European Journal of Internal Medicine 28 (2016) 52–58

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Is diabetes mellitus a risk factor for venous thromboembolism? A systematic review and meta-analysis of case–control and cohort studies

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ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form 4 October 2015
Accepted 5 October 2015
Available online 23 October 2015

Keywords:
Diabetes mellitus
Venous thromboembolism
Vascular disease
Risk factors

ABSTRACT

Objective: Diabetes mellitus is a well-established risk factor for atherosclerotic disease, but its role in the occurrence of venous thromboembolism (VTE) has not been elucidated. We conducted a meta-analysis of published cohort and case–control studies to assess whether diabetes mellitus is a risk factor for VTE.
Research Design and Methods: We systematically searched MEDLINE and EMBASE for case–control and prospective cohort studies assessing association between the risk of venous thromboembolism and diabetes. Odds ratios (OR) from case–control studies were combined while for prospective studies hazard ratios (HR) were combined. Models with random effects were used. Meta-analyses were conducted separately for raw and adjusted measures of association.
Results: 24 studies were identified including 10 cohort studies (274,501 patients) and 14 case–control studies (1,157,086 patients). Meta-analysis of the prospective cohort studies demonstrated a significant association between diabetes and VTE (HR 1.60; 95% CI 1.35 to 1.89). This association was no longer present after analysis of multi-adjusted HRs (HR 1.10; 95% CI 0.77 to 1.56). Meta-analysis of case–control studies showed a significant association between diabetes and VTE (OR 1.57; 95%CI 1.17 to 2.12), but this association was no longer present when adjusted ORs were used (OR 1.18; 95%CI 0.89 to 1.56).
Conclusions: The increased risk of VTE associated with diabetes mainly results from confounders rather than an intrinsic effect of diabetes on venous thrombotic risk. Therefore, no specific recommendations should apply for the management of diabetic patients at risk for VTE.
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1. Introduction

Diabetes mellitus has reached a pandemic state, with the disease now becoming increasingly prevalent not only in industrialized countries, but also in the developing world. In 2000, there were an estimated 175 million people with diabetes worldwide and by 2030 the projected number is around 360 millions [1]. Venous thromboembolism (VTE) is the third most common circulatory disorder in Western populations, and pulmonary embolism the third most common cause of death from cardiovascular disease after heart attack and stroke [2].

Venous stasis, hypercoagulability, and endothelial injury are the three main pathophysiological pathways implicated in thromboembolic disease. Diabetes mellitus has been considered as a potential risk factor for idiopathic VTE because some studies have demonstrated significant diabetes-related abnormalities in coagulability and endothelial function [3,4]. The proposed mechanisms to explain this hypercoagulable state in hyperglycemia may be the loss of the endothelial glycocalyx layer harboring the coagulation factors, the glycation of coagulation factors altering their activity, or an effect on the transcription of their genes. Hyperinsulinemia, which is often present in type 2 diabetes has been shown to have a prothrombotic effect as well. Damage to the vascular endothelium and endothelial dysfunction have been implicated in arterial events in patients with diabetes mellitus, and may also have a role in the pathogenesis of venous thrombotic events [4–6].

A 2007 meta-analysis about cardio-vascular risk factors and VTE reported a 1.4-fold increase in the VTE risk for patients with diabetes (OR, 1.42; 95% CI, 1.12 to 1.77) [7]. Nevertheless, this previous meta-analysis was not specifically designed to assess the association between diabetes and VTE, and did not provide separate results for adjusted or crude ORs. Similarly, a more recent meta-analysis [8] found an association between diabetes and VTE but this study pooled hazard ratios and odds ratios and did not consider the level of adjustment. Therefore, it remains unclear if the observed association was due to diabetes itself or confounders. In the meantime, more studies have been published and some recent and large case–control studies have questioned the association between diabetes and VTE and even suggested a possible protective effect of diabetes mellitus regarding the risk of VTE.[9] We

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http://dx.doi.org/10.1016/j.ejim.2015.10.001
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therefore aimed to systematically review available data on the association between VTE and diabetes and to evaluate the impact of confounders on this association.

1.1. Research design and methods

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [10]. Search strategy, study selection, data extraction and analysis were performed according to a pre-defined protocol.

1.2. Data sources and searches

A comprehensive search of Medline (1966 to February 2015) and Embase (January 1, 1980 to February 2015) was carried out separately by two of the authors (KG and TM) to identify published studies providing a quantitative estimate of the association between VTE and diabetes along with control groups. We also screened the reference list of the selected papers. The keywords or corresponding Medical Subject Headings (meSH) used for VTE were "pulmonary embolism", "deep venous thrombosis" or "venous thromboembolism" and for diabetes mellitus was "diabetes mellitus". The search was performed for English, French, Spanish, Italian and German language, and completed on 21 February 2015. The detailed search strategy is provided in the supplementary appendix Table S1.

1.3. Study selection

Retrieved publications were imported into a reference manager software (Endnote X6.0.1). After removing duplicate results, two investigators (KG and TM) reviewed the titles, abstracts, or full text articles. Any discrepancies concerning study inclusion were resolved by discussion between the two authors or with a third investigator (CM). We included prospective or retrospective studies comparing the incidence of venous thromboembolism in diabetic and non-diabetic patients. VTE was defined as a positive diagnostic work-up (lower-limb venous compression ultrasonography, computed tomography, ventilation-perfusion scan, angiography or autopsy) or diagnostic codes extracted from medical records. Diabetes was defined according to the presence of the Amercian Diabetes Association criteria, medical records or self-reporting.

We excluded all studies in which the entire population had a concomitant, major risk factor for VTE such as major surgery, pregnancy, or trauma. In case of multiple publications from the same cohort, the publication with the most updated data was used. Studies using hospitalizations rather than patients as units of analysis were excluded.

1.4. Data extraction and quality assessment

Data on the following characteristics were independently extracted by two authors (KG and TM): year of publication, study design (case–control studies or prospective cohort studies), study size and location, demographic characteristics of the population (mean age, percentage of women), prevalence of VTE, diagnostic criteria for diabetes and VTE, and the odds ratio (OR) or hazard ratio (HR) of VTE in diabetic patients compared with non diabetic patients. It was also noted whether the OR or HR was adjusted and the risk factors used for adjustment. If the OR was not reported, it was calculated using raw data in each group. The Newcastle-Ottawa Scale (NOS scale; NOS) for assessing quality of non-randomized studies in meta-analysis was used [11]. Each item in the NOS scale corresponded to one point. Studies could be awarded a maximum score of 16 points. Studies with a score of 12 points or more were considered to be of high quality and studies with a score between 8 and 11 of moderate quality.

1.5. Data synthesis and analysis

Separate meta-analyses were performed for case–control studies and prospective cohorts. ORs were used to assess the association between diabetes and the risk of VTE for case–control studies, and HRs were used for prospective studies. Random effect models were used [12]. The amount of heterogeneity was assessed with the I^2 statistic. Adjusted ORs and HRs were also pooled to assess the impact of the adjustment on the association between diabetes and the risk of VTE. Subgroup analyses were performed to separately evaluate cohort studies with basic (limited to demographic characteristics) or more extensive adjustment. The quality of studies was explored as a potential source of heterogeneity. Meta-regressions were conducted to assess the variation of the magnitude of association according to the NOS score. Moreover, a sensitivity analysis was performed to evaluate the impact of the diagnostic criteria for diabetes and VTE on the strength of association estimate by comparing studies using objective criteria (ADA criteria for diabetes, or validated diagnostic methods for VTE) and studies using medical reports or self reported diagnoses. For case–control studies, a sub-group analysis was also conducted to compare pooled ORs between studies using inpatients or population-based controls. Sensitivity analyses were conducted to check the robustness of the pooled ORs and of the pooled HRs by removing each study one-by-one.

Publication bias was assessed using inspection of the funnel plot, Egger's test, and the trim and fill method [13]. All statistical analyses were performed using the Meta for R package (version 3.0.1).

2. Results

2.1. Study selection

3,275 articles were identified by our literature search. There were 652 duplicate studies. 2,558 studies were excluded based on titles and

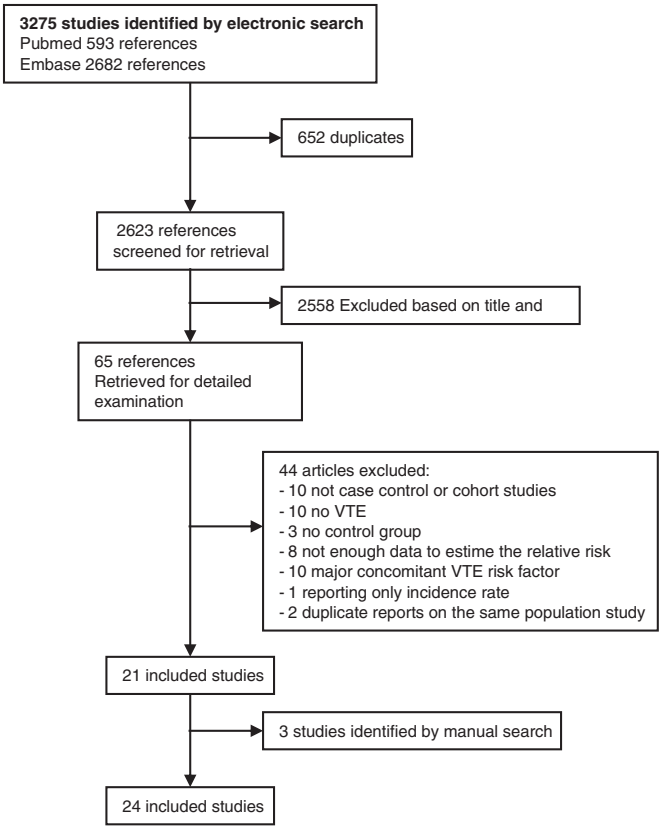

Fig. 1. Study Flow chart.

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