Association of irritable bowel syndrome and venous thromboembolism

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is associated with venous thromboembolism (VTE). Whether functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), are associated with VTE has not been determined. This nationwide study aimed to determine the risk of VTE in IBS outpatients in primary and specialist care.

Design: We performed two matched case-control studies. Cases (n = 90,502) were individuals in Sweden aged 18–80 years with a first hospital diagnosis of VTE between 2001 and 2010. Five controls (n = 452,510) from the Swedish Total Population Register were matched to each case for birth, sex, country of birth, and education level. Diagnosis of IBS was determined in the Swedish hospital outpatient register. This procedure was replicated for the primary care population. As the Primary Care data did not have nationwide coverage, we only included individuals that were registered in the Primary Care database. A total of 9766 cases of hospital diagnosed VTE individuals could be found in the Primary Care population and they were matched to 48,830 controls also from the Primary Health Care population. Conditional logistic regression was used to determine odds ratio (OR) for first VTE diagnosis.

Results: The adjusted OR for VTE when IBS was diagnosed in hospital outpatient care was 1.49 (95% confidence interval 1.33–1.67). The crude OR for VTE was 1.18 (0.94–1.48) when IBS was diagnosed in primary care.

Conclusions: This is the first study describing an association between VTE and IBS. The results suggest that specialist treated IBS patients have increased risk of VTE.

Abbreviations: IBS: Irritable bowel syndrome; OR: Odds ratio; CI: Confidence interval; IBD: Inflammatory bowel disease; ICD: International classification of disease; TPR: Total population register

Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterised by abdominal pain or discomfort. Abdominal pain can be relieved by defaecation and its onset coincides with a change in defaecation frequency or stool consistency [1–3]. It is one of the most common gastrointestinal conditions [4]. A number of disease mechanisms have been suggested but the pathophysiology of IBS remains poorly understood [1–3]. The pathophysiology is likely to be multifactorial and involves both genetic and environmental factors. Possible mechanisms include psychosocial factors, abnormal gastrointestinal motility, visceral hypersensitivity, mucosal inflammation after gastroenteritis, and small intestinal bacterial overgrowth [1–3]. IBS clearly differs from the acute phase of inflammatory bowel disease (IBD) [5]. The ulcerated mucosa in IBD is different from the normal mucosa seen in IBS. However, an increasing number of studies have reported activation of the immune system, increased gut permeability and mucosal serotonin availability, abnormalities of the enteric nerves, and changes in gut microbiota in IBS; all features which are associated with IBD [5]. It has been well established that IBDs are associated with an increased risk of venous thromboembolism (VTE) [6–10]. Uncontrolled disease and hospitalisation are major risk factors for VTE in patients with IBD [8,10]. Most inflammatory and autoimmune disorders are associated with an increased risk for VTE, and inflammation is an important driver of VTE risk [9–11]. However, no study has determined whether IBS patients, though IBS exhibits some features of IBD, have an increased risk of VTE.

Our aim was to estimate the risk of VTE among patients with IBS. Patients with IBS were diagnosed in the Swedish Nationwide Outpatient Care Register. We also determined VTE risk when IBS cases were diagnosed in a primary care database from four Swedish counties (Stockholm, Värmland, Gotland, and Uppsala).

Methods

To assess the association between IBS and VTE among individuals in Sweden, we linked comprehensive Swedish registers and health care data from several sources to form a database [12–17]. Linkage was also made to a primary care database, and 90,502 cases of VTE were matched to 452,510 controls. Conditional logistic regression was used to determine the odds ratio (OR) for VTE when IBS was diagnosed in hospital outpatient care. The OR was 1.49 (95% confidence interval 1.33–1.67) when IBS was diagnosed in hospital outpatient care.
healthcare database from four Swedish counties [12,18]. This
linkage was based on the unique individual Swedish 10-digit
personal ID number assigned to all residents in Sweden at
birth or immigration to the country. The ID numbers were
replaced with serial numbers in order to preserve confiden-
tiality. Our database contained the following sources: the
Swedish Total Population Register (TPR), the Swedish Hospital
Discharge Register, which included all hospitalisations in
Sweden between 1964 and 2010; the multi-generation
register, the Outpatient Care Register, which included
information from outpatient clinics covering all geographic
regions in Sweden from 2001 to 2010; and the primary
healthcare database which included information from 71 pri-
mary healthcare centres in the Swedish counties of
Stockholm, Värmland, Gotland, and Uppsala. The primary
healthcare database contains individual-level data during the
period 2001–2007 [12,18].

**Matched case-control study**

The dataset for these analyses was created by identifying
individuals from the Swedish Hospital Discharge Register
with diagnoses of VTE during the period 2001–2010. We
defined VTE based on the ICD-10 codes I80 (venous throm-
bosis of the lower extremities [except I80.0, i.e., superficial
thrombophlebitis]) and I26 (pulmonary embolism). We only
used main diagnoses to guarantee high validity. Furthermore,
the following restrictions were used: the VTE diagnoses had
to be registered between the ages of 18 and 80; individuals
with a VTE registration from 1997 to 2000 were excluded. In
total, we analysed 90,502 individuals; 60,244 (67%) were reg-
istered with venous thrombosis of the lower extremities and
30,258 (33%) with pulmonary embolism.

The exposure variable, IBS, was identified by the ICD-10
code, K58, in the Outpatient Care Register and the Primary
Care register, and IBS has been extensively studied in both
these databases [12,18]. In the Outpatient Care database 78%
of IBS patients between 2001 and 2010 were diagnosed in
departments of internal medicine including gastroenterology
departments.

In order to study the association between IBS and VTE we
used a case-control approach. Each VTE-case was matched
to five controls from the TPR based on year of birth, gender,
country of birth and education level. Adjusting for education
can help to diminish confounding by lifestyle factors. Edu-
cation level was categorised into three groups: low (0–9
years), middle (10–11 years) and high (12 years or more). The
control individuals from the TPR had to be alive and regis-
tered in Sweden at the time of the case’s VTE diagnosis and
not themselves be registered with VTE at the time of the VTE
diagnoses. An individual could only be selected as a control
individual once.

This procedure was replicated for the primary healthcare
population. As the Primary Health Care data did not have
national coverage, we only included individuals that were
registered in the Primary Health Care database (for any di-
agnosis). A total of 9771 cases of VTE could be found in the
Primary Health Care population and they were matched to
58,626 controls also from the Primary Health Care population.

The IBS diagnosis had to be registered in the Primary Health
Care Register, and the VTE diagnosis had to be registered in the
Hospital Discharge Register.

**Statistical analysis**

We used IBS registration in the outpatient register as the
main predictor variable in the models. The IBS registration
had to occur prior to the VTE registration. We also categor-
ised the timing of the IBS registration in relation to the VTE
registration into three groups (1–90 days prior, 91–365 days
prior and more than 365 days prior). Controls had to be reg-
istered for IBS prior to the day of the VTE diagnosis in the
corresponding case. We used conditional logistic regression
in order to study the difference in IBS registrations between
cases and controls. In the first model, we included IBS any
time prior to the date of VTE registration in the model. In
the following models we investigated whether the timing of
the IBS registration altered the IBS–VTE association. We then
investigated whether the association between IBS and VTE was
different for individuals of a different age at VTE diagno-
sis. Hence, we included an interaction term between IBS and
age at VTE diagnosis (mean 60.1 years). In additional analy-
ses, we first investigated whether individuals with colorectal
cancer, coeliac disease or inflammatory bowel syndrome
among IBS cases confounded the association between IBS
and VTE, by defining these individuals as non-IBS cases.
Secondly, we controlled for the following variables (the regis-
tration had to occur prior to the VTE registration) in supple-
mentary models: atrial fibrillation, alcoholism, COPD,
diabetes, heart failure, hyperlipidaemia, hypertension, obesity,
cancer any time before and within three months after VTE,
fractures or trauma 90 days before VTE, pregnancy (and abor-
tion) within 90 days before or childbirth 90 days before and
within six months after index date, hospitalised surgery
(90 days before index date). The definition of variables can
be found in the Supplementary material. We replicated the
first model using the Primary Health Care population. All stat-
estical analyses were performed in SAS 9.4.

**Results**

**Venous thromboembolism in hospital treated
outpatients with IBS**

Table 1 shows the characteristics of VTE cases diagnosed in
the hospital inpatient register (n = 90,502) and controls
(n = 452,510). VTE cases and controls from the TPR were
perfectly matched 1:5 for age, sex, education and country of
birth (Table 1). Potential VTE-related conditions and family
history of VTE were more common among VTE cases than
controls (Table 1). Among VTE cases, 458 (0.51%) had prior
IBS compared to 1405 (0.31%) among matched controls
(Table 2). This corresponds to an OR of 1.64 (95% confidence
interval [CI] 1.47–1.82)). The ORs were higher in the first year
after IBS diagnosis. The association between VTE and IBS was
significant also in a multivariate model control for several
VTE risk factors (OR = 1.49, 95% CI 1.33–1.67). Totally 59
(12.88%) of 458 IBS patients among VTE cases and 99 (7.05%)
of 1405 IBS patients among controls were also diagnosed
with colorectal cancer, coeliac disease or IBD (Table 2). However, the association between VTE and IBS was still significant even if we excluded patients with colorectal cancer, coeliac disease or IBD (OR = 1.53, 95%CI 1.37–1.72). There was also an interaction between age and VTE risk (p = .009). Younger IBS patients had higher OR for VTE than older IBS patients. There was no statistical interaction with sex and IBS.

Table 3 shows the association between risk factors adjusted for in the multivariate and VTE models. Adding any of these risk factors to the model did not affect the OR for VTE in IBS patients to any major degree. However, adding all of the risk factors decreased the multivariate OR to 1.49 (95%CI 1.33–1.67).

**Venous thromboembolism in primary health care treated outpatients with IBS**

The characteristics of cases (n = 9766) and controls (n = 48,830) are presented in Table 4. Prior IBS diagnosed in primary health care was associated with a slightly and non-significantly increased OR for VTE: 1.18 (95% CI 0.94–1.48). There was no significant association between time of IBS diagnosis before the VTE event and OR for VTE. Moreover, there was no interaction with sex or age and VTE risk.

**Discussion**

This is the first study linking IBS to an increased OR for VTE. Notably, this association was found in hospital outpatients and not in inpatients. The ORs were higher in the first year after IBS diagnosis, suggesting VTE risk is related to IBS disease activity. It is also possible that both diseases are related to high inflammatory activity that would cause both diseases [5,9–11]. Thus, hospitalisation does not explain the association. The weak non-significant association between IBS and VTE among primary health care treated patients may be related to lower power but may also reflect a biological gradient because specialist treated IBS cases are more likely to suffer from a more severe form of IBS than primary care.
Table 3. Results from the case-control study (specialist outpatients) of the association between risk factors and VTE showing how an adjustment with respective risk factor affects OR of VTE in IBS patients in the Swedish population.

| Risk factor                        | Odds ratio for VTE (univariate models) | Odds ratio for IBS (multivariate models including respective risk factor and IBS) |
|-----------------------------------|----------------------------------------|--------------------------------------------------------------------------------|
| Atrial fibrillation prior to VTE  | 1.33 (1.28; 1.39)                      | 1.63 (1.46; 1.81)                                                              |
| Alcoholism prior to VTE           | 1.57 (1.49; 1.66)                      | 1.64 (1.47; 1.82)                                                              |
| COPD prior to VTE                 | 2.13 (2.05; 2.21)                      | 1.58 (1.42; 1.76)                                                              |
| Diabetes prior to VTE             | 1.29 (1.24; 1.34)                      | 1.63 (1.47; 1.82)                                                              |
| Heart failure prior to VTE        | 1.85 (1.76; 1.94)                      | 1.64 (1.47; 1.82)                                                              |
| Hyperlipidemia prior to VTE       | 1.03 (0.89; 1.20)                      | 1.64 (1.47; 1.82)                                                              |
| Hypertension prior to VTE         | 1.41 (1.35; 1.47)                      | 1.62 (1.46; 1.81)                                                              |
| Obesity prior to VTE              | 2.81 (2.58; 3.05)                      | 1.62 (1.45; 1.80)                                                              |
| Cancer                            | 3.33 (3.26; 3.40)                      | 1.63 (1.47; 1.82)                                                              |
| Fractures or trauma               | 6.57 (6.30; 6.85)                      | 1.62 (1.46; 1.81)                                                              |
| Pregnancy or childbirth           | 3.62 (3.37; 3.89)                      | 1.63 (1.47; 1.81)                                                              |
| Surgery                           | 10.27 (9.95; 10.60)                    | 1.57 (1.40; 1.75)                                                              |
| All (multivariate model)          |                                        | 1.49 (1.33; 1.67)                                                              |

Table 4. Results from the case-control study of the association between IBS and VTE in a Swedish primary health care population.

| Risk factor                        | Odds ratio for VTE cases | Odds ratio for Controls |
|-----------------------------------|--------------------------|-------------------------|
| N                                 | 9766                     | 48,830                  |
| Mean age at VTE                   | 57.3 (15.4)              |                         |
| Age range                         | 18–80                    |                         |
| Males                             | 47.2%                    |                         |
| OR in Primary Health Care patients|                          |                         |
| Prior IBS                         | 95 (0.97%)               | 404 (0.83%)             |
| 0–90 days                         | 1 (0.01%)                | 20 (0.04%)              |
| 91–365 days                       | 12 (0.12%)               | 41 (0.08%)              |
| ≥365 days                         | 82 (0.84%)               | 343 (0.70%)             |
| Interaction with age at VTE       | p = 0.0722               |                         |
| Interaction with gender           | p = 0.182                |                         |

so far been linked to VTE [22,23]. Another potential mechanism is alterations in the gut microbiota, which is a common feature for IBS and IBD [5]. The influence of gut microbiota on VTE risk has, however, not been studied. The present study suggests that this could be an interesting research area to investigate.

Strengths and weaknesses in relation to other studies

To the best of our knowledge no other study has determined the association between VTE and IBS. A strength of our study is the inclusion of only IBS outpatients and not inpatients as hospitalisation may increase the risk of VTE. Another strength is the inclusion of both IBS patients diagnosed in primary health care and specialist outpatient care. A further strength is that the matched study only used patients hospitalised for VTE because this gives a very high specificity with a positive predictive value of 90% or more [24]. The Swedish patient registers have been validated for a large number of diagnoses and the positive predictive value is generally between 85% and 95% for most diagnoses [17]. The large study size is also an important advantage.

No information about IBS type could be obtained. We therefore do not know whether type of IBS affected the risk of VTE. Obesity is an important risk factor for VTE [25]. Whether obesity is a risk factor for IBS is unclear [26]. Adjusting for obesity in the present study did not affect the OR. As we had no access to weight in kg residual confounding may exist. We had no access to smoking data but a significant association between IBS and smoking cannot be confirmed [27]. Adjusting for COPD reflecting severe smoking history did not affect the results arguing against the importance of smoking as an unmeasured confounder. Moreover, cases and controls were matched on educational levels which are related to smoking behaviour. We had no access to medication regarding hormone replacement therapy or oral contraceptives. However, there were no interactions with sex arguing against that hormone therapy could explain our results. Moreover, there are conflicting studies and no convincing evidence whether hormone supplementation affects the risk for IBS or not [28]. We had no access to thrombophilia testing but for instance Factor V Leiden play a similar
role in IBD and non-IBD patients [29]. We therefore think it is unlikely that thrombophilia should play a stronger role in IBS patients compared to non-IBS patients with VTE in analogy with the situation for thrombophilia and IBD [29]. A limitation is that IBS patients that had not visited the health care centre for IBS are not included. Moreover, we do not have data on how the diagnosis was performed for IBS. However, we know that the Swedish hospital register has high validity around 85–95% for many diagnoses including VTE [17,24]. The Swedish Patient register has also been validated for IBS [30]. IBS diagnosis was judged to be correct in 70% of cases. In further 9.6% of cases, IBS was a probable diagnosis. Thus, in totally 79.6% IBS cases were correct or a probable diagnosis [30]. Moreover, only 5% of cases had an obvious incorrect IBS diagnosis [30]. A difference in accuracy was observed comparing departments of internal medicine (74%) and non-internal medicine departments (47%) [30]. However, we found that the majority of patients (78%) were diagnosed in departments of internal medicine including gastroenterology departments. The Swedish primary care database has not been validated but a general-practice-based database in the UK has been extensively validated [18,31]. The positive predictive value of an IBS diagnosis in the UK database was 77% [31]. Moreover, the gender and age distribution and associated comorbidities in IBS patients in the Swedish Primary Health Care database and also the Swedish hospital Register are similar to those in other studies of IBS [12,18]. This may indirectly suggest that the ICD-10 code K58 mostly identifies IBS patients in the primary health care database and also the Swedish hospital Register [12,18].

The study was performed in Sweden and whether the results may be generalised to other populations remains to be determined. However, the diagnostic criteria for IBS and VTE used in Sweden are the same as in other countries.

In conclusion, IBS diagnosed in hospital outpatients is associated with VTE, but not significantly in primary care diagnosed patients. Thus, IBS might not be such an innocent functional disorder as previously believed.

Ethical approval

The study was approved by the Ethics Committee of Lund University, Sweden (approval number 409/2008, with amendments approved on September 1, 2009 and January 22, 2010). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained but the presented data are anonymised and there is no risk of identification.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability

No additional data available due to Swedish regulation. However, the nationwide registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.

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