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PERIPHERAL ARTERIAL DISEASE

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Abstract:

Introduction: *The prevalence of peripheral artery disease (PAD) has been well examined in several studies in developed countries over the last three decades, and thorough explanations have been suggested on the prevalence, incidence, risk factors, and prognostic factors of the peripheral artery disease. Because of the epidemiological change in CVS conditions where a dramatic elevation of incidence and prevalence occurred in developing countries, we try to provide a more robust analysis and discussion of the epidemiology of peripheral artery disease throughout this review. On the other hand, because of the usual lack of information on the prevalence and incidence of peripheral artery disease in many low-income countries, most of the reliance is usually made on research conducted in developed countries and sometimes on research of other related conditions, specifically coronary heart disease and cerebrovascular diseases. In addition, we will describe measurements in populations, worldwide frequency, risk factors, and importance of peripheral artery disease.*

The term 'peripheral artery disease' is usually used in the medical literature, despite the presence of significant variations in the meanings of this definition based on the affected vessels and groups of included pathologies, like, fibromuscular dysplasia, atherosclerosis, and vasculitis. Throughout this Review, the use of the term 'peripheral artery disease' will be limited to atherosclerosis that involved the arteries that serve the lower extremity. This will be similar to the use of the term 'peripheral vascular disease' which is commonly used in everyday practice, but also sometimes used to include venous diseases and lymphatic diseases.

The clinical spectrum of peripheral artery disease is usually wide and can include individuals who are even asymptomatic along with those who have leg symptoms, especially intermittent claudication in which the pain in the calf usually occurs during exercise and can be relieved following rest. At the most severe end of the spectrum is the critical limb ischaemia (CLI), which is known as the presence of rest pain, ulceration, and gangrene, and can many times cause amputation.

Aim of work: *In this review, we will discuss Peripheral arterial disease*

Methodology: *We did a systematic search for Peripheral arterial disease in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *The epidemiology of peripheral artery disease seems to be increasing rapidly in developing countries, with some evidence that females may be more affected than males. A large number of cases are occurring in the Southeast Asia and Western Pacific regions. Surveys indicate that some populations in sub-Saharan Africa have peripheral artery disease. Although this Review suggests that factors such as poverty, industrialization, ethnicity, and infection might conceivably impact the development of peripheral artery disease, the traditional cardiovascular risk factors of smoking, diabetes, dyslipidaemia, and hypertension are likely to be the principal risk factors driving the epidemiological transition. The higher survival of the general populations also has an important effect by allowing the development of chronic diseases especially at older ages, as is the case with peripheral artery disease.*

Key words: *Peripheral arterial disease, epidemiology, presentation, complications, management.*

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INTRODUCTION:

The prevalence of peripheral artery disease (PAD) has been well examined in several studies in developed countries over the last three decades, and thorough explanations have been suggested on the prevalence, incidence, risk factors, and prognostic factors of the peripheral artery disease [1-2]. Because of the epidemiological change in CVS conditions where a dramatic elevation of incidence and prevalence occurred in developing countries [3], we try to provide a more robust analysis and discussion of the epidemiology of peripheral artery disease throughout this review. On the other hand, because of the usual lack of information on the prevalence and incidence of peripheral artery disease in many low-income countries, most of the reliance is usually made on research conducted in developed countries and sometimes on research of other related conditions, specifically coronary heart disease and cerebrovascular diseases. In addition, we will describe measurements in populations, worldwide frequency, risk factors, and importance of peripheral artery disease.

The term 'peripheral artery disease' is usually used in the medical literature, despite the presence of significant variations in the meanings of this definition based on the affected vessels and groups of included pathologies, like, fibromuscular dysplasia, atherosclerosis, and vasculitis. Throughout this Review, the use of the term 'peripheral artery disease' will be limited to atherosclerosis that involved the arteries that serve the lower extremity. This will be similar to the use of the term 'peripheral vascular disease' which is commonly used in everyday practice, but also sometimes used to include venous diseases and lymphatic diseases.

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METHODOLOGY:

We did a systematic search for Peripheral arterial disease in the emergency department using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Peripheral arterial disease, epidemiology, presentation, complications, management.

MEASUREMENT IN POPULATIONS:

Ankle–brachial index

The ankle–brachial index (ABI) is the ratio of systolic pressure at the ankle to that in the arm 6. The importance of this measurement is that when peripheral artery disease is severe enough to change arterial flow in the lower extremity during rest, the pressure at the ankle will significantly decrease. To distinguish between a reduced pressure due to peripheral artery disease and the presence of a general hypotension related to another etiology, the pressure at the ankle will be compared with the pressure at the arm by calculating this ratio.

Atherosclerosis impacts the upper extremity less commonly than the lower extremity but, to prevent the occurrence of bias owing to subclavian stenosis, the higher arterial pressure of the arms is used when calculating the index. normally, the ABI should be higher than 1 due to the pulse amplification phenomenon. An ABI that ranges between 1.10–1.25 is generally considered normal and an ABI that is less 0.90 is generally considered abnormal. A high ABI (that is higher than 1.40) can also be an indicative of the presence of stiff vessels, which are also highly associated with the presence of peripheral artery

disease [4]. Overall, ABI can give high sensitivity (up to eighty percent) and very high specificity (more than ninety-five percent) in the detection of peripheral artery disease 8. Evaluation of ABI during rest could possibly miss individuals with peripheral artery disease whose disease is only symptomatic following exercise but including a post-exercise ABI in large epidemiological research studies is often not possible. Given the ease of this measurement with the use of cheap equipment, the ABI is generally considered the first-choice for the screening to define both symptomatic and asymptomatic peripheral artery disease in most epidemiological studies, as well as during the everyday clinical practice.

In the year 2012, the calculation of the ABI was standardized in most studies 8. The presence of variations in the methods of measuring extremities blood pressures and assessing ABI before its general standardization can partially explain variations in the epidemiology of peripheral artery disease reported in similar populations by multiple studies. In addition, small variations have been detected in population values of the ABI according to gender and race, with a mildly less ABI in females (−0.02 when compared to males) and in black individuals (−0.02 when compared to whites) [5]. During a screening survey of more than 29,000 adult individuals without a history of CVS conditions in central Scotland, the average ABI was 1.01 (SD 0.11) in females and 1.06 (SD 0.13) in males 10. Whether this variation was due to 'normal' physiological variation among genders or was disease-related is unknown. The ABI is correlated with height; males on average are taller than females, but the standardization for height and cardiovascular risk factors only partially decreases the gender-specific differences. As a result, a single threshold (0.90) may not distinguish accurately the actual epidemiology of peripheral artery disease within all these subgroups. Whether different thresholds by gender must be used remains an area of debate and is not applied in most epidemiological studies.

Questionnaires

Multiple questionnaires have been widely used to assess in a standardized manner the presence of intermittent claudication among individuals with potential peripheral artery disease. The first questionnaire on intermittent claudication was proposed by Rose et al.11 but is not used anymore, because the development of two modified ones — the San Diego Claudication Questionnaire (SDCQ) [6] and the Edinburgh Claudication Questionnaire (ECQ)[6]— showed higher sensitivity, with all questionnaires having excellent specificity. These questionnaires have been translated into several languages [7], but more validated translations are still needed to allow for their uses in all countries around the word.

Although the use of these questionnaires, in addition to measuring ABI, can provide more accurate data on the epidemiology of both symptomatic and asymptomatic peripheral artery disease, these questionnaires have several limitations by not covering the whole range of symptomatic conditions. Indeed, many individuals with peripheral artery disease can have an atypical presentation of claudication, or do not manifest with pain because they do not walk a lot because of having other comorbidities [8]. Assessment of the range of peripheral artery disease clinical manifestations could be important, because the type of manifestations associated with the degree of walking impairment [8]. Also, more serious clinical presentations (pain at rest and ulcers or gangrene) could not be assessed using these questionnaires. Beyond claudication questionnaires, other indicators such as revascularization and amputation rates have been used as proxy measures of severe peripheral artery disease in populations [9].

Routine health statistics

Mortality rates statistics are usually used to describe the worldwide distribution of any condition, including peripheral artery disease, because most countries collect data on deaths. Also, ascertainment of mortality is often easier than other methods of detecting cases of disease. However, the benefits of mortality data in describing epidemiology of peripheral artery disease is very limited, because most patients with peripheral artery disease die from a coronary heart disease, a cerebrovascular event, or malignancies [10], and the cause of death is, thus, not described as peripheral artery disease. Very few patients die actually from a peripheral artery disease per se; in such cases, mortality is most likely caused by complications of CLI or of surgery.

similarly, health-service statistics, like diagnostic discharge data, are not usually beneficial because of the lack of availability in most countries. Also, when released, disease rates can be impacted more by variations in health-care-seeking behaviours and clinical decision-making than the true epidemiology of the condition. Even in developed countries with more developed health-care systems, like the US, patients' and clinicians' awareness of peripheral artery disease can be poor, causing in underdiagnosis. In addition, significant imprecision could occur in diagnostic coding because of the wide range of signs

and symptoms, the absence of a detailed knowledge of peripheral artery disease by coders, and the use of nonspecific International Classification of Diseases (ICD) 10 codes such as 170.2 (which codes for atherosclerosis of arteries of limbs) and 173.9 (which codes for peripheral vascular disease unspecified) [11]

WORLDWIDE FREQUENCY:

Low ankle–brachial index

In 2013, the worldwide epidemiology of peripheral artery disease was evaluated in a systematic review of population epidemiology with the use of an ABI that was less than 0.9 as an indicator of the presence of the disease [12]. Prevalence was compared among different populations living in developed countries and those living in developing countries. In developed countries, the prevalence of peripheral artery disease looked to be similar among both sexes, and to elevate consistently with age from around five percent at age 45–49 years to eighteen percent at age 85–89 years. In developing countries, on the other hand, prevalence rates also increased consistently with age but, compared with developed countries, age-specific rates seemed to be lower in males and slightly higher in females (up to age sixty-five years). In developing countries, prevalence rates seemed to be higher in females than in males, with more pronounced relative differences at younger ages (6.3 percent versus 2.9 percent at age 45–49 years compared with 12.3 percent versus 10.1 percent at age 75–79 years).

Using the age-specific and sex-specific results on prevalence in developed and developing countries, the numbers of cases of peripheral artery disease in years 2000 and 2010 in these countries were estimated based in the age and gender distributions of the populations. Over the ten-year period, the number of cases around the world was found to elevate by around ¼ to approximately 200 million, but with a higher relative increase in developing countries (29%) than in developed countries (13%). Such studies show the significant effect that a changing age structure of the population is likely to have on the global epidemiology of peripheral artery disease. More analysis at WHO Regional level, including standardization of the prevalence of risk factors [13], assumed that the highest number of peripheral artery disease cases in 2010 were in the developing countries in Southeast Asia and Western Pacific regions.

Evidence on the epidemiology of peripheral artery disease in developing has been derived from surveys including the ABI in individual countries. No multinational epidemiological studies are published, so the true variation in epidemiology among different countries is not clearly known. Even within countries, differences may change based on different characteristics of the selected populations and variation in measurement techniques. In China, as an example, the prevalence in five surveys of populations with mean ages 60–70 years varied between 2.5 percent and 6.9 percent among males and 1.7 percent and 10.4 percent among females 30. On the other hand, in a study in subSaharan Africa involving the Republic of the Congo and the Central African Republic, in which the same survey methods were used, a probable real difference in prevalence was detected between the two included countries (12.2 percent versus 17.4 percent; P = 0.007) [14]. Many more studies using adjusted methods to measure peripheral artery disease in developing countries are needed to establish a precise picture of the epidemiology of condition.

A fairly consistent conclusion in surveys in developing countries is the elevated prevalence of a low ABI among females when compared to males. The reasons behind this difference are not well understood, although, as we previously said, small differences in ABI population distributions, with ABI usually less in females when compared to males, may be part of the hypothesis. gender-specific differences in height can be more obvious in some developing countries, causing a lower ABI in females when compared to males. The principal risk factor for peripheral artery disease — smoking — is usually more common in males than in females in developing countries, and is thus not likely to affect the females' preponderance. On the other hand, females may be exposed to second-hand cigarette smoke. Another possible cause for the gender differential is a potential survival advantage from coronary heart disease and cerebrovascular events in females, causing the development of peripheral artery disease in an atherosclerotic-susceptible individual, although this explanation is not likely, with the higher female-to male ratios are specifically obvious at younger ages. This age difference may, however, be related to the finding that, as peripheral artery disease becomes more severe (as it does with age), males are more commonly affected [15].

RISK FACTORS:

The classic CVS risk factors (including smoking, diabetes, dyslipidaemia, hypertension) and several metabolic and inflammatory variables have been well studied in association to peripheral artery disease in

developed countries.

Cigarette smoking has been well known to be an essential risk factor for peripheral artery disease for more than one century and several research studies have concluded a significant and persistent correlation between smoking and all types of peripheral artery disease. Smoking is considered to be the most important risk factor for developing peripheral artery disease and at least doubles the risk compared with that of nonsmokers . The higher the amount smoked, either at the time when assessed or cumulatively over a lifetime, the greater the risk of developing peripheral artery disease and the higher the severity of disease. Smoking could look to elevate the risk of developing peripheral artery disease more than that of coronary heart disease. Smoking cessation is correlated with a decreased risk of peripheral artery disease, but is likely to take more than twenty years of cessation to decrease the level of risk to that of individuals who have never smoked before. Smoking can also increase the risk of asymptomatic peripheral artery disease, which elevates the possibility that younger adult smokers may already be increasing their risk of peripheral artery disease many years prior to the onset of symptomatic disease. The worldwide effect of smoking is less likely to abate substantially. Recent studies conclude that the number of smokers will significantly increase from 794 million in 2010 to reach 872 million in 2030, although the prevalence per head of population will decrease slightly, specifically in developed countries [16].

Diabetes has also been shown in several epidemiological studies to be linked with the risk of developing both asymptomatic and symptomatic peripheral artery disease, including diseases with atypical symptoms. The risk of intermittent claudication is about double as high in individuals with diabetes as in individuals without diabetes. The risks of peripheral artery disease increase proportionally with the severity of diabetes: for every one percent elevation in hemoglobin A1c level, the risk of peripheral artery disease elevates by 26 percent. Moreover, the duration of diabetes and use of insulin are linked with higher risk46. The relative risks of CLI associated with diabetes are much higher than those of intermittent claudication, with the risk of major amputation around fivefold higher in individuals with diabetes than in individuals without diabetes47. This finding is possibly due to diabetes-associated sensory neuropathy, microangiopathy, and infection, as well as a specific pattern of peripheral artery disease affecting more distal arteries with less possibilities for revascularization. The global high prevalence of diabetes linked with higher incidence of obesity is likely to cause a higher proportion of peripheral artery disease cases being diabetes-related, especially with a concomitant decline in cigarette consumption, at least in developed countries. Projected trends from the year 2013 to the year 2035 show that the number of patients who have diabetes will increase globally from 382 million to 592 million patients [17].

Dyslipidemia has been studied in epidemiological studies on the etiology of peripheral artery disease, but due to the various lipid fractions are highly interrelated, detecting the most important factors has been found to be challenging. Serum triglyceride levels were proven in many early clinical studies to be strongly associated with peripheral artery disease, but in most large epidemiological studies have not been independently related after adjusting for other lipids. On the other hand, overall cholesterol levels remained correlated with peripheral artery disease in multivariate analysis in most studies, as did low HDL-cholesterol levels. In fact, a combined ratio of total to HDL cholesterol looks to be the best predictor of peripheral artery disease. In the Physicians' Health Study of incident peripheral artery disease, the ratio of total to HDL cholesterol had the strongest correlation with peripheral artery disease of any lipid measure, so that patients in the top quartile of the ratio had nearly four times the risk of claudication compared with those in the bottom quartile. The San Diego Population Study also found that the total to HDL cholesterol ratio was an independent predictor of peripheral artery disease. Studies have also shown that plasma lipoprotein(a) and apolipoprotein B levels were independently associated with the risk of developing peripheral artery disease [18].

CONCLUSIONS:

The epidemiology of peripheral artery disease seems to be increasing rapidly in developing countries, with some evidence that females may be more affected than males. A large number of cases are occurring in the Southeast Asia and Western Pacific regions. Surveys indicate that some populations in sub-Saharan Africa have peripheral artery disease. Although this Review suggests that factors such as poverty, industrialization, ethnicity, and infection might conceivably impact the development of peripheral artery disease, the traditional cardiovascular risk factors of smoking, diabetes, dyslipidaemia, and hypertension are likely to be the principal risk factors driving the epidemiological transition. The higher survival of the general populations also has an important effect by allowing the development of chronic diseases especially at

older ages, as is the case with peripheral artery disease.

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