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CLINICAL AND ANGIOGRAPHIC PROFILE OF ASYMPTOMATIC CORONARY ARTERY DISEASE IN PATIENTS UNDERGOING PERIPHERAL ANGIOGRAM

Cardiology

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ABSTRACT

Background: Peripheral arterial disease (PAD) and coronary artery disease (CAD) are parts of the spectrum of Atherosclerotic cardiovascular disease (ASCVD) . Although the prevalence and severity of PAD increases with age, the affected population remain asymptomatic . Peripheral arterial disease, whether symptomatic or asymptomatic, had been found to be a risk factor for non-fatal and fatal coronary disease and cerebrovascular events . Subjects presenting with lower limb PAD are high risk group for concomitant CAD, and thus necessitate screening and treating of CAD.

Aim Of The Study:

1. To know the proportion of asymptomatic coronary artery disease in patients with aorto iliac lesions
2. To determine the clinical and angiographic profiles of asymptomatic coronary artery disease

Materials and Method: Overall, 141 consecutive patients with PAD, undergoing peripheral angiogram between January 2017 and January 2018 were included after satisfying inclusion and exclusion criteria. Participants were subjected to peripheral angiogram of the lower limbs and coronary angiogram on the same session. The coronary lesions were quantified using Coronary artery Syntax Scores, while the peripheral lesion were quantified using TransAtlantic Inter-Society Consensus Document II (TASC II) and Total Peripheral Score (TPS). **Results:** Among the 141 patients analysed, 75.18% had underlying CAD. A moderately positive correlation was found between the TPS and Syntax score (Pearson correlation = 0.575, $p < 0.0001$). A TPS cut-off value of 6 was found to be predicting severe CAD (with Syntax score > 32) $p < 0.001$). Among the lower limb arterial segments femoropopliteal arterial segment lesion was the most predictive arterial segment for presence of severe CAD with sensitivity of 97.6% and specificity 31% ($p=0.008$) Among the risk factors analysed diabetes mellitus was the strongest predictor of increased the risk of CAD in patients with PAD, with an odds ratio of 7.796 for having multi-vessel CAD [95% CI = 2.749-22.104, $P<0.001$] and syntax score of more than 32 [OR=3.737 (95% CI-1.081-12.915) P=0.037] in multivariate regression analysis. **Conclusion:** The proportion of asymptomatic CAD among lower limb peripheral artery disease was observed in 75.18% of the volunteers. A TPS score higher than 6 was found to be predictive of severe CAD. Among the lower limb artery segments femoropopliteal arterial segments is the most predictive of the arterial segments to estimate severe CAD. Cardiovascular risk factors such as diabetes, hypertension, sex, age and smoking significantly increased the risk of CAD. Thus, simultaneous coronary artery evaluation may be considered in patients with lower extremity peripheral artery disease esp., femoropopliteal artery segment stenosis in the presence of coexisting diabetes, and multiple cardiovascular risk factors.

KEYWORDS

INTRODUCTION

Peripheral arterial disease is an occlusive arterial disease, involving major arteries distal to the aortic arch. The prevalence of PAD in the lower limbs increase with increasing age, at upto 10% to 25% in age above 55 years.(7) Usually the affected individuals are asymptomatic. It has shown that PAD is a risk factor for non-fatal and fatal CAD and cerebrovascular events. Patients with PAD alone have the same relative risk of death from cardiovascular cause as those with coronary or cerebrovascular disease.(1,8) While it is generally assumed that patients with severe PAD have concomitant severe CAD, the prevalence of significant CAD in patients with severe PAD varies widely from 28% to 94% in published reports.—(3,913) This variability is in part attributable to differences in how CAD was defined (≥50% or ≥70% diameter stenosis) and diagnosed (on history alone, electrocardiogram, stress testing, or diagnostic coronary angiography), and the location of PAD.

METHODS

Setup, Study Design And Patient Population

The study was a single-centre, hospital-based, prospective observational study, conducted at Department of Cardiology, Government Medical College, Kottayam, which is a regional tertiary care centre. During the study period of January 2017 to January 2018, 141 consecutive patients with PAD were recruited. Patients who were older than 35 years of age, diagnosed to have PAD, in the absence of previously diagnosed coronary artery disease, structural heart diseases and congenital heart diseases, were subjected to electrocardiogram and echocardiogram. These patients underwent conventional peripheral and coronary angiograms, which were analysed and quantified using TASC II and Syntax scores, respectively. Patients with known history of structural & congenital heart diseases, and coronary artery disease were excluded.

Data Collection

Data was collected in a proforma made specifically for the study. The cases were selected in accordance to the aforementioned inclusion and exclusion criteria. The purpose of the study was explained to the subjects in their language of understanding and informed written consent was taken. A detailed history, clinical examination and the following investigations were carried out. Electrocardiogram, echocardiogram, conventional peripheral and coronary angiogram were taken provided that the renal function allowed for the latter. Peripheral angiograms were taken during the same session, via a transradial approach using 5 French pigtail catheters, while coronary angiograms were performed using 6 French catheters. Stenosis beyond 50% of luminal diameter was considered significant for lower extremity PAD. The angiograms, thus obtained, were subjected to analysis. Coronary artery stenoses of more than 50% luminal diameter in arteries at least 1.5 mm in diameter were added further to calculate total Syntax score. The patients were then grouped into low (syntax score ≤22), intermediate (syntax score 23–32) and high (syntax score ≥ 33) syntax score subgroups. TASC II classification was utilised to assess the extension and severity of the lower limb PAD. Total peripheral score (TPS), a scoring system was then developed to

quantify the cumulative lesions burden of PAD. Three lower limb arterial segments (aorto-iliac, femoropopliteal and below knee) were assigned a numeric value, namely, normal segments = 0 point, TASC A lesion = 1 point, TASC B lesion = 2 points, TASC C lesion = 3 points, TASC D lesion= 4 point. The total score was calculated for every patient and this score was termed as the total peripheral score (TPS). The patients were also grouped into normal, single vessel CAD and multi-vessel CAD, and angiographic characteristics and number of cardiovascular risk factors were compared. By analysing the data with the receiver operating characteristic (ROC) curves an attempt was made to determine if a cut-off TPS value might be used for estimating the high Syntax subgroup patients. Nonetheless, attempt was made to find out most valuable disease segment that could help in predicting a high score for the Syntax subgroup in PAD patients.

Definitions

CAD was defined as ≥ 50% angiographically luminal narrowing of coronary arteries. CAD severity was defined according to the number of obstructive coronary arteries corresponding to 50% or more narrowing and categorized into following subgroups:

1. Normal coronaries
2. Single vessel disease > 50% stenosis in a one coronary artery
3. Two vessel disease > 50% stenosis of two coronary artery segments
4. Three vessel disease > 50% stenosis of three coronary artery segments
5. Left main coronary artery disease > 50% stenosis of Left main coronary artery (LMCA)
6. LMCA stenosis without additional diseased vessels were categorized as Left main stenosis (LMS) only.
7. Multi-vessel CAD (MVD) was defined as 2- or 3-VD and LMS.

Stenoses of more than 50% were accepted as significant for lower extremity PAD. Claudication is a pain, cramp or sense of fatigue in a muscle group of the lower extremity related to sustained exercise and relieved promptly by a few minutes of rest while standing evenly on both feet. A diagnosis of hypertension was defined as a history of antihypertensive drug use or at least two blood pressure measurements ≥ 140/90 mmHg during the course of hospital stay. Diabetes was diagnosed when patients were taking an oral hypoglycemic agent, using insulin, had a fasting glucose level ≥ 126 mg/dL or glycosylated hemoglobin (HbA1c) ≥6.5%. A diagnosis of dyslipidemia was made when a patient had a history of statin use, had a total cholesterol level ≥ 200 mg/dL or triglyceride (TG) level ≥ 150 mg/dL. Cerebrovascular disease was defined as a focal neurological deficit lasting beyond 24 hours which resulted in irreversible brain damage or body impairment. Patients who had smoked within the last year were considered smokers.

Data Analysis

The data were assessed using Pearson correlation coefficient, logistic regression analysis, wherever necessary, with the help of SPSS software (v22.0). A probability less than 0.05 was considered significant.

RESULTS

The study was conducted in Government Medical College, Kottayam to study the clinical profiles of patients with PAD. Total of 141 patients with pad were consecutively analysed. The study predominantly included males (86.50%) with males more than 50 years amounting to 80.1% of the study population. The mean age was 59.5 ± 8.9 years. Among the risk factors analysed, smoking was the most common risk factor (80.1%), followed by dyslipidemia (69.5%), hypertension (64.5%) Diabetes mellitus (61%), family history of IHD (28.4%) in descending frequency. About three-fourths of the study subjects revealed to have concomitant CAD, although none of them had symptoms pointing to the same. Of patients with CAD, multivessel CAD was predominant with a frequency of 63.83% while single vessel CAD occurred in 11.35 %. The prevalence of two vessel disease observed was 12.76 %, while three vessel disease and LMCA disease were observed in 47.52 % and 3.55 % respectively. After analysing the CAG of 141 patients with syntax score and PAG with TPS score the two scores was correlated using statistical methods. The correlation and regression method, the findings indicates a moderately positive correlation between the TPS and Syntax score (Pearson correlation = 0.575, p < 0.0001) . By analysing the predictive value of total peripheral score as a screening tool to predict a significant coronary artery disease using ROC curve, it was observed that subjects with total peripheral score more than 6 has syntax score of more than 32 with a sensitivity of 82.9% and a specificity of 77% (p-value less than 0.0001). Moreover, among the arterial segments of lower limb, patients with femopopliteal disease had high syntax score, with a sensitivity of 97.6% and a specificity of 31%. (AUC-0.643, p<0.008).

While analysing the risk factors for CAD and PAD, diabetes (OR-7.796 (95% CI-2.749-22.104); P<0.001) and dyslipidaemia [OR-5.631 (95% CI-1.829-17.334 P<0.003)] were observed as the independent predictors of concomitant multi-vessel CAD and PAD in the logistic regression analysis. In patients with PAD and CAD with syntax score of more than 32, diabetes mellitus [OR-3.737 (95% CI-1.081-12.915, P< 0.037)] and hypertension [OR-3.818 (95% CI-1.276-11.428, P<0.017)] are the significant risk factors by binary logistic regression method. This shows that diabetes was an independent predictor of multivessel disease and CAD with high syntax score.

Thus considering the risk factors of significant CAD in patients with PAD smoking, diabetes mellitus, systemic arterial hypertension and dyslipidaemia may be considered as risk factors in predicting CAD in patients with lower extremity PAD. Therefore, screening of CAD should be considered in PAD patients with these risk factors. In addition, lifestyle modification, like cessation of smoking, do help in the management of PAD patients.

DISCUSSION

In this observational study, PAD predominantly affected those above the age of 50 years. Studies have shown that the incidence of PAD increases in a linear fashion with age, with a sharp increase after 75 years of age.(2,14) On top of this, Davey et al elucidated that PAD reduces the life expectancy as well when compared with unaffected population.(7,15)

Male predilection has been noted across various study populations, with twofold increased risk of the disease in men as compared to that in women.—(2,8,16) However, this gender difference was not noted in the study by Selvin et al.(14) Our study population had a male predominance with more than three fourths being men. Hultgren et al found that amputation rates as well as survival rates in 234 subjects with PAD, did not differ in between the two sexes despite matching them for age. It was also found that female sex is in itself a risk factor for developing PAD, however in the later part of life.—(16) Although we did not quantify the symptoms, women usually tend to have more severe symptoms.—(16)

Multiple risk factors were assessed for, and smoking (80.1%) had the highest frequency in our study population. Smoking has remained the single major risk factor in the development of PAD in various studies, followed by systemic hypertension, diabetes and dyslipidemia, to name a few.——(3,9,1719) The Framingham Heart Study has discerned smoking as one of the risk factors in cardiovascular disease as well."(2,20) Smoking doubles the risk of PAD irrespective of the sex.(2) Smoking cessation improved ankle pressure and exercise intolerance in the study by Quick et al.(21) Astonishingly, Jonasan et al noticed that rest pain never occurred in patients when assessed after a year of smoking cessation.(22) In a systematic review of 17 studies by Willigendael, 2.3 fold increase in symptomatic PAD in current smokers, and 2.6 fold increase in reformed smokers, was seen, with a strong increase in heavy smokers.(23) Smoking drastically increases the incidence of PAD more than that of CAD.(4)

Other risk factors are dyslipidaemia (69.5%), hypertension (64.5%), diabetes mellitus (61%) and lastly, family history of IHD (28.4%). Hypertension increased the risk for PAD by 2.5 fold in men and four fold in women, among to the Framingham study population.(2) Cigarette smoking, impaired glucose tolerance, and hypertension were powerful predisposing factors. Impaired glucose tolerance was a greater risk in women than in men, and glycosuria carried a greater risk than other indicators of impaired glucose tolerance. Hypertension increased risk 2.5- to fourfold, respectively, in men and women.(2) Persistent hyperglycemia has been well studied and documented as a risk factor in the development of ASCVD.–(14,24) Increased incidence of major adverse cardiovascular events (MACE), amputation and death in diabetics was shown by Beckman et al. –(24) The United Kingdom Prospective Diabetes Study (UKPDS) group also identified elevated Glycosylated Hemoglobin (HbA_{1c}) as an independent risk factor in the development of PAD, along with systemic hypertension, smoking and CAD.————————(25) Diabetes in PAD impairs lower limb functional status owing to coexisting peripheral neuropathy, which in turn worsens the quality of life, along

with the functional impairment caused by CAD ————(26) Jude et al and Beckman et al concluded that the diabetes led to poor outcomes despite revascularization when compared with non-diabetics.————(24,27) Addressing the aforementioned risk factors would improve the outcomes in PAD and CAD to a great extent.

Herzter et al., encountererd CAD in at least 60% of the patients, while Valentine et al noted that 72% of patients with lower limb PAD had CAD, and Her et al. noted that asymptomatic CAD occurred in 69.5% of patients with PAD. (3,17,28) Marisco et al., came across CAD in 68% of patients in a cohort of 200 patients with PAD, with 55% patients having significant CAD, while Duran et al., showed that 72 % of 231 patients with PAD had concomitant CAD. (10,29) We came across CAD in 75.18% in the study population demonstratable by conventional coronary angiogram, which is slightly higher than what has been seen in the previous studies. It is worthwhile to mention that most of these patients had no cardiac symptoms in our study.

When looking at the CAD profile of the patients, the coronary angiograms showed that the prevalence of single vessel disease was 11.35 % and multivessel disease was 63.83%. Two vessel disease was observed in 12.76 % and three vessel disease in 47.52 % while LMCA disease was observed in 3.55 %. Sukhija et al reported a higher prevalence of multivessel disease (63%) and LMCA disease (18%) in patients with PAD compared with those without PAD. (12) Ishihara et al, explicated that the severity of the coronary artery disease affected the prognosis of patients with lower extremity PAD.(30) It is clear that multivessel CAD is a frequent accompanier of lower limb PAD. In the study by Cho et al. CAD frequented in 62% of patients with PAD, of whom 72% had multivessel disease, yet only 13% complained of angina.(13) Anticipation and early identification of CAD in these patients might improve the survival and reduce the adverse outcomes substantially.

Coronary and peripheral angiograms were performed and were analysed for calculation of syntax and TPS scores, respectively. A moderately positive correlation was noted among the two scores (Pearson correlation = 0.575, p < 0.000). While studying the receiver – operator curve (ROC), it was found that participants with a TPS of more than 6 were found to have a syntax score of 32 with a sensitivity of 82.9% and specificity of 77%(p value less than 0.0001).

Vuruskan et al., showed similar observations in individuals with lower limb PAD ""(31)

Various lesions along the peripheral arterial tree were assessed for predicting a high syntax score, using ROC curve. Femoropoplitieal segments had a sensitivity of 97.6% and specificity of 31% in the prediction of high syntax scores (p<0.008). Vuruskan et al., also noticed that critical femoropopliteal stenoses were associated with a high syntax score in the study involving 178 individuals with lower extremity PAD. ""(31) Habib et al encountered more aorto-iliac PAD in patients with CAD.(9) King et al. reported more profunda femoris disease in diabetics while Strandness et al. came across infrapopliteal disease more frequently.(32,33) Autopsy studies have found the presence of significant iliac and carotid artery stenoses in individuals who had died of myocardial infarction.(4)

Previous studies and our observations showed that lower limb PAD lesion location affects the severity of CAD which can affect the prognosis in patients with lower limb PAD.

Using logistic regression analysis, various risk factors were studied, among which diabetes (OR-7.796 (95% CI-2.749-22.104); P<0.001) and dyslipidaemia(OR- 5.631 (95% CI-1.829-17.334 P<0.003) were observed as the independent predictors of concomitant multi-vessel CAD. Syntax score of more than 32 was associated with diabetes mellitus (OR-3.737 (95% CI-1.081-12.915 P< 0.037and hypertension(OR-3.818 (95% CI-1.276-11.428 P<0.017), by binary logistic regression method. Thus diabetes was an independent predicator of multivessel CAD and high syntax scores.

Thus considering the risk factors of significant CAD in patients with PAD diabetes mellitus systemic hypertension and dyslipidaemia may be considered as risk factors for CAD in patients with lower extremity PAD. Screening of CAD should be considered early in PAD patients with these risk factors, along with specific management for better outcomes.

Limitations

The small sample size undermines the validity of the study and hence larger sample size would have improved the shortcomings. However, time constraint did not allow us to overcome this.

CONCLUSION

Peripheral arterial disease is a bothersome disease state with significant limitation of quality of life along with adverse outcomes. PAD is often associated with subclinical CAD, especially in the presence of common risk factors. CAD has remained the most common cause of mortality amounting to about 40-60%, especially in those with large vessel PAD. (4,34) Diabetes mellitus, systemic hypertension, dyslipidemia and smoking are the risk factors, which can be modified by pharmacological therapy and lifestyle changes, thereby improving outcomes. Of course, anticipation and early detection of the subclinical disease, would allow us to treat, modify and slow down the progression of disease.

Conflict of Interest

There was no conflict of interest among the authors.

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