



Regular Article

Diabetes is associated with increased risk of venous thromboembolism: A systematic review and meta-analysis



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ARTICLE INFO

Article history:

Received 10 August 2014

Received in revised form 2 November 2014

Accepted 5 November 2014

Available online 14 November 2014

Keywords:

Diabetes

Venous thromboembolism

Meta-analysis

ABSTRACT

Aims: Increasing evidence suggests an association between diabetes and risk of venous thromboembolism (VTE); however, the results are inconsistent. We conducted a systematic review and meta-analysis of all epidemiological evidence to clarify association of diabetes with risk of VTE.

Methods: We searched MEDLINE and EMBASE to retrieve all relevant articles. Pooled effect estimates were calculated through a random-effects model.

Results: Sixteen articles involving 803,627,121 participants and 10,429,227 VTE patients were included. Pooled analysis of all evidence suggested that diabetes was associated with increased risk of VTE (HR, 1.35; 95%CI, 1.17–1.55; $p = 2.92 \times 10^{-5}$), with evidence of small-study effect ($p = 0.024$) and heterogeneity ($I^2 = 87.1\%$, $p < 0.001$). However, when analysis was restricted to high quality cohort studies, the association remained significantly (HR, 1.36; 95%CI 1.11–1.68; $p = 0.004$), with no evidence of publication bias ($p = 0.192$) and heterogeneity ($I^2 = 23.2\%$, $p = 0.245$).

Conclusions: Diabetes is associated with increased risk of VTE, which may have implications for the primary and secondary prevention of VTE.

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Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), are major sources of morbidity and mortality [1]. Previous studies indicated that cancer, trauma, surgery or medical illness as well as pregnancy are major risk factors for VTE [2]. However, a significant proportion (26%–47%) of VTE is currently classified as apparently unprovoked in the absence of those above mentioned risk factors [3]. Recognition of other risk factors may substantially support new strategies for both primary and secondary prevention of VTE [4].

Recent studies have linked diabetes to VTE. It has been observed that many clotting factors including fibrinogen, factor V, factor VII, factor VIII, factor X, factor XI, factor XII, kallikrein, and von Willebrand factor are elevated in diabetes mellitus [5,6]. Besides, platelet activity is higher in diabetes patients [7]. Thus, diabetes has been regarded as a prothrombotic condition and was expected to increase the risk of VTE. Several epidemiological studies have investigated this issue, but the results were conflicting. Some reported a positive association between diabetes and risk of VTE [8,9], whereas others failed to detect a significant relationship [10,11]. Therefore, we conducted a comprehensive meta-analysis to

summarize all published epidemiological evidence on the association between diabetes and risk of VTE.

Methods

Our analysis was conducted in accordance with the statement of preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Tables S1 and S2) [12]. We searched Medline and Embase for potentially relevant studies by using the key words “diabetes” and “VTE”. We restricted the search to studies in humans, and the articles should be written in English. We retrieved further information by a manual search of references from recent reviews and relevant published original studies. The literature search was completed in April 2014.

Study Selection

Two reviewers assessed titles, abstracts, and full texts of the initially identified studies to determine eligibility independently. Studies were included if they met the following criteria: (1) the article was written in English; (2) with reported RR, HR, or OR estimates describing the relationship between diabetes and risk of VTE. We used broad inclusion criteria for studies, including all types of VTE (DVT and PE) and diabetes status (assessed by medical record or self-reported). Discrepancies in opinion as to whether studies should be selected were resolved by consensus or consultation with a third author. And we assessed agreement between reviewers with the kappa statistics [13]. Strength of agreement

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was leveled as poor (<0.00), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) or almost perfect (0.81–1.00).

Data Extraction

Two independent reviewers used a predesigned data abstraction form (Table S3) to extract relevant information from the included studies. The form included questions on study name, authors, publication year, study site, number of participants, study design, covariates included in the statistical models, assessment of exposure and outcome. After this, the two forms from the two reviewers were compared in a point by point manner, and discrepancies were resolved by discussion with a third investigator and by referencing the original report. The quality of the included studies was assessed according to the Newcastle -Ottawa quality assessment scale [14]. The detailed criteria for assessing study quality were included in the supplementary files (Table S4 and S5). High quality was defined as score > 5 in case-control studies and score > 6 in cohort studies. Besides, agreement between reviewers regarding study characteristics (categorical variables including study design, source of controls, VTE validation, diabetes conformation, comparability of cases and controls on the basis of the design or analysis) was assessed with the kappa statistics [13].

Statistical Analysis

The relationship between diabetes and VTE was quantified by HR estimate. For case-control studies, we used OR as a surrogate measure in that the overall prevalence of VTE in the general population is low, and the OR approximates the HR [15]. We extracted HRs and ORs from the included articles and pooled together through a random-effects meta-analysis to measure the relationship between diabetes and the risk of VTE. Forest plots were produced for visually assessing the pooled estimates across studies. The between study heterogeneity was qualitatively assessed through the Q test ($p < 0.10$ was considered indicative of significant heterogeneity) and was quantified by the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, moderate, and high level of heterogeneity, respectively) [16,17]. Funnel plot asymmetry and Egger’s linear regression was used to detect publication bias [18,19]. Besides, we also used the trim and fill analysis procedure to further assess the possible effect of publication bias [20]. Sensitivity test was performed to evaluate whether the pooled results could have been affected markedly by a single study. Moreover, stratified

analyses were performed to evaluate the influences of study characteristics on pooled results. A two side p value of <0.05 was considered statistically significant. All analyses were performed with STATA software version 11 (StataCorp, College Station, Texas).

Results

Study Selection

According to the search strategy, our initial search identified 1667 citations. After the first round of screening based on titles and abstracts, 47 articles remained for further evaluation. We therefore examined those articles in more detail, and 31 articles were excluded for reasons shown in Fig. 1. Finally, 16 articles (18 studies) meeting our inclusion criteria were finally included in the meta-analysis [8–11,21–32]. The inter-reviewer reliability for the study selection was almost perfect (kappa = 0.97).

Study Characteristics

Characteristics of the 18 selected studies were shown in Table 1. The presence or absence of well recognized risk factors of VTE cases were listed in Table S6. The total number of participants included in this meta-analysis was 803,627,121, with 10,423,707 reported VTE outcomes. The inter-reviewer reliability for the data extraction was almost perfect (kappa ranged 0.89–1.00). The studies varied with regard to how results were presented. One study reported results separately by sex [25] and 1 study reported results separately by baseline measurement of HBA1C levels [21]. With regard to study location, most (12 studies) were from U.S.[8–11,21,23,24,26,28–30], 1 from Norway [22], 3 (2 articles) from Denmark [25,27], 1 from Netherlands [32] and 1 from Sweden [31]. Most of the studies comprised both men and women, while 3 studies included only men [25,28,31], and 5 studies only women [8,10,25,27,30]. With regard to diabetes status, most studies refer to both types of diabetes, only 1 study refers to type 2 diabetes [29]. Adjusted HR was available for most studies, except that 4 studies reported the crude results without adjustment [9,24,28,30].

Diabetes and Risk of VTE

Among the 18 cohorts from the 16 included articles, 14 reported positive findings, with 10 of them being statistically significant. Seven

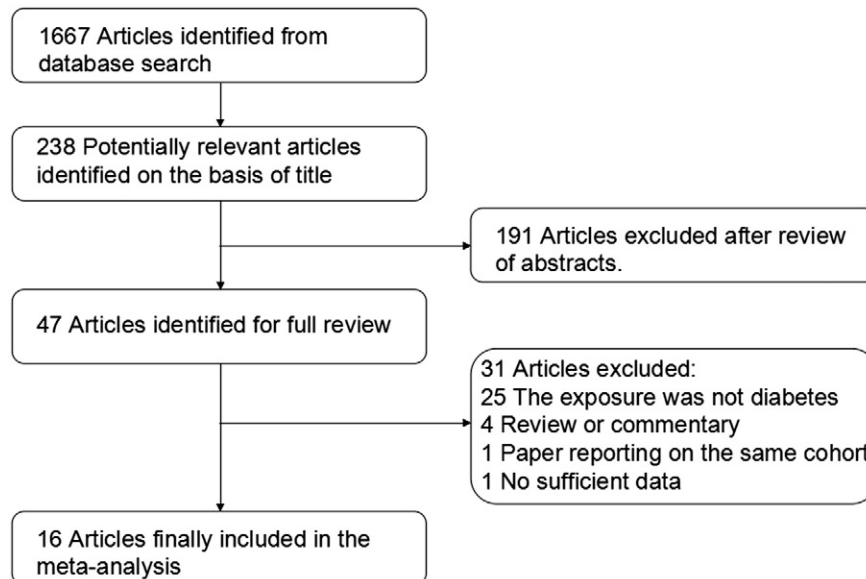


Fig. 1. Literature Search for the Meta-analysis.

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