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Full Length Article

Fasting plasma glucose, oral glucose tolerance test, and the risk of first-time venous thromboembolism. A report from the VEINS cohort study.

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ABSTRACT

Introduction: It remains unclear whether high plasma glucose levels are associated with venous thromboembolism (VTE). This study investigated the association between fasting plasma glucose (FPG), oral glucose tolerance test (two-hour post-load plasma glucose (2HPG)), diabetes, and VTE.

Materials and methods: The population-based, prospective Venous thromboEmbolism In Northern Sweden (VEINS) cohort study included 108,025 residents of Västerbotten County in northern Sweden. The participants were aged 30 to 60 years and had no previous VTE events. They were included from 1985 onwards and were followed until a VTE event, death, emigration, or the study end on September 5, 2014. All underwent a health examination that measured weight, height, FPG, and 2HPG and included a questionnaire regarding smoking, education level, and history of diabetes. Potential VTE events were identified by an extensive diagnosis registry search and were validated by reviewing medical records and radiology reports.

Results: An objectively verified first-time VTE event was experienced by 2054 participants during 1,496,669 person-years of follow-up. In univariable analysis, there were associations between FPG, 2HPG, diabetes, and the risk of VTE. These associations disappeared after adjustment for potential confounders (age, sex, body mass index, cancer at inclusion, education level, smoking, and hypertension). The adjusted hazard ratios were 1.01 (95% confidence interval 0.83–1.23) for diabetes, 1.01 for each standard deviation of FPG (95% confidence interval 0.97–1.05), and 0.96 for each standard deviation of 2HPG (95% confidence interval 0.91–1.00).

Conclusions: There were no independent associations between FPG, 2HPG, diabetes, and future risk of VTE.

1. Introduction

High levels of plasma glucose and diabetes have been suggested to result in disturbances in blood coagulation and fibrinolysis that lead to a prothrombotic state [1]. Notably, there is an increase in the levels of fibrinolytic markers before the manifestation of type 2 diabetes [2]. While the increased risk of arterial thromboembolic events in people with diabetes is well documented [3,4], the association between diabetes and the risk of venous thromboembolism (VTE) remains a matter of debate. Meta-analyses of original studies and, in one case, a meta-analysis of individual participant data, show diverging results regarding the association between diabetes and VTE [5–10]. The definition of the predictor (diabetes) and the outcome (VTE event) differ in the individual studies included in the meta-analyses, making it difficult to draw definite conclusions regarding the association between diabetes and the risk of future VTE.

Previous studies have shown no associations between high levels of plasma glucose, glycated hemoglobin A (HbA_{1c}), and VTE [5,11–16]. Surprisingly, one study found that participants with the lowest plasma glucose levels had the highest risk of VTE among participants with plasma glucose levels in the normal range [5]. Thus, it remains uncertain whether diabetes and glucose levels are independent markers of an increased risk of VTE. Accordingly, we conducted a large prospective population-based cohort study to investigate the relationship of glucose levels, as reflected by diabetes, fasting plasma glucose (FPG) levels, and oral glucose tolerance with the risk of future first-time VTE. To our

Abbreviations: 2HPG, Oral glucose tolerance test two-hour post-load plasma glucose level; CI, Confidence interval; CT, Computed tomography; DVT, Deep vein thrombosis; FPG, Fasting plasma glucose; HbA_{1c}, Glycated hemoglobin A; HR, Hazard ratio; ICD, International Classification of Diseases; MRI, Magnetic resonance imaging; OGTT, Oral glucose tolerance test; SD, Standard deviation; VEINS, Venous thromboEmbolism In Northern Sweden; VIP, Västerbotten Intervention Programme; VTE, Venous thromboembolism

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knowledge, no previous prospective study has evaluated the association between oral glucose tolerance at baseline and the risk of VTE. Our hypothesis was that diabetes, FPG, and oral glucose tolerance are associated with the risk of future first-time VTE.

2. Materials and methods

2.1. Study design

The Venous thromboEmbolism In Northern Sweden (VEINS) study was a cohort study conducted in Västerbotten County in northern Sweden (population ~260,000). Starting in 1985, the inhabitants of Västerbotten County were invited to participate in health examinations, termed the Västerbotten Intervention Programme (VIP), when they were 30, 40, 50, and 60 years old (or, since 1996, 40, 50, and 60 years old). The health examinations were performed at the participants' primary healthcare centers and included measurements of height and weight, blood pressure, and FPG, an oral glucose tolerance test (OGTT), and a questionnaire about self-reported diabetes, education level, and smoking habits [17]. Participants in the VIP health examinations from 1985 onwards were included in the present study (VEINS) and were followed as a cohort until they experienced a first-time VTE event, emigration, or death or until the end of follow-up on September 5, 2014. Health examination data from each participant's first health examination was used. The VEINS cohort included 108,025 individuals.

2.2. Measurements and definitions

FPG and OGTT two-hour post-load plasma glucose (2HPG) levels were measured in capillary blood samples using point-of-care equipment, and the participants were instructed to fast overnight before sampling. Diabetes was defined as self-reported diabetes, self-reported treatment with oral antidiabetics or insulin, FPG ≥ 7.0 mmol/L, or 2HPG ≥ 12.2 mmol/L. FPG was performed in all participants. OGTT was performed in subjects without known diabetes and with FPG < 7.0 mmol/L [17]. OGTT was performed according to the World Health Organization recommendations using 75 g of glucose [18].

Blood pressure was measured in a supine position using a manual sphygmomanometer on the right mid-arm at heart level. Participants were asked to rest for at least 5 min before the blood pressure was measured. Two measurements were taken and the average of these measurements was recorded. Since 1 September 2009, all blood pressure measurements were made in a sitting position. Blood pressure measurements taken in a sitting position were calibrated to make them comparable to previously collected measurements [19]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported treatment with antihypertensive medication. Education level was dichotomized into higher education, defined as having more than a secondary school education, or no higher education. Smoking habits were dichotomized into ever smokers (active smokers or previous smokers) and never smokers. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Cancer at inclusion was defined as a diagnosis of cancer registered in the Swedish Cancer Registry before the health examination or up to two years after the health examination, to account for delays in registration of malignant disease.

2.3. Identification and validation of VTE events

Potential VTE events between 1985 and September 5, 2014 were identified by a diagnosis registry search for specific International Classification of Diseases (ICD) diagnostic codes. In order to minimize the risk of overlooking potential VTE events, an extended list of ICD codes was used (Appendix A). The diagnosis registry was searched for diagnoses made at all three hospitals, both at inpatient and outpatient visits, at emergency department visits, and at primary health care visits in Västerbotten County. The Cause of Death Register was searched for a subset of the ICD codes.

All potential cases of VTE were then validated by one of the authors (MJ), who reviewed radiology reports and/or medical records. A pulmonary embolism was considered to be verified when it was confirmed by pulmonary angiography, computed tomography (CT), magnetic resonance imaging (MRI), high probability ventilation-perfusion scan, or autopsy. A DVT of the lower or upper extremity or an abdominal VTE was considered to be verified when it was confirmed by venography, ultrasonography, CT, MRI, or autopsy. A cerebral venous thrombosis was considered to be verified when it was confirmed by CT, MRI, or autopsy. Participants who had a VTE event registered as the main cause of death and who underwent autopsy were regarded as having a verified VTE.

Only first-time VTE events were included. To avoid the inclusion of recurrent VTE events, VIP participants with one or more of the ICD diagnostic codes for potential VTE events (see Appendix A) before the VIP health examination were excluded.

2.4. Categorization and characterization of VTE events

Individuals were categorized into four groups based on the location of the VTE: pulmonary embolism; lower extremity DVT; upper extremity DVT (defined as thrombosis of the deep upper extremity veins, the superior vena cava, the internal jugular vein, the subclavian vein, the innominate vein, the azygos vein, or the axillary vein); VTE in the veins of the abdomen; or cerebral venous thrombosis (defined as thrombosis of the veins of the central nervous system). Individuals with multiple concurrent thrombosis locations were classified hierarchically into one of the following groups: 1, pulmonary embolism; 2, lower extremity DVT; 3, upper extremity DVT; or 4, VTE in the veins of the abdomen or cerebral venous thrombosis. Individuals with a verified DVT and symptoms of pulmonary embolism were classified into the pulmonary embolism group.

2.5. Statistical analysis

Numbers and proportions and means and standard deviations (SDs) were used to describe baseline characteristics. Spearman's rank-order correlation was used to test correlations between continuous variables. FPG and 2HPG levels were assessed both as a continuous variable per SD and in categories with FPG and 2HPG in quartiles. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between the studied determinants and VTE. For categorical variables, the proportional hazards assumption was tested graphically using Kaplan-Meier plots and plots of the log-minus-log of the survival function versus the survival time, with separate curves for each level of the categorical covariates. For continuous variables, the proportional hazard assumption was tested by creating plots of the partial residuals and subsequently fitting a line to the partial residuals. Proportional hazards were assumed for all variables.

Three models were constructed for each of the explanatory variables i.e. diabetes, FPG, and 2HPG. The first model was univariable, the second model was adjusted for age and sex, and the third model was adjusted for a set of potential confounders (age, sex, body mass index, hypertension, smoking, education level, and cancer). Only cases with no missing values for any of the adjustment variables that were included in model 3 were included in models 1, 2, and 3 (complete cases analysis). Stratified analyses were performed to test the associations between the determinants and VTE events in different locations (pulmonary embolism, lower and upper extremity DVT, abdominal vein thrombosis and cerebral venous thrombosis), and separately for women and men. Tests for trend were performed by entering the ordinal