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Relationship between Glomerular Filtration Rate with Ankle Brachial Index in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study

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Abstract
Type 2 Diabetes Mellitus (DM) is associated with a spectrum of chronic complications, notably diabetic kidney disease and peripheral artery disease (PAD). The assessment of PAD can be readily accomplished via the ankle-brachial index (ABI) measurement. Given the rising prevalence of diabetes globally, it is imperative to elucidate the interrelation between renal function and PAD. This study used a retrospective and cross-sectional study involving 146 Type 2 DM and PAD patients. The glomerular filtration rate (GFR) stages were analyzed for PAD presence. Variables such as gender, age, and smoking status were examined. The Ankle Brachial Index (ABI) was used to diagnose PAD. Of the participants, 54.7% were male, and 84.7% were aged 50 or older. PAD prevalence was 51.3%. A significant association was found between GFR stages and PAD ($p < 0.05$), with PAD prevalence increasing from 10.6% at Stage 1 to 80.0% at Stage 5. Males had higher PAD incidence (61.0%) compared to females (39.0%). Older participants (≥50 years) exhibited a higher PAD prevalence (84.4%). To sum, the study confirms a significant association between declining kidney function and increased PAD incidence, highlighting the need for targeted interventions and early detection strategies to improve patient outcomes.
Key words: Type 2 Diabetes Mellitus, diabetic kidney disease, peripheral artery disease, glomerular filtration rate, Ankle Brachial Index.

Introduction

Type 2 DM is a group of metabolic disorders characterized by hyperglycemia resulting from abnormalities in insulin secretion, insulin action, or both, leading to various chronic complications in the eyes, kidneys, nerves, and blood vessels (PERKENI, 2019). In 2021, the International Diabetes Federation (IDF) estimated that at least 463 million people worldwide aged 20-79 years had diabetes (International Diabetes Federation, 2021). With the aging population, the prevalence of diabetes is projected to increase to 111.2 million in the 65-79 age group. This number is expected to rise to 578 million by 2030 and 700 million by 2045. According to IDF projections, Indonesia ranked seventh among the top ten countries with the highest number of diabetes cases in 2019, with 10.7 million cases. It is estimated that by 2030, diabetes will be the seventh leading cause of death in Indonesia (International Diabetes Federation, 2021; Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia, 2013).

According to Riskesdas, the prevalence of diabetes mellitus diagnosed by doctors among the population of all ages in Central Java Province is above the national prevalence, with almost all provinces experiencing an increase since 2013. In 2020, a health profile survey of South Sulawesi Province indicated that the highest increase in diabetes cases was in Makassar city, with 18.305 residents affected (Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia, 2013).

Complications arising from DM can involve macrovascular and microvascular blood vessel disturbances, such as chronic kidney and PAD. Diabetic kidney disease is characterized by albuminuria, a decrease in the GFR, or both, accompanied by diabetes mellitus, which can lead to chronic kidney disease (Assem et al., 2021). Diabetic kidney disease is the leading cause of

chronic kidney disease, accounting for approximately 44% of new cases. Chronic kidney disease is a global health problem with various risk factors. In the United States, out of about 24 million people with diabetes mellitus, around 180.000 suffer from chronic kidney disease. In Indonesia, among the population aged 18-70 years across four central provinces, the prevalence of chronic kidney disease was found to be about 12.5%. Microalbuminuria is often present at the time of type 2 DM diagnosis. Diabetic kidney disease, a microvascular complication of type 2 DM, is characterized by the presence of microalbuminuria (30mg/day) without kidney impairment, along with increased blood pressure, leading to a decrease in glomerular filtration and eventually resulting in end-stage renal failure (Criqui & Aboyans, 2015).

PAD affects 12-14% of the general population. In the United States, about 8.5 million individuals aged over 40 years suffer from PAD (American Diabetes Association, 2022). Type 2 diabetes mellitus doubles the risk of PAD, which increases the mortality and morbidity of individuals with type 2 diabetes mellitus. A study conducted in seven Asian countries, including Indonesia, found that 17.7% of the type 2 diabetes mellitus population had PAD. The incidence of PAD in patients with chronic kidney disease is associated with age, with a 28% increased risk for every 10-year increment in age. Both microalbuminuria and PAD increase the risk of cardiovascular mortality (Hsieh et al., 2009). This study aims to determine the GFR profile in patients with diabetic kidney disease with or without PAD.

Materials and Methods

Study design

This research is a retrospective study employing a cross-sectional design. This study examines the characteristics and relationship of GFR stages in patients with diabetic kidney disease, both with and without PAD.

Study setting and population

In this study, 150 subjects were initially involved, but 4 were excluded for failing to meet the criteria. As a result, the final sample size consisted of 146 individuals who met the specified criteria. All participants had Type 2 diabetes mellitus and PAD, were aged between 40 and 60, and had no history of heart disease. The study included outpatients and inpatients at Dr. Wahidin Sudirohusodo Hospital in Makassar. The sample was selected from this population, and the study lasted from January 2024 until the required sample size was obtained.

Variables

The study considers three types of variables: independent, dependent, and confounding. The independent variables are diabetic kidney disease and PAD. The dependent variable is the GFR, while the confounding variables include obesity, dyslipidemia, and hypertension.

Ankle Brachial Index measurements

ABI is a non-invasive vascular screening test to detect PAD. The ABI is a non-invasive vascular screening test to identify PAD. The ABI is determined by comparing the systolic blood pressure measurements at the ankle with those at the brachial artery in the arm, obtained through direct measurements of both the patient's arms and legs. The interpretive criteria for ABI values are as follows: an ABI value greater than 1.4 suggests suspected arterial calcification, values between 1.0 and 1.4 are considered normal, values between 0.91 and 0.99 are categorized as borderline, and an ABI value of 0.90 or less indicates abnormal findings. ABI boasts high sensitivity, specificity, and commendable accuracy in diagnosing PAD, making it the most cost-effective tool for detection.

Sample size

The sampling process was executed through consecutive sampling methodology, in which individuals who satisfied the predetermined inclusion criteria were sequentially enlisted until the necessary sample size was attained. This process was underpinned by a sample size calculation, employing the formula proposed by Lemeshow et al. (1997), which ascertained that a minimum of 73 participants was required for the study.

Data analysis

Data analysis was performed using SPSS version 25. The analysis methods included both descriptive and statistical tests. Descriptive analysis was employed to obtain general information about the study sample. The statistical methods used included calculating mean values, standard deviation (SD), and frequency distribution. The Chi-Square test was used for statistical testing, with results considered significant if the p-value was less than 0.05. The findings will be presented in narrative form, supplemented with tables and figures.

Ethical consideration

The Health Research Ethics Committee at the Faculty of Medicine, Hasanuddin University, Makassar, has reviewed and approved all study protocols. Prior to commencement, informed consent was obtained by clearly explaining the research background, objectives, and benefits, as well as the procedures for biopsy sample collection and examination that the study subjects would undergo.

Results

Table 1 outlines the initial demographics of the study participants at Dr. Wahidin Sudirohusodo Hospital. Of the 150 individuals, 82 (54.7%) were male and 68 (45.3%) were female. Most participants were 50 or older, making up 84.7% of the group. The distribution of participants with and without PAD was almost equal, with 77 (51.3%) having PAD and 73 (48.7%) not

having PAD. Additionally, the participants were spread across different stages of the GFR, with the highest number in Stage 1 (31.3%) and the lowest in Stage 5 (6.7%).

In Table 2, the data presents the correlations between gender, age group, smoking status, and PAD. The findings indicate that a majority of female patients, 55.9%, were affected by PAD, revealing a statistically significant difference in PAD occurrence between genders ($p < 0.05$). On the other hand, individuals aged 50 years or older showed a higher prevalence of PAD at 48.8%. However, the statistical analysis suggests that age is not significantly associated with PAD occurrence ($p > 0.05$). Moreover, non-smokers were found to have a higher proportion of PAD at 54.0%, indicating a statistically significant difference in PAD occurrence based on smoking status ($p < 0.05$).

According to the data presented in Table 3, most patients in Stage 1 were female, accounting for 38.2%. This indicates no significant correlation between gender and the distribution of GFR stages, suggesting that gender does not significantly impact GFR stages ($p>0.05$). Similarly, in terms of age, the most significant proportion of patients in Stage 1 were 50 years or older, representing 31.5%. This analysis reveals no statistically significant difference between age groups and the distribution of GFR stages, suggesting that age does not significantly affect GFR stages ($p>0.05$). Regarding smoking status, the majority of patients in Stage 1 were non-smokers, making up 37.0%. This data implies that there is no statistically significant difference between smoking status and the distribution of GFR stages, indicating that smoking status does not significantly influence GFR stages ($p>0.05$).

In Table 4, an analysis was conducted to explore the correlation between GFR stages and PAD using the Chi-Square test, which revealed a notable link between GFR stages and the presence of PAD. The early stages (Stage 1) show a relatively low incidence of PAD. However, as the GFR

stage advances, the occurrence of PAD increases significantly, with a majority of patients in Stages 3a, 3b, 4, and 5 exhibiting PAD. This indicates that PAD is more widespread among patients with higher GFR stages, suggesting that reduced kidney function is linked to an elevated risk of PAD.

Discussion

Most participants were men (54.7%) aged 50 or older (84.7%). Most participants had Stage 1 GFR PAD (31.3%), and a small number had Stage 5 PAD (6.7%). These findings align with previous research indicating that PAD is more prevalent in males and becomes more common with age (Criqui et al., 2015). However, several studies have shown similar PAD risk between men and women after menopause (Goodney et al., 2014; Allison et al., 2015; Hirsch et al., 2016; Selvin et al., 2016). The study also underscores the importance of monitoring kidney function in PAD patients and recommends early detection, especially in men aged 50 years or older (Hiatt et al., 2001). It advocates for a comprehensive approach to managing PAD and suggests health policies that support early detection and prevention (Bonaca et al., 2015). The study aims to provide insights and a framework for developing more effective prevention and treatment programs, ultimately improving the quality of life for patients (Norgren et al., 2007).

The study found that a higher percentage of men (61.0%) have PAD compared to women (39.0%). Men were also more likely to be at GFR Stage 2 (64.7%), while women were more often at Stage 1 (55.3%) and Stage 4 (60.0%). These findings are consistent with previous studies showing that men tend to be at higher GFR stages and have a higher prevalence of PAD (Norgren et al., 2007). However, conflicting results from other studies exist, including no significant difference in PAD prevalence between genders or a more frequent decline in kidney function in women in specific populations (Fowkes et al., 2017). To enhance the health outcomes

of patients with PAD and impaired GFR, especially in men aged 50 and above, it is crucial to implement educational programs targeting PAD risk and early detection (Liu et al., 2018). Additionally, it is essential to adopt sex-specific clinical interventions and a multi-disciplinary approach (Norgren et al., 2007). Moreover, health policies supporting the prevention and management of PAD, along with community-based programs, can potentially reduce prevalence and enhance the quality of life for patients (Bonaca et al., 2017).

The study showed that patients aged ≥50 years had a higher prevalence of PAD (84.4%) than those aged <50 years (15.6%), with a predominance of elderly patients at higher GFR stages, such as stage 3b (95.0%). These findings are supported by studies confirming an increased risk of PAD with advanced age (Criqui & Aboyans, 2015; Matsushita et al., 2015). However, other studies suggest that lifestyle and genetic factors may be more influential than age (O'Hare et al., 2014). Recommendations include routine screening for PAD at age ≥50 years, the development of health management strategies specific to elderly patients, and health campaigns to raise awareness about the risk of PAD and impaired GFR (Norris et al., 2016).

The data regarding the distribution of patients by GFR stage indicates a direct correlation between declining renal function and the prevalence of PAD. For instance, only 10.6% of patients at Stage 1 had PAD, whereas 80.0% of those at Stage 5 had PAD. This observation is consistent with existing research that links decreased GFR to a heightened risk of PAD, particularly in individuals with chronic kidney disease and low GFR (O'Hare et al., 2014; Matsushita et al., 2015). Nonetheless, certain studies posit that lifestyle, comorbidities, and genetics may exert a more significant influence than the decline in kidney function (Norris et al., 2016; Kalantar-Zadeh et al., 2017). In response to this, it is advised that specialized interventions be formulated to target amendable risk factors (Kalantar-Zadeh et al., 2017; Singh et al., 2014).

Additionally, educational initiatives must be introduced for patients suffering from chronic kidney disease, informing them of the risks associated with PAD and proposing strategies for its prevention (Hirsch et al., 2015).

The analysis using the Chi-square test revealed a notable relationship between the GFR stage and the prevalence of PAD, indicating an increase in PAD incidence with declining kidney function. This correlation is bolstered by research demonstrating that reduced GFR is linked to a heightened risk of PAD, particularly in the later phases of chronic kidney disease (O'Hare et al., 2014). Diminished GFR exacerbates vascular conditions and speeds up the progression of atherosclerosis, thereby contributing to a higher occurrence of PAD (Hirsch et al., 2018). Although some studies propose that lifestyle and comorbidities may exert a more significant influence than the decline in renal function, it is recommended to regularly monitor GFR, manage modifiable risk factors, and educate patients about the risk of PAD (Criqui et al., 2016; Bashir et al., 2018; Singh et al., 2020).

This study has some limitations in terms of analyzing other factors, such as risk factors for PAD in patients with impaired GFR. Further research on risk factors that influence the development of PAD in both men and women is also needed to understand the mechanism of this disease better. Additional studies are needed to comprehend the differences in PAD prevalence between the sexes in the broader population and to develop more effective interventions for the prevention and treatment of PAD.

Conclusion

The study examined the connection between the GFR stage and PAD incidence and drew several conclusions. Most participants were male, aged 50 years or older, with PAD. The analysis revealed a notable correlation between the GFR stage and PAD, showing a higher prevalence of

PAD as kidney function declined, from 10.6% at Stage 1 to 80.0% at Stage 5. Male and an advanced age can be a risk factor for PAD prevalence. This study reaffirmed the significant association between the GFR stage and the incidence of PAD.

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Conflict of Interest

There is no conflict of interest in this study.

Informed Consent

All subjects provided written informed consent.

Author Contributions

RUP collected data, contributed data or analytical tools, conceived and designed the analysis, performed the analysis, and wrote the paper. HR, AMA, SB, IM, and AAZ proofread and validated the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Figure & Tables

Table 1. Distribution of characteristics of research subjects

Characteristics	Frequency (N=150)	
	n	%
Gender		
Male	82	54.7%
Female	68	45.3%
Age Groups		
<50 years	23	15.3%
≥50 years	127	84.7%
PAD		
Yes	77	51.3%
No	73	48.7%
GFR Stage		
Stage 1	47	31.3%
Stage 2	34	22.7%
Stage 3a	19	12.7%
Stage 3b	20	13.3%
Stage 4	20	13.3%
Stage 5	10	6.7%

GFR: Glomerular Filtration Rate, PAD: Peripheral Artery Disease.

Table 2. Distribution of respondents' characteristics with peripheral arterial disease incidence

Characteristics	Peripheral Artery Disease		p-value
	PAD	Non-PAD	
Gender			
Male	35 (42.7%)	47 (57.3%)	0.049
Female	38 (55.9%)	30 (44.1%)	
Age Groups			
< 50 years	11 (47.8%)	12 (52.2%)	0.492
≥ 50 years	62 (48.8%)	65 (51.2%)	
Smoking Status			
Yes	19 (38.0%)	31 (62.0%)	0.047
No	54 (54.0%)	46 (46.0%)	

Chi-square test

Table 3. Distribution of respondents' characteristics with glomerular filtration rate

Characteristics	Glomerular Filtration Rate						p-value
	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5	
Gender							
Male	21 (25.6%)	22 (26.8%)	14 (17.1%)	11 (13.4%)	8 (9.8%)	6 (7.3%)	0.374
Female	26 (38.2%)	12 (17.6%)	5 (7.4%)	9 (13.2%)	12 (17.6%)	4 (5.9%)	
Age Groups							
< 50 years	7 (30.4%)	9 (39.1%)	2 (8.7%)	1 (4.3%)	2 (8.7%)	2 (8.7%)	0.278
≥ 50 years	40 (31.5%)	25 (19.7%)	17 (13.4%)	19 (15.0%)	18 (14.2%)	8 (6.3%)	
Smoking Status							
Yes	10 (20.0%)	15 (30.0%)	10 (20.0%)	9 (18.0%)	3 (6.0%)	3 (6.0%)	0.861
No	37 (37.0%)	19 (19.0%)	9 (9.0%)	11 (11.0%)	17 (17.0%)	7 (7.0%)	

Chi-Square Test

Table 4. Relationship between glomerular filtration rate stage and peripheral arterial disease

Stage_GFR	PAD		Value	Asymp. Sig. (2-sided)
	Non PAD	PAD		
Stage 1	42 (89.4%)	5 (10.6%)	59.829	0.000
Stage 2	19 (55.9%)	15 (44.1%)		
Stage 3a	3 (15.8%)	16 (84.2%)		
Stage 3b	5 (25.0%)	15 (75.0%)		
Stage 4	2 (10.0%)	18 (90.0%)		
Stage 5	2 (20.0%)	8 (80.0%)		

Chi-Square Test

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