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Serum Homocysteine Level and Ankle-Brachial Index In Peripheral Arterial Disease

Yanna Indrayana[1,a)], Herpan Syafii Harahap[2,b)]

[1] *Department of Cardiology and Vascular Disease, Faculty of Medicine, Universitas Mataram*
[2] *Department of Neurology, Faculty of Medicine, Universitas Mataram*

[a)]Corresponding author: Yanna Indrayana, Faculty of Medicine, Universitas Mataram. Jalan Pendidikan No.37 Mataram, West Nusa Tenggara. Postal Code 83125. Phone Number: 081234720714. Email: yannaindrayana@unram.ac.id
[b)]Herpan Syafii Harahap, Faculty of Medicine, Universitas Mataram. Jalan Pendidikan No.37 Mataram, West Nusa Tenggara. Postal Code 83125. Phone Number: 08175770062. Email: herpanharahap@yahoo.co.id

Abstrak. Pasien dengan *peripheral arterial disease* (PAD) atau penyakit arteri perifer memiliki risiko kematian yang lebih tinggi dibandingkan dengan populasi normal. Saat ini diketahui terdapat beberapa faktor risiko yang relatif baru untuk terjadinya PAD, salah satunya adalah homosistein. Penelitian yang ditujukan untuk menginvestigasi peran kadar homosistein serum sebagai biomarker derajat keparahan penyakit arteri perifer berdasarkan *indeks ankle-brachial* (ABI) pada berbagai populasi saat ini masih terbatas dan belum pernah dikerjakan di Kota Mataram. Penelitian ini merupakan penelitian potong-lintang yang bertujuan untuk menginvestigasi hubungan antara kadar homosistein serum dan ABI pada 77 pasien PAD rawat jalan di Rumah Sakit Siti Hajar, Mataram. Diagnosis PAD didasarkan pada ABI<0,9. Kadar homosistein serum saat puasa diperiksa dengan menggunakan teknik ELISA. Data karakteristik yang dikumpulkan adalah jenis kelamin, usia, hipertensi, diabetes melitus, dan kategori indeks massa tubuh (IMT). Terdapat korelasi signifikan antara peningkatan kadar homosistein serum dan penurunan ABI. Faktor risiko utama untuk terjadinya PAD pada subjek yang diteliti adalah hipertensi, diabetes melitus, dan kelebihan berat badan/obesitas. Kadar homosistein serum merupakan prediktor keparahan PAD yang diukur menggunakan ABI.
Keywords: kadar homosistein serum, *ankle-brachial index*, penyakit arteri perifer

Abstract. Patients with peripheral arterial disease have a higher risk of death compared to normal populations. There are several relatively new risk factors significantly increase the vulnerability to suffer from peripheral arterial disease, one of which is homocysteine. Studies investigating the role of serum homocysteine level as a biomarker of the severity of peripheral arterial disease based on ankle-brachial index (ABI) in different population were still limited and it was never been studied in Mataram. This was a cross-sectional study aimed to investigate the correlation between serum homocysteine level and ABI in 77 peripheral artery disease (PAD) outpatients in Siti Hajar Hospital, Mataram. The diagnosis of PAD was based on ABI<0.9. Fasting serum homocysteine level was examined using the ELISA technique. Characteristic data collected were gender, age, hypertension, diabetes mellitus, and body mass index (BMI) category. There was significant correlation between the increase of serum homocysteine level and the decrease of ABI. The main risk factors for peripheral arterial disease in the subjects are hypertension, diabetes mellitus, and overweight/obesity. Serum homocysteine level is a predictor of peripheral arterial disease severity measured using ABI.
Keywords: Serum homosisteine level, ankle-brachial index, peripheral arterial disease

INTRODUCTION

At present, cardiovascular diseases (CVDs) is still becoming the main cause of mortality around the world. In 2016, 17.9 million people died due to CVDs, representing about 31% of total death with all causes (World Health Organization, 2017). The prevalence of cardiovascular diseases is predicted to continue to increase, especially in developing countries, since the prevalence of its risk factors is also increasing (Stewart, Manmathan, & Wilkinson, 2017). Riset Kesehatan Dasar (Riskesdas) survey conducted in 2013 showed that the prevalence of cardiovascular diseases in Indonesia, a representation of developing country, is about 1.5% from total population (Badan Penelitian dan Pengembangan Kesehatan, 2013). Similar with the number of death globally, about 37% of deaths in Indonesia is attributable to cardiovascular dieases (Cardiovascular Division and Health Services Research Centre, 2017).

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INTRODUCTION

At present, cardiovascular diseases (CVDs) is still becoming the main cause of mortality around the world. In 2016, 17.9 million people died due to CVDs, representing about 31% of total death with all causes (World Health Organization, 2017). The prevalence of cardiovascular diseases is predicted to continue to increase, especially in developing countries, since the prevalence of its risk factors is also increasing (Stewart, Manmathan, & Wilkinson, 2017). Riset Kesehatan Dasar (Riskesdas) survey conducted in 2013 showed that the prevalence of cardiovascular diseases in Indonesia, a representation of developing country, is about 1.5% from total population (Badan Penelitian dan Pengembangan Kesehatan, 2013). Similar with the number of death globally, about 37% of deaths in Indonesia is attributable to cardiovascular dieases (Cardiovascular Division and Health Services Research Centre, 2017).

Cardiovascular diseases is a group of diseases consisted of coronary heart disease, cerebrovascular disease, and peripheral arterial disease. Peripheral artery disease (PAD) is the common manifestation of systemic atherosclerosis especially involving arteries other than coronary artery, most common in lower extremity arteries (Kohlman-Trigoboff, 2019). Globally, its prevalence is high, especially in low-to-middle income countries, estimated about 28.7% (Criqui & Aboyans, 2015). Since most of PAD are unfortunately asymptomatic, it is commonly underdiagnosed and undertreated (Olin & Sealove, 2010). Peripheral arterial disease, either symptomatic or asymptomatic, are associated with increased risk of cardiovascular mortality in cohort study and its early diagnosis and reduction risk management is important (Sartipy, Sigvant, Lundin, & Wahlberg, 2018). Therefore, the diagnosis of PAD in the primary care setting has important prognostic value (Diehm, et al., 2009). In clinical practice, screening and diagnosis of PAD can be conducted using simple and non-invasive instrument named *ankle-brachial index* (ABI) (Campia, Gerhard-Herman, Piazza, & Goldhaber, 2019).

The major risk factors of PAD are similar to those of coronary artery disease and cerebrovascular diease, including older age, male, hypertension, diabetes mellitus, overweight/obesity, and cigarette smoking (Bennett, Silverman, Gill, & Lip, 2009). The prevalence of those risk factors are quite high among Indonesian population (Mihardja, Soetrisno, & Soegondo, 2014; Rachmi, Li, & Baur, 2017; Rosjidi, Isro'in, & Wahyuni, 2017; Harahap & Indrayana, 2018; Peltzer & Pengpid, 2018). Optimal management to those risk factors is the crucial in the management of PAD and it may reduce the overall cardiovascular mortality (Shammas, 2007). In recent years, some relatively new risk factors for PAD have been proposed, including homocysteine (Bennett, Silverman, Gill, & Lip, 2009).

Homocysteine is an intermediate product of the amino acid methionine metabolism produced via the transmethylation pathway. In normal condition, homocysteine that is formed will be metabolized either via remethylation or transsulfuration pathway. In the remethylation pathway, homocysteine is converted back to methionine either via folate-dependent or folate-independent remethylation pathway. In the transsulfurationpathway, homocysteine is converted to cysteine (Cacciapuoti, 2018). The remethylation pathway through folate-dependent pathway is dependent on folic acid, B2 and B12 vitamins, while transsulfuration pathway is dependent on B6 vitamin (Barroso, Handy, & Castro, 2017). Therefore, the total plasma concentration of homocysteine (tHcy) is influenced by blood concentrations of folic acid, B12 and B6 vitamins (Hankey, 2018). In the blood circulation, a level of homocysteine <13 μmol/L is considered normal, while a level ≥13 µmol/L is considered hyperhomocysteinemia (Cacciapuoti, 2018).

Since homocysteine was proposed to be associated with the progression of atherosclerosis, now it is considered to be the risk factor of PAD. Meta-analysis of epidemiologic study showed that homocysteine level in PAD patients was higher than those healthy subjects (Khandanpour, Loke, Meyer, Jennings, & Armon, 2009). The role of homocysteine in the pathogenesis of PAD can be influenced by ethnic variation. This was the first study investigating the correlation between serum homocysteine level and severity of PAD determined based on ABI in the sub-population of Mataram, West Nusa Tenggara.

METHOD

This was cross-sectional study involving 77 asymptomatic peripheral artery disease outpatients visiting Siti Hajar Hospital, Mataram, during the period of May to October 2019. The diagnosis of peripheral artery disease in those patients were based on their ankle-brachial index (ABI) <0.9. The exclusion criteria are the coexistence of some medical conditions, i.e chronic kidney disease, liver disease and hypothyroid based on medical records, and prior history of consumption folic acid, B6 and B12 in the last three months. This study was approved by Komisi Etik Penelitian Kesehatan Universitas Mataram (No. 233/UN18.F7/ETIK/2019).

The characteristics data of the subjects collected in this study were age, gender, hypertension, diabetes melitus, and cigarette smoking based on their medical records. The data of body mass index (BMI) of each subject was also collected by measuring weight in kilogram (kg) divided by height in square meters (m^2) (Hicks, et al., 2018). The BMI was categorized into three groups, namely underweight (BMI<18.5 kg/m^2), normoweight (BMI 18.5-24.9 kg/m^2), overweight/obese (BMI≥25 kg/m^2). Since overweight and obesity are risk factors for PAD, they are grouped into one group, the overweight/obesity group respectively (Murata, et al., 2015).

The ABI was measured by comparing the ratio of higher of the systolic blood pressure of the two ankle arteries of the limb and higher of the two systolic blood pressure of the upper arms using hand held vascular Doppler Bestman BF-520T. The ABI<0.9 was diagnostic for PAD (Rac-Albu, Iliuta, Guberna, & Sinescu, 2014). The serum samples for the examination of homocysteine level were obtained from 5cc of overnight (8 to 10 hours) fasting

blood samples of the patients. The serum homocysteine level was measured in Laboratory of Hepatika, Mataram, using FineTest® Human HCY (Homocysteine) ELISA Kit (Kit Product Code HCY161119).

The data of age was presented as mean (95%CI), while data of gender, hypertension, diabetes mellitus, cigarette smoking, and BMI category were presented as frequency. The statistical analysis of the correlation of the serum homocysteine level and ABI was based on Spearman test. The result of statistical analysis were significant if $p<0.05$.

RESULT AND DISCUSSION

The incidence of peripheral artery disease (PAD) are mostly determined by the existence of its both major and relatively new risk factors. Homocysteine is a representative of relatively new risk factors for PAD which are getting more attention from the researchers in recent years. In the present study, the characteristic data of the subjects representing the major risk factors as well as serum hocysteine level representing the relatively new risk factor for PAD were obtained (table 1). The results showed that most of subjects are hypertensive, suffered from diabetes mellitus, overweight/obese, but with a small frequency of male gender and those who had cigarette smoking habits. The higher frequency of hypertension, diabetes mellitus, and overweight/obese among subjects with PAD in the present study was in accordance with the results of previous studies in different populations (Alvim, et al., 2018; Krishnan, Geevar, Mohanan, Venugopal, & Devika, 2018). The mean of age of subjects are 57 years old. The population of subjects aged 40 years and older in Indonesia are at high risk for cardiovascular disease (Maharani, Sujarwoto, Praveen, Delvac, Tampubolon, & Patel, 2019).

TABLE 1. The characteristics of the subjects

Category	Mean (95% CI), unless otherwise stated
Gender, n(%)	
Male	16 (20.8)
Female	61 (79.2)
Age (years)	57.38(54.94 – 59.82)
Cigarette smoking, n(%)	
Yes	3 (3.9)
No	74 (96.1)
Hypertension , n(%)	
Yes	55 (71.4)
No	22 (28.6)
Diabetes mellitus, n(%)	
Yes	43 (55.8)
No	34 (44.2)
BMI category, n(%)	
Underweight (<18.5 kg/m^2)	4 (5.2)
Normoweight (18.5-24.9 kg/m^2)	29 (37.7)
Overweight/obese (≥25 kg/m^2)	44 (57.1)
ABI	0.79 (0.77 – 0.81)
Homocysteine (µmol/L)	4.79 (4.43 – 5.15)

CI=confidence interval; BMI=body mass index; ABI=ankle-brachial index

The present study showed that most of the subjects are female (79,2%). This result contrast with existing reference which showed that male gender was the risk factor for PAD (Bennett, Silverman, Gill, & Lip, 2009; Alzamora, et al., 2010; Aggarwal, Loomba, & Arora, 2012). However, other study conducted by Rafie *et al*. showed similar result with the present study in which female gender had a higher frequency (Rafie, et al., 2010). These different results may be due to differences ethnic of the subjects studied. The differences of ethnic studied affect the role of various vascular risk factors in the pathogenesis of PAD (Bennett, Silverman, Gill, & Lip, 2009). The small frequency of subjects who had cigarette smoking habit are mostly due to small frequency of male subjects.

All of the well-known risk factors mentioned above as well as hyperhomocysteinemia contribute to the abnormal ankle-brachial index (ABI) (Campia, Gerhard-Herman, Piazza, & Goldhaber, 2019). The present study showed that

the mean of the serum homocysteine level were in the normal range. It is interesting that there was no subject which were PAD patients that showed elevation in serum homocysteine level (table 1). In the context of the existence of frequency of subjects with PAD who had mild-moderate to severe hyperhomocysteinemia, this result is contradictive with the results of a meta-analysis and previous studies conducted in different populations (Khandanpour, Loke, Meyer, Jennings, & Armon, 2009; Weragoda, Seneviratne, Weerasinghe, & Wijeyaratne, 2016; Preethi & Hemachandran, 2019). It can be proposed that diverse ethnic groups may have different serum homocysteine profiles. However, statistical analysis showed that there was significant correlation between the increase of serum homocysteine level and the decrease of ankle-brachial index (ABI) (table 2). It suggested that even in the normal range, the increase of serum homocysteine level are correlated with progression of peripheral artery disease, but it still need further investigation.

TABLE 2. The correlation between serum homocysteine level and ABI

	Mean (95%CI)	**r**	**p-value**
Homocysteine	4.79	-0.323	0.004*
ABI	0.79		

*Significant ($p<0.05$)

The mechanism by which homocysteine is responsible for the progression of peripheral arterial disease is not well established yet. Theoretically, its role is mediated via its effect to the progression of atherosclerotic plaque of arterial wall and the generation of hypertension by several mechanisms. First, homocysteine may induce oxidative stress via activation of NADPH oxidase resulting in the generation of reactive oxygen specises (ROS) (Omae, Nagaoka, Tanano, & Yoshida, 2013). This ROS is responsible for the decrease of bioavailability of nitric oxide (NO), a molecule important for vasodilatation, and this will lead to vasoconstriction and hypertension (Lai & Kan, 2015). In addition, NO which react to superoxide (O_2^-), a kind of ROS, to form peroxynitrite ($ONOO^-$) will facilitates further atherosclerotic plaque progression and decrease of vascular compliance resulting in arterial hypertension (Mury, Chirico, Mura, Millon, Canet-Soulas, & Pialoux, 2018). Second, the homocysteine-induced oxidative stress is also responsible for the activation of matrix metalloproteinases (MMPs), zinc-containing endopeptidases secreted by connective tissue as well as proinflammatory cells. In the atherosclerotic plaque, MMPs degrade elastin matrix separating the intima form the media and induce collagen synthesis. These process will result in smooth-muscle cells migration from the media to the intima, the increase of intima-media thickness, and the decrease of elastin/collagen ratio which eventually induce vascular hypertrophy and endothelial dysfunction, the hallmark of hypertension (Vacek, Rehman, Neamtu, Yu, & Givimani, 2015). Third, homocysteine alters transsulfuration pathway, a kind of its metabolism pathway, resulting in decrease of hidrogen sulfide (H_2S) production (Yang & He, 2019). Hydrogen sulfide (H_2S) is well known as a vasorelaxant molecule produced by vascular tissue and decrease of its production will lead to vascular constriction and hypertension (Sen, Mishra, Tyagi, & Tyagi, 2010). However, further study is still needed to investigate whether the theories described above have significant negative correlation with ABI, as shown by the result of the present study.

CONCLUSION

The serum homocysteine level negatively correlates to ankle-brachial index (ABI). The identifiable risk factors of peripheral arterial disease (PAD) were age, female gender, hypertension, diabetes mellitus, overweight/obesity, and serum homocysteine level, but not cigarette smoking. The role of ethnicity in influencing serum homocysteine level still needs further investigation.

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