial disease in diabetes mellitus. What factors are predictive? Arch Intern Med 1991; 151: 717 – 21.
19. Couch NP. On the arterial concequences of smoking. J Vasc Surg 1986; 3: 807-12.
20. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapo B: The unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. Ann Intern Med 2001; 135: 447-59.
21. Brunzell JD, Chait A. Diabetic dyslipidemia : pathology and treatment. Dalam : Porte D, Sherwin R.S editors. Diabetes Mellitus. 5th ed. Connecticut : Appleton&Lange; 1997. p. 1077-95.
22. Soegondo S. Peran kolesterol HDL sebagai faktor protektif penyakit jantung koroner. In: Bawazier LA, Alwi I, Syam AF, Gustaviani R, Mansjoer A, editors. Prosiding simposium Pendekatan holistik penyakit kardiovaskular. Naskah lengkap Pendidikan Kedokteran Berkelanjutan Bagian Ilmu Penyakit Dalam FKUI; 23 – 25 Februari 2001; Jakarta: Pusat Informasi dan Penerbitan Ilmu Penyakit Dalam FKUI; 2001. 67-9.
23. Fujimoto WY. The importance of insulin resistance in pathogenesis of type 2 diabetes mellitus. Am J Vigna GB, Fellin R. Dyslipidemia in peripheral vascular disease. Curr Opin Lipidol 1996; 7: 254-9.