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Review

The association of obesity with cardiovascular events in patients with peripheral artery disease

Oliver Cronin [a], Dylan R. Morris [a], Philip J. Walker [a,b,c,d], Jonathan Golledge [a,b,e,*]

[a] Queensland Research Centre for Peripheral Vascular Disease, School of Medicine and Dentistry, James Cook University, Townsville, QLD 4811, Australia
[b] University of Queensland, School of Medicine, Discipline of Surgery, Herston, QLD 4029, Australia
[c] University of Queensland, Centre for Clinical Research, Herston, QLD 4029, Australia
[d] Department of Vascular Surgery, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia
[e] Department of Vascular and Endovascular Surgery, The Townsville Hospital, QLD 4811, Australia

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ABSTRACT

Objectives: This systematic review aimed to summarise published evidence that has assessed the association of obesity with major cardiovascular events (CVEs) (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) in patients with peripheral artery disease (PAD).
Methods: Studies investigating the association of markers of obesity with CVEs were identified by searching the PUBMED database. To be eligible for inclusion studies had to report an established measure of adiposity, i.e. body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) or an imaging technique to quantify adipose distribution.
Results: A total of 9319 patients with PAD were followed for a mean of 1.0–5.7 years in the 7 studies identified. Four studies assessed BMI; one study assessed BMI and WC; one study assessed BMI, WC and WHR; one study assessed WHR. Both of the studies which assessed multiple adipose measures reported a more powerful positive association of WC with CVEs than BMI; one study reported less CVEs in obese subjects as defined by BMI; one study reported a negative association of overweight but not obesity, defined by BMI, with CVEs; one study reported an inverse association of BMI >20 with CVEs; one study did not find a significant association between WHR and cardiovascular death; one study did not find a significant association between BMI and CVEs. Meta-analysis of reported risk ratios found a mild positive association between combined measures of obesity and CVEs in patients with PAD (RR 1.09; 95%CI 1.03–1.16, $P = 0.006$; random effects model).
Conclusion: This meta-analysis suggests that obesity is an independent risk factor for CVEs in patients with PAD however larger and more homogeneous studies using equivalent anthropometric measures are needed for more definitive evidence.

Contents

* Corresponding author. Queensland Research Centre for Peripheral Vascular Disease, School of Medicine and Dentistry, James Cook University, Townsville, QLD 4811, Australia. Tel.: +61 7 4781 4730; fax: +61 7 4781 5945.
E-mail address: jonathan.golledge@jcu.edu.au (J. Golledge).

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1. Introduction

Lower limb peripheral artery disease (PAD) has a prevalence of 12%–15% in subjects aged over the age of 65 years and affects between 8 and 10 million people in the United States [1,2]. The cost of PAD (including PAD associated hospitalisations, medications, deductibles, copayments and coinsurances) has been reported as $5955 per PAD patient per year in the United States [3]. It has been established that patients with PAD have a high incidence of major cardiovascular events (CVEs) and cost-effective secondary prevention interventions are urgently needed for this patient population [4–8].

Obesity is an established risk factor for incident CVEs in the general population [9–11]. Some studies have suggested obesity is a risk predictor of CVEs in patients with coronary heart disease [12–17]. Visceral adiposity, as assessed by waist circumference (WC) and waist-to-hip ratio (WHR), has been suggested as having a more powerful association than total adiposity, as assessed by body mass index (BMI), with CVEs in some populations [15–19]. Visceral adiposity has been implicated in the production of a specific sub-set of adipokines which promotes the progression and complications of atherosclerosis [20,21]. However there is a paucity of literature that has assessed the association of body adipose distribution, specifically visceral adiposity with major CVEs in PAD populations. It is possible that interventions targeted at reducing visceral adiposity, such as specific exercise regimens, could have benefit in specific patient populations [22,23].

Many patients with lower limb athero-thrombosis are asymptomatic although patients may experience muscle pain on exertion known as intermittent claudication which impacts on walking ability and quality of life in these patients [24–26]. PAD patients are typically sedentary and high rates of obesity have been reported in these subjects [25,27,28]. Developing interventions which are effective in reducing the high rate of obesity in PAD patients would need to take into account the walking impairment of this patient group [24] but would be worthwhile if such therapies could impact on the high event rate in these subjects. The association of obesity and adipose distribution with CVEs in patients with PAD has however received relatively little attention. This review aimed to critically appraise published studies which have assessed the association of obesity with CVEs in patients with PAD to clarify whether obesity is an important risk factor in this population.

2. Methods

2.1. Protocol and focus

This systematic review was performed with a standardised written protocol (not published) that followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The review was focussed on studies which assessed the association of obesity or the distribution of adiposity with CVEs in PAD patients.

2.2. Search criteria

A search was conducted of literature that was available up to 21st December, 2012. The PubMed database was searched using the following terms: “peripheral artery disease” AND “cardiovascular events”; “atherothrombosis” AND “cardiovascular events”; “claudication” AND “cardiovascular events”; “abdominal aortic aneurysm” AND “cardiovascular events”; “critical limb ischaemia” AND “cardiovascular events”. In addition, reference lists were searched from relevant literature reviews and studies to increase the publication yield.

2.3. Eligibility criteria

To be eligible studies were required to focus on the association of obesity with CVEs in PAD patients. For inclusion studies had to be published before 21st December, 2012. Publications were restricted to human studies. There was no limit on study size or published language. Included studies had to use a recognised measure of adiposity, namely BMI, WC, WHR or employ imaging techniques such as computed tomography angiography (CTA) or ultrasonography to quantify adipose distribution.

Inclusion criteria required CVEs to have been recorded in a prospective study focussed on a PAD population. Studies were excluded if: CVEs were not assessed prospectively; PAD results could not be distinguished from other studied populations; and an objective measure of obesity was not performed. Measures of adipose distribution were excluded if they were not statistically assessed by a multivariate analysis to assess their independent association with CVEs.

2.4. Data extraction

One author extracted the data from the identified studies. Any uncertainty was resolved by discussion between authors. Data extracted from eligible literature included: study design, age, gender, smoking history, hypertension, diabetes mellitus, obesity assessment measure, obesity prevalence, definition of PAD, assessment of PAD, definition of CVEs, assessment of CVEs, the type of statistical analyses, relative risks (RR), 95% confidence intervals (95%CI), *P* values and author conclusions.

2.5. Data analysis

Data was transcribed into an excel document. The data reported varied in format. Where possible, the data format was standardised to include both numbers and percentages. A combined risk ratio for the association of obesity (as measured by BMI, WC or WHR) with CVEs in PAD patients was calculated using a random effects model. Reported risk ratios and 95% confidence intervals were analysed with Comprehensive Meta-Analysis v2 software (Biostat, Inc.). Publication bias was assessed by assessment of funnel plot asymmetry. Heterogeneity analysis was performed using the Cochran *Q* test and I^2 index. The contribution of individual studies to the combined risk ratio was evaluated with leave-one-out sensitivity analysis.