Metabolic syndrome as a risk factor for peripheral artery disease: a systematic review and meta-analysis

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Abstract

Background: Metabolic syndrome is a well-known risk factor for cardiovascular disease; however, it has not been determinate if it is associated with peripheral arterial disease (PAD). Hence, this systematic review aimed to evaluate metabolic syndrome as a risk factor for the development of PAD.

Methods: We conducted a systematic review searching in four databases: 1) PubMed, 2) Web of Science, 3) Scopus, and 4) Embase until March 2021. We included cohort studies that evaluated the risk of PAD in patients with and without metabolic syndrome. Study selection, data extraction, and risk of bias analysis were performed independently by two authors. We used a random-effects model to conduct a meta-analysis of effect measures (HR, RR, y OR). Individual analyses were performed according to the diagnostic criterion used for metabolic syndrome.

Results: We included 7 studies with a total of 43 824 participants. Most of the studies were performed in the general adult population. The metabolic syndrome and PAD diagnostic criteria were heterogeneous. Almost all studies using RR found an association between metabolic syndrome and the development of PAD (RR: 1.31; CI 95%: 1.03 – 1.59; I^2: 15.6%). On the other hand, almost all the studies that used HR found no association between the two variables. All studies had a low risk of bias.

Conclusions: The association between metabolic syndrome and the risk of developing PAD is inconsistent. However, patients with metabolic syndrome should undergo testing to rule out PAD due to the high prevalence of risk factors in this population.

Introduction

Metabolic syndrome is a complex syndrome that involves high levels of glucose and lipids in the blood, as well as high blood pressure and central obesity (1). Although there is no global data, it has been estimated that over a billion people live with metabolic syndrome (2). Peripheral artery disease (PAD) is a chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. Is the second most frequent cardiovascular disease after coronary artery disease affecting 200 million people worldwide (3,4). Patients with PAD have a double risk of all-cause mortality and myocardial infarction (5). Several systematic reviews confirm that metabolic syndrome increases the risk of cardiovascular events and deaths by 2-fold (6–8). But none has assessed the association with the risk of developing PAD (6). Hence, the objective of the present systematic review was to evaluate metabolic syndrome as a risk factor for PAD.

Methods

We conducted a systematic review according to the indications of the guidelines of the 2020 Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA)(9).

The study protocol is registered in the PROSPERO platform (CRD42021234516).

Study selection

We included cohort studies that reported the following measures of effect: relative risk (RR), odds ratio (OR), hazard ratio (HR), or that reported data that allowed estimation of the RR, OR, or HR of the association of interest.

Literature search and study selection

Five databases were searched for articles: 1) PubMed, 2) Web of Science/Core collection, 3) Scopus, 4) Embase, and 5) Web of Science/MEDLINE. The search was conducted on March 26, 2021. There were no restrictions regarding language or date of publication.

The titles and abstracts of the results were independently reviewed to identify potentially relevant studies for inclusion. These potential studies were reviewed in full text and independently. In addition, the reference list of all included studies was reviewed to complement the search.

Data extraction

The data of interest were extracted independently by the authors.

Risk of bias

The risk of bias assessment of the included studies was done based on the New Castle-Ottawa scale (10) independently by the investigators.

Statistical analyses

We conducted a random-effects meta-analysis using the DerSimonian and Laird method and performed separate meta-analyses for adjusted and non-adjusted estimates.

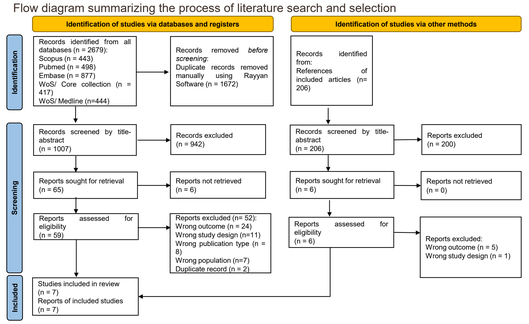
Results

From 1007 studies identified after eliminating duplicates, 7 studies were included in the review with a total of 43,824 participants. Most of the studies were conducted in the general population (11-15), and the follow-up time of almost all the studies was longer than 9 years.

All studies using RR (2,11,13,16) found an association between metabolic syndrome and the development of PAD, with the exception of one study (12) (RR: 1.31; CI 95%: 1.03 – 1.59; I^2: 15.6%). We found association according to the studies that used the ATP III classification and the JIS (2,11, 13, 16), but not according to AHA/NHLBI (12).

When meta-analyzing two studies that presented adjusted RRs and used the JIS classification for metabolic syndrome, we found

Flow diagram summarizing the process of literature search and selection



an association between metabolic syndrome and the development of PAD. (RR: 1.31; 95% CI: 1.03 - 1.59, I^2: 15.6%) (11,13).

On the other hand, we did not evidence an association between both variables in the studies that used HR (12,15,16), with the exception of one study(11).

Discussion

This systematic review and meta-analysis, based on cohort studies, included 7 studies and found inconsistent results regarding the association between metabolic syndrome and the development of PAD. Four of the five included studies that used RR found an association between both variables (2,11,13,16). While the studies that used HR or OR found no association (12,14-16), except for one study(11).

The most important difference we observed was that none of the studies in which they found a significant association adjusted for the diabetes variable (2,11,13,16). On the other hand, all the studies that used HR as a measure of association and adjusted for diabetes found no association (12,15). These results suggest that diabetes could be the true risk factor and not the metabolic syndrome itself.

We found some limitations of the included studies. Although all the studies used a validated criterion to define metabolic syndrome and PAD, these were heterogeneous among themselves. In addition, the measures of effect among the studies were not equal, because some used HR, others RR or OR, which could make the estimation vary and does not allow us to compare the studies directly. However, in general, most of the studies had a low risk of bias.

We recommend that future studies use the ATP III, NHBLI, or JIS definitions of the metabolic syndrome because they are more applicable in clinical practice and have similar criteria when defining metabolic syndrome, unlike other definitions (IDF, WHO, among others). For the definition of PAD, we recommend following the American Heart Association or European Society of Cardiology criteria that include: clinical history, physical examination suggestive of PAD, or an ABI at rest ≤ 0.90 (3,17).

Although we did not find clear evidence that metabolic syndrome is a risk factor for PAD, periodic control examinations should be performed in this population given that 7% of patients with metabolic syndrome have asymptomatic PAD(18). In addition, efforts should be made to reduce the risk factors identified in these patients to avoid the progression of atherosclerosis and insulin resistance, since this population has a 5 to 10 times greater risk of developing diabetes and twice the risk of developing cardiovascular disease in 5 years (8,19).

Characteristics of cohort studies assessing the relationship between metabolic syndrome and peripheral artery disease (n=7).

Study id	Country	Follow up (years)	n	Age (years) mean ± SD	Sex Male (%)	Metabolic syndrome diagnostic criteria	Peripheral artery disease diagnostic criteria	Main finding	Adjusted variables
Rana – 2006 (2)	Netherlands	-	1698	44.3 ± 12.0	49.4	ATP III	Peripheral arterial bypass graft, percutaneous invasive interventions, intermittent claudication in combination with at least one unequivocal result of one of the following: ankle/arm index <0.9 or a stenosis (>50%) on an angiogram or duplex scan	RR: 1.97; 95% CI: 1.13 - 3.45	Sex, smoking, LDL, statin use
Wang – 2007 (22)	Finlandia	14	1212	69.0 ± 2.9	35.1	ATP III WHO IDF AHA/NHLBI	Lower extremity amputation due to ischemic vascular disease or peripheral revascularization (angioplasty or surgery)	HR: 1.36; 95% CI: 0.73 - 2.51 HR: 1.68; 95% CI: 0.89 - 3.17 HR: 1.32; 95% CI: 0.72 - 2.43 HR: 1.29; 95% CI: 0.69 - 2.40	Age, sex, history of myocardial infarction, physical activity, diabetes.
Conen – 2009 (23)	USA	13	27111 26900	52.4 ± 4.5 -	0	ATP III	Intermittent claudication and / or peripheral artery surgery, including catheter interventions with consequent confirmation of the case	RR: 1.83; 95% CI: 1.60 - 2.07 HR: 1.14; 95% CI: 0.75 - 1.73	None Age, smoking, cholesterol, exercise, hsCRP, sICAM-1
Wild – 2009 (19)	Scotland	15	762	65.0 ± 5.6	48.8	AHA/NHLBI	Intermittent claudication or rest pain, ulcer or gangrene or vascular surgery or amputation	HR: 1.29; 95% CI: 0.69 - 2.40 RR: 1.25; 95% CI: 0.99 - 1.50	Age, sex, smoking, CVD, diabetes, low ABI, LDL, haemostatic factors, inflammatory markers None
Skilton - 2011(21)	France	9	3592	47.2 ± 9.7	49.1	AHA/NHLBI	ABI <0.90	OR: 1.03; 95% CI: 0.47 - 2.25	Age, sex, education, family situation, employment, smoking
Garg – 2014 (18)	USA	14	4632	72.8 ± 5.6	40.1	Joint interim statement of the IDFTFEP; NHLBI; AHA; WHF; IAS	Incident clinical PAD: self-report with consequent confirmation of the case by a committee. Incident low ABI: A decline in ABI of at least 0.15 and to 0.9 or less.	HR: 1.47; 95% CI: 1.11 - 1.94 RR: 1.26; 95% CI: 1.00 - 1.58	Age, sex, race, clinic site, alcohol, smoking, blocks walked, CVD, LDL
Vidula- 2015 (20)	USA	3	4817	61.1 ± 10.0	46.3	Joint interim statement of the IDFTFEP; NHLBI; AHA; WHF; IAS	ABI <0.90 in conjunction with an ABI decline >0.15 or medical record confirmed hospitalization for symptomatic lower extremity PAD	RR: 1.78; 95% CI: 1.04 - 2.82	Age, sex, race, education, smoking, LDL, statin use, urinary albumin creatinine ratio, exercise, blocks walked, ABI

PAD: Peripheral artery disease, ATP III: Adult Treatment Panel III, WHO: World Health Organization, IDF: International Diabetes Federation, AHA: American Heart Association, NHLBI: National Heart, Lung, and Blood Institute, IDFTFEP: International Diabetes Federation Task Force on Epidemiology and Prevention, WHF: World Heart Federation, IAS: International Atherosclerosis Society, LDL: Low-density lipoprotein, CVD: Cardiovascular disease, ABI: Ankle-brachial index

Conclusions

This systematic review and meta-analysis of longitudinal studies found inconsistent results among the included studies regarding the association between metabolic syndrome and PAD. Possibly, this association may be confounded by the diabetes variable. However, patients with metabolic syndrome should undergo testing to rule out PAD due to the high prevalence of risk factors in this population. In addition, control of the components of the syndrome, especially glucose and lipids, would be important to prevent complications.

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