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Coexistent atherosclerotic renal artery and lower limb peripheral artery disease in patients with symptomatic triple vessel coronary artery disease

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Abstract
Objective: The study was designed to estimate the prevalence of concomitant peripheral artery disease (PAD) in patients with symptomatic triple vessel coronary artery disease (TV-CAD) and to determine the associated risk factors.
Materials and Methods: A total of 48 newly diagnosed patients with symptomatic critical triple-vessel coronary artery disease on coronary angiogram were included in the study. These patients had not undergone any previous revascularization procedure (Percutaneous coronary intervention (PCI) or Coronary Artery Bypass Grafting (CABG). The coronary, renal and lower-limb angiograms were performed via the femoral artery access. Patients identified to have critical triple vessel coronary artery disease, also had renal and lower-limb angiographic shoots taken through hand-injections.
Results: The coexistence of atherosclerotic renal artery stenosis (ARAS) and lower-limb peripheral artery disease (LL-PAD) was seen in 33 % cases (16 out of 48). Only one patient of the overall 16 patients who had LL-PAD was symptomatic for the LL-PAD and the patient had a history of intermittent claudication. A significant number of patients, who were noted to have LL-PAD during the study showed involvement of below knee arteries e.g. Anterior Tibial Artery (ATB) and Posterior Tibial Artery (PTB), which were typically in the 4-5 mm diameter range.
Conclusion: The presence of multiple risk factors should prompt evaluation for PAD in patients identified to have multi-vessel CAD, as both CAD and LL-PAD often co-exist and have similar risk-factor profile. Also, patients with concomitant atherosclerotic disease may benefit with more intensive revascularization strategies and novel anti-thrombotic approaches.

Keywords: atherosclerosis, coronary artery disease, peripheral arterial disease, multi-vessel disease

Introduction

Coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular (CvD)/carotid artery disease all stem from underlying atherosclerosis, which is highly prevalent across the globe. Atherosclerosis is characterized by diseased endothelium, low-grade inflammation, lipid accumulation, and plaque formation within the intima of the vessel wall [1]. It is a disease with generalized manifestations with coronary, carotid and peripheral involvement. Atherosclerosis can complicate into plaque rupture or erosion with ensuing arterial occlusion resulting into ischemic events e.g. myocardial infarction, stroke, peripheral or limb ischemia and cardiovascular death. The prevalence of CAD is observed to be high in patients suffering from PAD [2]. Both, CAD and PAD have similar pathogenesis and risk factors like comorbidities including long standing hypertension, diabetes mellitus, hyperlipidemia, smoking and obesity. It is clinically proven that the prognosis worsens if the disease involves more than one arterial bed which is indicative of diffuse atherosclerosis. Although majority of the evidence regarding atherosclerotic diseases come from the economically affluent nations, the low and middle-income nations bear a major financial and medical burden along with the considerable mortality and morbidity [1].

The Global Burden of Diseases (GBD) study has estimated the global prevalence of CAD to be around 154 million in 2016, which represents 32.7% of the global burden of cardiovascular disease. The American Heart Association (AHA) estimated a prevalence of CAD of 15.5 million for a period of 2009 to 2012. A systematic review and analysis showed that globally, a total of 236.62 million people aged 25 years and older had peripheral artery disease, among whom 72·91% were in low-income and middle-income countries [3]. Co-existence of peripheral artery disease (PAD) in patients with ischaemic coronary arterial disease have been reported with increased mortality, thus highlighting the need for aggressive therapy in these set of patients [4]. Moreover, secondary preventive measures e.g. lifestyle changes for modifiable risk factors, prophylactic use of antithrombotic drugs and therapy for existing co-morbidities should be exercised to improve prognosis. The European Society of Cardiology (ESC CCS) recommends adding a second antithrombotic drug to aspirin for long-term secondary prevention in patients with high or a moderate risk of ischemic events such as those with diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m2. Treatment options for dual antithrombotic therapy in combination with aspirin 75 − 100 mg daily in patients who have

a high or moderate risk of ischaemic events, and do not have a high bleeding risk are clopidogrel, prasugrel, ticagrelor and low dose rivaroxaban (2.5mg bid) [5].

REACH (REduction of Atherothrombosis for Continued Health) is an integrated, international registry designed to focus on patients with stroke, MI, PAD, and multiple risk factors. As per the registry, there is an established atherothrombotic disease in more than one vascular bed e.g. approximately 18–35% of patients with CAD also had PAD and/or CvD and approximately 46–68% of patients with PAD also had CAD and/or CvD. In a prospective dataset of GenePAD study, Patients ≥40 years with suspected CAD were screened for PAD. Around 23.0% of the patient population was confirmed to have concomitant CAD and PAD. It is well known that PAD is underdiagnosed, which was supported by the GenePAD study as only 7% of the patients that were diagnosed during the study had a history of prior diagnosis of PAD [1]. Bhatt and colleagues, on behalf of the REACH Registry Investigators, looked at over 7,000 patients with symptomatic PAD. It was observed that 63% of patients with PAD had polyvascular disease, i.e. concomitant symptomatic cerebrovascular or cardiovascular disease or both [6]. Approach to a patient with PAD includes a comprehensive vascular examination, non-invasive procedures as well as invasive angiography, which is considered as the 'gold standard' in diagnosis of PAD. The non-invasive procedures include measurement of the resting ankle brachial pressure index with measurement of the toe-brachial pressure index, transcutaneous oxygen assessment, or exercise testing and duplex ultrasound. Digital subtraction angiography was conventionally considered the 'gold standard' for evaluation of the extent of the disease in PAD. However, it has been outmoded by computed tomography angiography and magnetic resonance angiography primarily due to the non-invasive nature and a high sensitivity and specificity [7]. Clinical guidelines for the management of CAD and PAD have been developed by several societies and organizations like ESC guidelines [8], ESC-EASD, ESVM. Secondary prevention of CV events recommendations includes the control of diabetes mellitus, hypertension through lifestyle modification, pharmacological therapies e.g. statins, antiplatelets and antithrombotic drugs with a special emphasis on patient education. PAD is emerging as a significant tool for risk stratification of patients with coronary artery disease or cerebrovascular disease [11]. There is also a strong evidence suggestive of concomitant presence of triple vessel coronary artery disease in patients with peripheral artery disease [12]. However, the converse i.e. data on the prevalence of peripheral artery disease in patients with multi-vessel coronary artery disease is scarce. The current study was designed considering the fact that India is the focal point for the global epidemic of non-communicable diseases e.g. type 2 diabetes mellitus, metabolic syndrome and change in lifestyle patterns and the availability of India-specific data is limited [13]. This study aims to give an impetus for the screening and surveillance of PAD in all patients with triple-vessel coronary artery disease.

Materials and Methods

Objective

To estimate the prevalence of concomitant peripheral artery disease *viz*: atherosclerotic renal and lower limb arterial disease (ARAS and LL-PAD), in patients with symptomatic triple vessel coronary artery disease (TV-CAD). The study was conducted in accordance to the ethical principles guiding human research - Declaration of Helsinki and was approved by a local ethics committee.

Aims

To study amongst those with triple vessel coronary artery disease (TV-CAD):

- The coexistence of atherosclerotic renal artery stenosis (ARAS) and lower-limb peripheral artery disease (LL-PAD).
- Verify symptomology attributable to PAD in those with LL-PAD.
- Pattern of arterial disease involvement in those with LL-PAD.
- Determine association of risk-factors for atherosclerosis (*viz*: Hypertension, Diabetes mellitus, Dyslipidemia, Smoking/ Tobacco habit, Fa/H of CAD/ PAD) in those with co-existent polyvascular disease.

Subjects

A total of 48 patients, who were newly diagnosed with symptomatic critical triple-vessel coronary artery disease on coronary angiogram were included in the study. These patients had not undergone any previous revascularization procedure (Percutaneous coronary intervention (PCI) or Coronary Artery Bypass Grafting (CABG). The renal function parameters were in the normal range i.e. Serum Creatinine < 1.4mg/dl and Blood urea < 38mg/dl.

Angiographic study

- The coronary, renal and lower-limb angiograms were performed via the femoral artery access.
- Critical disease was defined as presence of ≥70% stenosis in the reference vessel (as determined by the supervising cardiologist).
- Patients identified to have critical triple vessel coronary artery disease, also had renal and lower-limb angiographic shoots taken through hand-injections.

Cathlab specifics

Contrast Media

Non-ionic, water-soluble contrast medium - Brand: Iopamiro 370 containing equivalent of 18.5 g of iodine.

Cathlab Machine

Philips Allura Xper FD 10.

Catheter Used

6 Fr Judkins left (JL) for left coronary cannulation. 6 Fr Judkins right (JR) for obtaining images from RCA, Renal arteries and Lower limbs angiograms.

Statistical Analysis

Statistical analysis and graphs were developed using MS-EXCEL Worksheet for WINDOWS TM.

Results

Overall, 48 patients with triple vessel coronary artery disease (TV-CAD) were included in the study. 34 patients out of the total 48 enrolled in the study were over 60 years of age. The coexistence of atherosclerotic renal artery stenosis (ARAS) and lower-limb peripheral artery disease (LL-PAD) was seen in 33 % cases (16 out of 48). Two-third cases did not have significant ARAS and/or LL-PAD. (Figure 1) Considering that co-existing of LL-PAD places the patients with CAD in a higher risk category, screening for PAD in all patients with multi-vessel CAD should be mandatory and could yield substantial patient load with this co-morbidity [14].

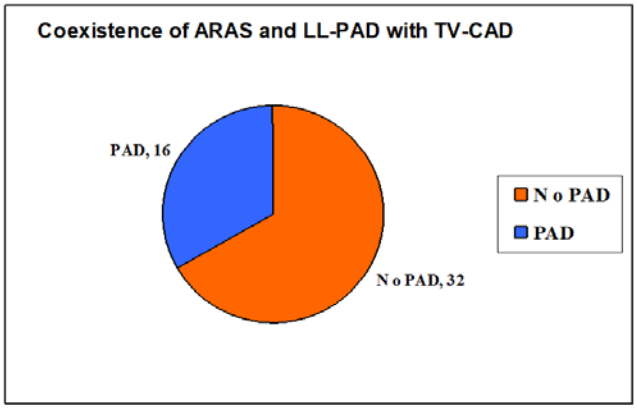

Fig 1: Co-existence of atherosclerotic renal artery stenosis (ARAS) and lower-limb peripheral artery disease (LL-PAD) in TV-CAD

Only one patient of the overall 16 patients who had LL-PAD was symptomatic for the LL-PAD and the patient had a history of intermittent claudication. This is in line with findings from other major studies and registries, which suggests the silent nature of LL-PAD, with symptoms seen in less than 50% patients with documented LL-PAD [15]. The onus of identifying LL-PAD in high-risk patients with CAD therefore lies with the physician and not the patient, as the patient may have very little to contribute in terms of history of symptoms. A significant number of patients, who were noted to have LL-PAD during the study showed involvement of below knee arteries e.g. Anterior Tibial Artery (ATB) and Posterior Tibial Artery (PTB). These vessels in a large number of patients showed calcification of their walls and collateralization resulting in reformation at ankle level (Figure 2). These arteries typically were in the 4-5 mm diameter range, unlike the External Iliac Artery and Superficial Femoral Artery, which invariably are > 6mm in diameter. This raises the issue of possible differences in pathophysiology of atherosclerosis in arteries < 5mm diameter (which would also include the coronary arteries as in this study) vis-à-vis the pathophysiology of atherosclerosis in larger arteries with diameter > 6mm. Presence of atherosclerotic arterial disease in arteries with larger diameters like External Iliac, Superficial Femoral (and maybe Carotid) arteries may not truly be reflective of similar atherosclerotic disease in smaller caliber arteries like the coronary arteries.

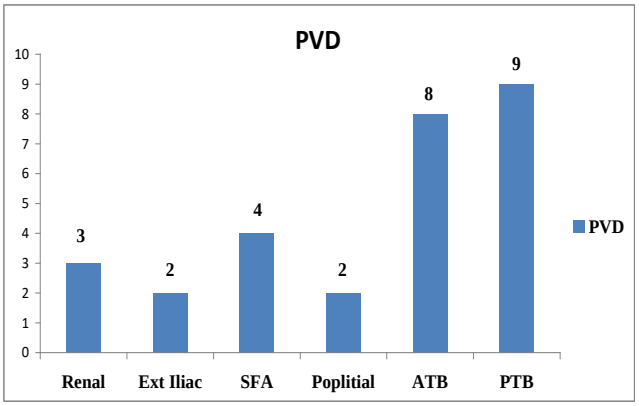

Fig 2: Pattern of peripheral arterial involvement in lower-limb peripheral artery disease (LL-PAD)

Amongst the 16 patients in this study with co-existent PAD, a significant number (13 out of 16) of patients had 2 or more risk factors of atherosclerosis e.g. hypertension, type II diabetes mellitus, dyslipidemia, smoking, tobacco, family history of coronary artery disease or peripheral artery disease. None of the patients had a family history of PAD (Figures 3).

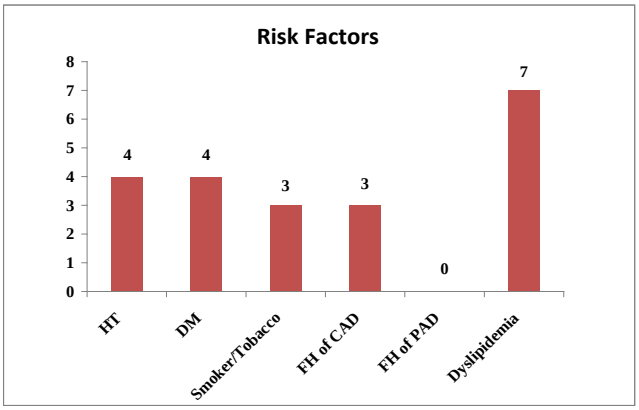

Fig 3: Risk factors for atherosclerosis in study population

The pattern of vascular involvement was studied in association with risk factors like hypertension and diabetes. A total of 13 patients had co-existent hypertension and few of them had disease in multiple arterial territories as depicted in Figure 4.

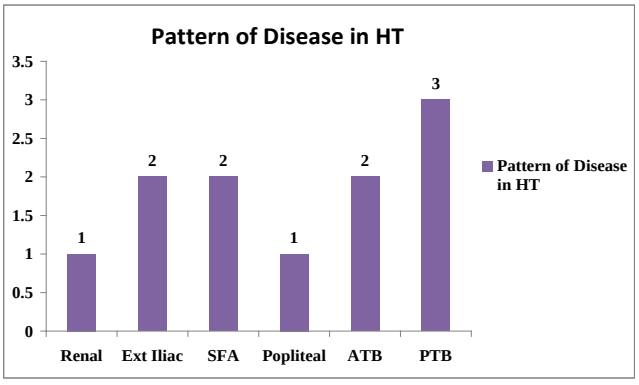

Fig 4: Pattern of PAD in patients with selected risk factor (Hypertension)

Discussion

PAD is recognized to be associated with increased incidence of CAD and also multivessel disease, thus it is considered as a significant risk factor for cardiovascular events. The prevalence of PAD is reported to increase with age and ranges from 1-3% in the forties and >20% in the eighth decade. The age-adjusted prevalence of PAD is approximately 12% and an estimated 27 million adults >55 years of age in Europe and North America have PAD. It is also proven that almost 40% of the patients at high cardiovascular risk (i.e. age ≥70 years, diabetic, known cardiovascular disease) have PAD.[16] PAD is mostly under-diagnosed because it is asymptomatic and also because the ankle-brachial index (ABI) is not routinely measured. Thus, PAD falls in the spectrum of diseases that remain under-diagnosed and under-treated. These factors highlight the fact that early detection of PAD in patients with CAD would prevent the disease progression and also serve as an effective measure for secondary prevention in patients with CAD [17]. The probability of developing cardiovascular events depends on the severity and extend of atherosclerosis e.g. diffuse or systemic disease, plaque disruption, possibility of thrombus formation and development of embolus. The probability is heightened by risk factors like type 2 diabetes mellitus, chronic kidney disease, hyperlipidemia and hypertension [18]. A study was conducted in the Arabian Middle Eastern region to investigate the predictors and prevalence of asymptomatic PAD among patients undergoing coronary angiography [17]. It was observed that, an overall prevalence of asymptomatic PAD among patients with and without CAD of 14.7% and 4.5%, respectively. The primary factors for failure of diagnosis observed were lack of awareness among physicians and the asymptomatic nature of PAD. Considering the increasing significant morbidity and mortality associated with PAD, it becomes imperative for clinicians to care about PAD. The estimated 5-year mortality rate for patients with PAD is 30% with symptomatic PAD causing a decrease in quality (QoL). Mortality in these patients are a result of myocardial infarction and stroke. Concomitant CAD and PAD has grave prognosis and lower QoL than patients with either of the disease alone [16].

The REACH registry [19], an international, prospective, observational study that enrolled patients with established CAD, cerebrovascular disease or PAD, or with at least three atherosclerotic risk factors, observed that approximately 25% of patients had manifestations of thrombosis in more than one arterial bed. The study detected that 24.8% of patients with CAD had concomitant disease in other vascular beds, thus highlighting the prevalence of multi-vessel atherosclerosis. Furthermore, presence of these comorbidities is associated with major adverse cardiovascular events (MACE). The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial observed that patients with the highest risk of recurrent vascular events include those with disease in ≥2 vascular beds, a history of HF, renal insufficiency defined as an eGFR <60 ml/min, or diabetes. It was also observed that patients with ≥1 of these high-risk features (as defined by REACH or CART analysis) have a 2-fold increase in vascular events compared with patients without these high-risk features. It concluded that the combination of low-dose rivaroxaban and aspirin reduces the absolute risk of vascular complications by 3%, i.e. approximately 30 events prevented for every 1,000 patients treated for 30 months [20].

A study evaluated the comparative determinants of 4-year CV event rates in stable patients at risk of or with atherothrombosis. A total of 45,227 patients with baseline data were included in this 4-year analysis. In both patient sub-sets i.e. having ischemic events at baseline and stable atherosclerosis without ischaemic events, polyvascular disease was considered as a significant risk factor in addition to diabetes. CV mortality and morbidity leading to hospitalizations in patients with polyvascular disease was seen in 47.14% patients with prior ischemic events at baseline and 45.01% patients with stable atherosclerosis. The study concluded that polyvascular disease is the strongest predictor of future ischemic events. Diabetes mellitus and history of previous ischemic events in the recent past (prior 12 months) are also associated with risk elevation [21]. These observations can help physicians in identifying high risk populations mandating intensive preventive efforts with novel therapies.

A comprehensive clinical approach that encompasses prevention, detection and early intervention for PAD, is the need of the hour. Although therapies aiming to reduce the underlying cardiovascular risk e.g. antithrombotic agents, statins, anti-hypertensive agents are recommended, patients with PAD are often treated less intensively that those with an adverse CV event or stoke. Ankle-brachial index (ABI) is a non-invasive, inexpensive, universally accepted tool and an ABI <0.9 has a sensitivity and specificity of >95% for the diagnosis of PAD. However, it is often not performed due to the current risk-stratification strategies based on medical history and symptomatology. ABI improves the accuracy of the Framingham Risk Score which predict CV events in high-risk individuals including patients with CAD. Incorporation of ABI for patients enrolling in 'health checks' and also in routine practice in cardiology, endocrinology, neurology, vascular surgery, and geriatrics shall certainly help in early diagnosis and timely intervention of PAD [16]. Several antithrombotic strategies, including potent antiplatelet agents with or without oral anticoagulants, have been evaluated to reduce the residual ischemic risk of patients with stable CAD or PAD. The COMPASS trial has demonstrated the efficacy of a combination of rivaroxaban 2.5 mg BD (low dose) and aspirin 100 mg OD in reducing ischemic events in stable CAD or PAD, with an increase in major bleeding but similar rates of fatal and intracranial bleeding as compared to aspirin.[22] A study conducted by Darmon *et al* evaluated the balance of ischemic and bleeding risks according to the presence of more than or equal to 1 enrichment criteria in "COMPASS-eligible" patients. The study concluded that in stable patients with high risk of an atherothrombotic event, those with multiple enrichment criteria (e.g. age > 65 years, asymptomatic carotid stenosis > 70%, diabetes mellitus, heart failure, chronic kidney disease, PAD, history of ischaemic stroke, current smoking status) had a greater increase in ischemic events than in bleeding risk. Thus, this subset may be considered to benefit from low-dose rivaroxaban plus aspirin therapy.[23] This data needs to be verified in larger studies or pooled with data from other similar studies before we decisively use these findings to identify patients who are highly likely to have co-existent vascular disease. The presence of multiple risk factors should prompt evaluation for PAD in patients identified to have multi-vessel CAD. Such an evaluation may be non-invasive or invasive. Only one patient of the overall 16 patients who had LL-PAD was

symptomatic, again underlying the strong possibility of LL-PAD being under-reported and under-diagnosed.

Conclusion

Atherosclerosis of multiple vascular territories is a significant predictor for cardiovascular mortality & morbidity. PAD is largely asymptomatic and remains one of the most under-diagnosed and under-treated diseases. Patients with atherosclerotic disease in multiple vascular territories benefit from nuanced and intensive medical therapy like Dual Pathway Inhibition (DPI) strategy over conventional anti-platelet only strategy. The prevalence of PAD in patients with CAD is high in Indian population sub-set; and the presence of multiple risk factors should prompt evaluation for PAD in patients identified to have multi-vessel CAD.

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