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## ABO Blood Group Type and the Risks of Peripheral Artery Disease in Type II Diabetes Mellitus

Dedy Pratama

*Division of Vascular and Endovascular Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, dr Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, dedygpratama@yahoo.com*

Adi N.D Puruboyo

*Training Program in Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, dr Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, danangpurmd@gmail.com*

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Cover Page Footnote

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## ABO Blood Group Type and the Risks of Peripheral Artery Disease in Type II Diabetes Mellitus

Dedy Pratama,<sup>1, ID</sup> Adi N.D Puruboyo.<sup>2</sup>

1. Division of Vascular and Endovascular Surgery, 2 Training Program in Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, dr Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

Corresponding author: [dedypratama@yahoo.com](mailto:dedypratama@yahoo.com) Received: 26/Feb/2023 Accepted: 08/Jun/2023 Published: 23/Jun/2023

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### Abstract

**Introduction.** Peripheral artery disease (PAD) is a common complication of diabetes mellitus (DM), affecting up to 20% of people over 65. Blood type is hypothesized to influence PAD, although it has yet to be extensively studied. We aim to investigate the correlation between ABO blood group type and the severity of PAD in patients with type II DM.

**Methods.** We conducted a cross-sectional study on DM type II patients with PAD at the Cipto Mangunkusumo National Hospital in Indonesia between January 2022 to June 2022. PAD was diagnosed based on the ankle-brachial index (ABI) measurement. The PAD severity was grouped into mild (ABI 0.7-0.9) and moderate-severe (ABI <0.7). Patients were categorized as O blood type and non-O (A, B, and AB).

**Results.** Of 366 patients included, 194 with O type and 172 with non-O type. No significant difference in the occurrence. PAD was significantly more severe in non-O blood type patients ( $p = 0.041$ ). Longer periods of diabetes (OR 10.325, CI95% 5.108-20.871,  $p < 0.001$ ) and hypertension (OR 4.531, CI95% 1.665-12.326,  $p < 0.003$ ) were risk factors for more severe PAD.

**Conclusion.** ABO blood group type was not significantly associated with the occurrence of PAD in patients with type II DM. Non-O blood type was associated with more severe PAD, while more prolonged periods of diabetes and hypertension were found to be significant risk factors for more severe PAD.

**Keywords:** diabetes mellitus, peripheral arterial disease, ABO blood group.

### Introduction

Diabetes mellitus (DM) is a highly prevalent disease globally, especially in countries like Indonesia, where it affects a significant portion of the population with a prevalence of 1.5% over the total population.<sup>1-3</sup> One common complication of DM is peripheral artery disease (PAD), which often goes undetected due to its asymptomatic nature.<sup>4</sup> By the time PAD is diagnosed, it has usually progressed to an advanced stage with ulcer formation or gangrene.<sup>5</sup> The ankle-brachial index (ABI), a commonly used screening method, is not very effective in detecting PAD in individuals with type 2 diabetes and those over 65 years old.<sup>6</sup> More advanced screening methods, such as Doppler ultrasonography, angiography, or CT angiography, are expensive and not easily accessible.

Blood type has emerged as a potential risk factor for PAD, although limited studies have been conducted on this topic. Multi-Ethnic Study for Atherosclerosis (MESA) studies in African-Americans and other ethnic populations have shown a significant correlation between blood type A and lower ABI values.<sup>7</sup> Another study found a link between non-O blood groups and the development of PAD and ischemic stroke, possibly due to increased vWF and FVIII levels.<sup>8</sup> However, no research has been done on the relationship between blood type and the severity of PAD in Indonesia. Therefore, this study aims to investigate the correlation between ABO blood type, the prevalence of PAD, and the severity of PAD in Indonesian patients with diabetes mellitus. These findings will serve as valuable primary data for further research on risk factors and early detection of PAD.

### Method

A cross-sectional study proceeded on DM type II patients diagnosed with PAD and came to dr Cipto Mangunkusumo General Hospital (CMGH), Indonesia, from January 2022 to June 2022. The diagnosis of PAD was instituted by measuring the ankle-brachial index (ABI). The severity of PAD was grouped into mild PAD (ABI 0.7-0.9) and moderate-severe PAD (ABI <0.7). The characteristics identified for the study were age, sex, body mass index, diabetes duration, hypertension, and dyslipidemia. The patients were categorized according to the ABO blood group into O and non-O (A, B, and AB) blood types. Collected data were then analyzed using SPSS for Macintosh ver. 25. Sociodemographic characteristics of subjects were analyzed descriptively. The correlation between ABO blood type and the severity of PAD was analyzed using the Chi-square test. The data was then analyzed for its correlation with the severity of PAD using the Chi-square test and multivariate analysis. The outcomes are the occurrence of PAD and the severity of PAD. The Research Ethics Committee Faculty of Medicine, Universitas Indonesia, approved the ethical clearance number KET-561/UN2.F1/ETIK/PPM.00.02/2021.

### Results

Three hundred and thirty-six subjects were enrolled in the study. The baseline subjects' characteristics are presented in Table 1. The correlation analysis between the ABO blood type group and the occurrence of PAD was 172 subjects (47%) with a p-value of 0.780. While to the correlation with clinical characteristics and the severity of PAD, the risk factors of more severe PAD were a longer period of diabetes (OR 10.325 (CI95% 5.108-20.871),  $p < 0.001$ ) and hypertension (OR 4.531 (CI95% 1.665-12.326),  $p < 0.003$ ). The details are presented in Table 2.

## Discussion

In this study, no statistically significant correlation between blood group types and the prevalence of PAD. However, a higher prevalence of PAD showed in the O blood group (53%) than in the non-O blood group (47%). Group O is also the sample with the largest number. This result follows the prevalence of blood type O, which is indeed higher than other groups in the general population, so the number of samples with blood type O was more remarkable in this study. The finding of the highest number of O samples was also observed in the study by Sabino et al.<sup>9</sup>

In this study, a statistically significant correlation was found between ABO blood group types and the severity of PAD. The data obtained in this study is that blood group O has a lower number of moderate-to-severe PAD than the non-O blood group (29.4% vs. 39.5%), with OR having a protective effect (OR = 0.56). This is per the findings of several previous studies, such as the studies of Pike et al.<sup>10</sup> and Sabino et al.,<sup>9</sup> which found a higher frequency of PAD in the non-O group, even though these studies were not divided based on the degree of severity. This is presumably due to the correlation between phenotype groups and several characteristics regarding blood clotting factors, as previously described.<sup>9</sup>

Based on previous studies, several hypotheses explain the relationship between the ABO and PAD blood systems. It was found that blood group A had higher rates of VTE, heart disease, and ischemic stroke.<sup>9,10</sup> Some explanations for this phenomenon are increased levels of Factor VIII and vWF in the plasma of PAD patients in group A, which cause chronic inflammation and cause atherosclerosis, as well as the presence of ABO locus pleiotropism which caused an increase in total serum cholesterol levels in this group. The difference in Factor VIII and vWF levels is thought to be caused by the heterogeneity of blood group determining genes, although the mechanism is still uncertain.<sup>10,11</sup> However, these theories are unproven. Various previous studies have attempted to prove the mechanism of the ABO blood group on the occurrence of arterial events through the mediation of vWF and Factor VIII. Still, this analysis is complicated because high levels of vWF and Factor VIII proteins can only indicate an atherosclerotic inflammatory process and cannot be influenced by blood group. Pike et al. found that the relationship between blood type and the incidence of PAD was only significant in the African-American race group.<sup>11</sup> It is thought to result from an antigenic determinant effect of ABO on vWF structure, leading to an increase in vWF clearance rate.<sup>11</sup> As a consequence, the survival of vWF is longer in non-O samples, and circulating levels of vWF and Factor VIII lead to the release of bioactive molecules that have been found to promote the development of atherosclerosis and PAD through endothelial dysfunction and inflammatory response.<sup>11</sup>

In this study, it was found that hypertension is one of the significant factors that affect the severity of PAD. Hypertension is a risk factor known to be associated with PAD. Despite limited study evidence on how these characteristics influence the incidence of PAD, it was found that patients with hypertension had a higher risk of experiencing PAD and experiencing PAD with a more severe degree.<sup>12</sup> Previous studies have suggested that 50% to 92% of patients with PAD have a history of hypertension. Hypertension also increases the occurrence of claudication by 2.5 to 4 times in both men and women with hypertension.<sup>13</sup>

In addition to hypertension, the condition of diabetes mellitus was found to be significant in influencing the severity of PAD ( $p < 0.001$ ) and exacerbating the occurrence of PAD with the proportion of moderate-severe patients in patients with DM  $\geq 5$  years far more than those with

DM  $< 5$  years (46.4% vs. 8.5%). These results are in line with a study by Wang et al. with 5,345 (38.5%) subjects suffering from diabetes mellitus; the majority ( $n = 5,134$  [96.1%]) had type II DM. Wang et al. found 15.9% of PAD patients with diabetes mellitus compared to 10.4% of PAD patients without DM (5.5% absolute risk difference; adjusted hazard ratio: 1.43; 95% CI: 1.28-1.61;  $p < 0.001$ ),<sup>13</sup> although this supporting study did not include the length of time the patient had diabetes mellitus, it could be interpreted as a confounding factor such as DM to PAD. Wang et al. also found that every 1% increase in HbA1c was associated with a 14.2% increase in the relative risk for cardiovascular disease or the risk of a major adverse cardiovascular event (MACE) (95% CI: 1.09-1.20;  $p < 0.0001$ ).<sup>14</sup>

This study had several limitations, namely its cross-sectional study design that needs a causal correlation, causing the lack of causality between variables. Moreover, the sampling was carried out using secondary data taken from medical records. Thus, there is still a potential for other confounding factors that still need to be considered or managed to control. One of the potential confounding variables is the HbA1c level. Previous studies have shown that the risk of PAD increases by 30% for every 1% increase in HbA1c in patients with diabetes mellitus.<sup>15</sup> However, our center's HbA1c examination had yet to become routine. For the upcoming research, we suggest the examination of the coagulation factor further to classify the PAD severity in each blood group type.

## Conclusions

The ABO blood type was not associated with the occurrence of PAD. The non-O blood type was associated with more severe PAD among DM type II patients. Other risk factors of more severe PAD were a longer period of diabetes and hypertension.

## Disclosure

The authors declare no conflict of interest.

## Acknowledgment

None.

## Role of authors

Conceptualization DP, ANDP, Data curation DP, ANDP, Formal analysis DP, ANDP, Funding acquisition DP, ANDP, Investigation DP, ANDP, Methodology DP, ANDP, Project administration ANDP, Resources DP, Software DP, Supervision DP, Validation LS, Visualization DP, ANDP, Writing original draft preparation DP, ANDP, Writing review and editing DP, ANDP.

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