META-ANALYSIS

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Epidemiologic Association between Inflammatory Bowel Diseases and Type 1 Diabetes Mellitus: a Meta-Analysis

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ABSTRACT

Background & Aims: Patients with inflammatory bowel diseases (IBD) are at high risk of developing several autoimmune diseases. However, the epidemiological connection between IBD and type 1 diabetes mellitus (T1DM) remains controversial. This meta-analysis aimed to determine the association between the two diseases.

Methods: A literature search was performed using Medline, Embase, and Central databases from inception to December 31, 2019. Studies evaluating the prevalence of T1DM in patients with IBD and controls were included. Statistical analysis was performed with a random effects model using the generic inverse variance method.

Results: After the literature research, five cross-sectional studies and one case-control study met the inclusion criteria. A total of 45,103 participants with Crohn's disease (CD) and 76,046 with ulcerative colitis (UC) were included. The pooled odds ratios (ORs) of T1DM were 1.16 (confidence interval [95% CI]: 0.87–1.55) in patients with CD and 1.20 (95% CI: 0.90–1.59) in patients with UC compared with the control groups. Significant heterogeneity was observed (CD: I^2=70% and UC: I^2=80%) in the complete analysis. Subgroup analysis stratified by study region was performed. Recalculated results indicated a positive association between CD and TD1M in Northern Europe with an OR of 1.65 (95% CI: 1.43–1.90; I^2=0%). Patients with UC in Israel were at a higher risk of developing T1DM with an OR of 1.70 (95% CI: 1.38–2.09; I^2=0%).

Conclusion: The complete meta-analysis suggests no association between IBD and T1DM. However, the subgroup analysis indicated that patients with CD or UC from specific regions may be at a higher risk of developing T1DM than those without IBD.

Key words: inflammatory bowel diseases – Crohn's disease - ulcerative colitis – diabetes mellitus type 1 – meta-analysis.

Abbreviations: CD: Crohn's disease; IBD: inflammatory bowel diseases; SCFA: short-chain fatty acids; T1DM: type 1 diabetes mellitus; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel diseases (IBD), which incorporate Crohn's disease (CD) and ulcerative colitis (UC), are immune-mediated disorders targeting the gastrointestinal tract [1, 2]. As reported in a systematic review, the incidence rates of UC and CD per 100,000 people range from 8.8 to 23.1 and 6.3 to 23.8 in North America, 0.97 to 57.9 and 0 to 15.4 in Europe, and 0.14 to 6.5 and 0.07 to 8.4 in Asia, respectively [3, 4]. The pathogenesis of IBD is associated with genetic susceptibility, gut microbiota, and other environmental factors [1, 2, 5, 6]. Emerging evidence has demonstrated that patients with IBD are at a high risk of developing other autoimmune diseases, including psoriasis, asthma, and multiple sclerosis [7-9]. The presence of these conditions in patients with IBD can affect the clinical therapy and outcomes [10, 11]. Therefore, it is of great significance to understand the co-existence of IBD and other immune-mediated diseases.

Type 1 diabetes mellitus (T1DM) is a juvenile-onset autoimmune disorder caused by the destruction of pancreatic beta cells [12, 13]. The incidence of T1DM has dramatically increased worldwide by 2–5% [14, 15]. Moreover, both genetic factors, including variants in *HLA, INS, PTPN2*, and *IFIH1* genes, and environmental factors, including diet, gut microbes, and infection, play important roles in the development of

T1DM [16-18]. Interestingly, several studies have reported a strong linkage between IBD and T1DM. Two diseases were suggested to share similar immune-mediated pathogenesis, which indicated a potential epidemiologic association [19-21]. However, epidemiologic studies evaluating the prevalence or incidence of T1DM in patients with IBD have revealed inconsistent results [22-24].

Therefore, this meta-analysis aimed to assess the association between IBD and T1DM.

METHODS

Search strategy

Relevant studies were searched in Medline, Embase and Central databases from inception to December 31, 2019. The search strategy combined the following medical subject headings terms and free text terms: "inflammatory bowel disease" or "Crohn's disease" or "ulcerative colitis" and "diabetes mellitus" or "diabetes mellitus, type 1." The full search strategy in Medline is available in Supplementary file 1. The reference lists of relevant articles and reviews were also examined to prevent omission.

Study eligibility and selection criteria

The inclusion criteria were as follows: (1) observational research, including cross-sectional studies, case-control studies, and cohort studies; (2) studies conducted in patients with a confirmed diagnosis of CD, UC, and T1DM; (3) studies with availability of control groups (patients without IBD) or those that provided a comparison between patients with IBD and the general population; (4) studies that assessed the prevalence/incidence of T1DM in patients with IBD and control group; and (5) studies with available odds ratio (OR)/ relative risk or hazard ratio/incidence rate ratio with 95% confidence intervals (CI) or sufficient data for calculation. Reviews, animal studies, case reports, letters, comments, conference abstracts, and non-English publications were excluded. Studies that reported a smaller sample size from the overlap database were also excluded.

Titles and abstracts were screened, and obviously irrelevant articles were excluded. The full texts of the remaining studies were then reviewed for inclusion. The study selection was performed by two independent investigators. Disagreements were resolved by the involvement of a third reviewer.

Data extraction

The following data were abstracted into a standard form: author name, year of publication, study country, design, methods used to identify T1DM and IBD, population characteristics, including mean age and sex, sample size, and OR with 95% CI. The authors were contacted if there was missing information in the selected articles.

Data extraction was carried out by two investigators independently and disagreements were resolved through a full discussion with a third reviewer.

Risk of bias

The quality of the selected articles was assessed by two independent researchers using the Joanna Briggs Institute critical appraisal checklists (Supplementary file 2). Studies were considered to be low risk and acceptable when they fulfilled at least 70% of the items in the checklists. Publication bias was not examined due to the small number of included studies.

Statistical analysis

A meta-analysis of cross-sectional and case-control studies was conducted using review manager software (version 5.3). ORs from each study were pooled using the inverse variance weighting method. Heterogeneity was assessed using Cochran's Q test and inconsistency index (I^2) tests. Heterogeneity was considered significant if $I^2>50\%$ and $p<0.05$. Meta-analysis was conducted using a fixed effects model when heterogeneity was acceptable ($I^2\leq50\%$). Alternatively, a random effects model was applied when $I^2>50\%$. The pooled results were presented as a point estimate with 95% CI. A subgroup analysis stratified by the mean age of patients with IBD or the study region was also performed.

RESULTS

Literature search

The literature search returned 3,388 records after duplicates were removed. Titles and abstracts were then screened, and 3,350 publications were excluded. After reviewing the full text of the 38 remaining articles, we found six studies contained seven analyses that met the inclusion criteria. The selection procedure and reasons for exclusion are shown in Fig. 1.

Study characteristics and quality assessment

Table I shows the baseline characteristics of the studies. We included five cross-sectional studies and one case-control study [24-29]. Cohen et al. [25] obtained the data of patients with IBD from two databases (MarketScan and IMS) separately. They defined their work as a case-control study. However, the temporal relationship between T1DM and IBD could not be established according to their methods. Therefore, we classified it as a cross-sectional study.

Studies were carried out in the United States, Finland, Denmark, and Israel. All studies obtained the data from regional medical databases. Target cases were identified by searching diagnosis codes or medical history documents. The exact diagnosis criteria of target diseases and the date when diagnosis was confirmed were not available in each study. Overall, 45,103 CD and 76,046 UC participants were involved. Most of the research comprised middle-aged patients, whereas Virta et al. [26] and Ghersin et al. [29] reported data from children and adolescents. Patients with nonspecific unclassified IBD were excluded because of an unclear diagnosis and a much smaller sample size. All studies provided a comparison of the T1DM prevalence between patients with IBD and healthy controls.

After quality assessment, all studies were considered acceptable. However, most studies only compared patients with IBD with age and sex-matched controls. Other confounding factors, including smoking, alcohol consumption, medicine use, and socioeconomic status, were not well identified and addressed. Detailed information on quality assessment are shown in Supplementary file 3.

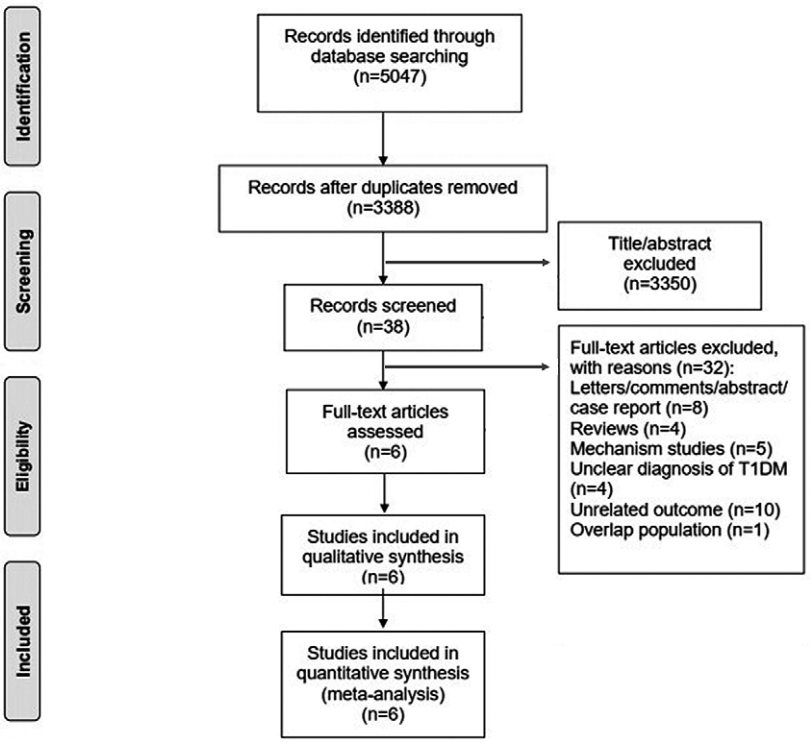

Fig. 1. Flowchart summary of study identification and selection.

Statistical analysis

As shown in Fig. 2, the ORs of T1DM in patients with IBD compared with controls were pooled in the meta-analysis using random effects models. Data of patients with CD and UC were calculated separately. The pooled estimates were 1.16 (95% CI: 0.87–1.55) in the CD group and 1.20 (95% CI: 0.90–1.59) in the UC group, indicating that there was no association between IBD and T1DM. Significant heterogeneity was observed in the complete analysis (CD: I^2=70%, UC: I^2=80%).

We performed a subgroup analysis stratified by study region. Studies were divided into the United States, Israel, and Northern Europe groups. As shown in Figs. 3 and 4, both CD and UC patients in the United States were not associated with T1DM (CD: 1.08 [95% CI: 0.84–1.40], I^2=0%; UC: 0.89

Table I. Characteristics of the included studies

Study	Study design	Country	Methods used to identify IBD	Methods used to identify T1DM	Mean Age of IBD patients	Female (%) IBD patients	Sample size of IBD patients	Odds ratio
Weng X, 2007 [24]	Cross-sectional	USA	Searching diagnosis code (ICD-9)	Searching diagnosis code (ICD-9)	52	52.5	CD:4021 UC:7525	CD: 1.10 [0.78-1.57] UC: 0.86 [0.64-1.17]
Cohen R (MarketScan), 2008 [25]	Cross-sectional	USA	Searching diagnosis code (ICD-9)	Searching diagnosis code (ICD-9)	53.5	55.5	CD:7401 UC:10104	CD:0.95 [0.57-1.58] UC: 0.93 [0.61-1.42]
Cohen R (IMS), 2008 [25]	Cross-sectional	USA	Searching diagnosis code (ICD-9)	Searching diagnosis code (ICD-9)	46.7	55.7	CD:9267 UC:11220	CD: 1.19 [0.69-2.05] UC: 0.89 [0.54-1.47]
Virta LJ, 2012 [26]	Case-control	Finland	Searching diagnosis code (ICD-9)	Searching diagnosis code (ICD-9)	10.2	43	CD:233 UC:362	CD: 1.33 [0.14-12.89] UC: 0.50 [0.06-4.00]
Halling ML, 2017 [27]	Cross-sectional	Denmark	Searching diagnosis code (ICD-10)	Searching diagnosis code (ICD-10)	53	54	CD:13343 UC:31066	CD: 1.65 [1.43-1.90] UC: 1.68 [1.55-1.83]
Bar Yehuda S, 2019 [28]	Cross-sectional	Israel	Searching diagnosis code (ICD-10)	Searching diagnosis code (ICD-10)	47.8	49.1	CD:6364 UC:6261	CD: 0.93 [0.73-1.19] UC: 1.70 [1.38-2.10]
Ghersin I, 2019 [29]	Cross-sectional	Israel	Searching medical records	Searching medical records	17.1	36	CD:595 UC:296	CD: 0.50 [0.03-8.06] UC: 1.00 [0.06-16.21]

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; T1DM: type 1 diabetes mellitus

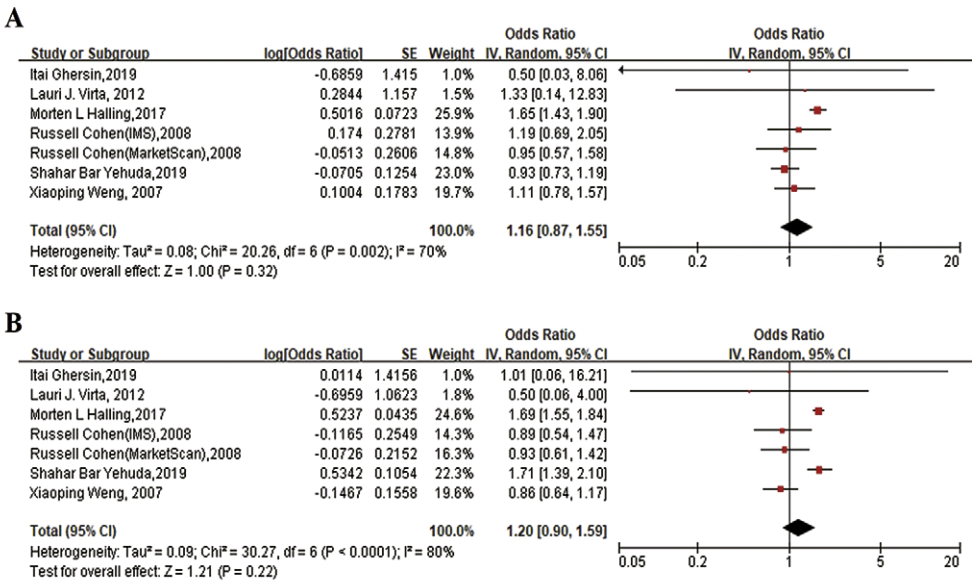

Fig. 2. Forest plot and pooled estimates assessing the association between T1DM and CD (A) or UC (B). CD, Crohn's disease; UC, ulcerative colitis; T1DM, type 1 diabetes mellitus.

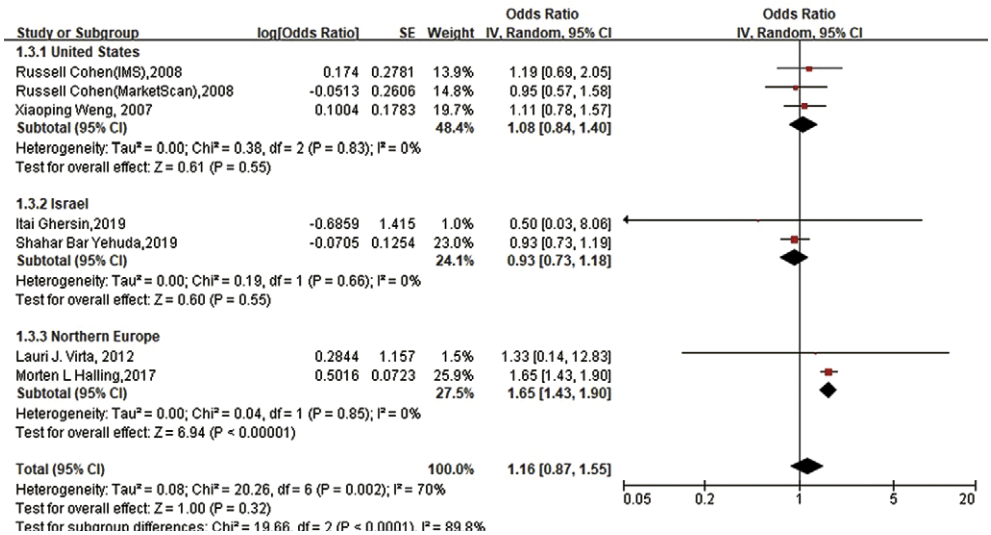

Fig. 3. Forest plot and pooled estimates evaluating the association between T1DM and CD stratified by study region. CD, Crohn's disease; T1DM, type 1 diabetes mellitus.

[95% CI: 0.71–1.11], I^2=0%). Interestingly, the recalculated results revealed a positive association between CD and TD1M in Northern Europe with an OR of 1.65 (95% CI: 1.43–1.90; I^2=0%). In addition, patients with UC in Israel were more likely to develop T1DM with an OR of 1.70 (95% CI: 1.38–2.09; I^2=0%). Furthermore, we conducted another subgroup analysis based on the mean age of patients with IBD. The studies were divided into two groups with a mean age of <18 or ≥18 years. The outcomes were not significantly different from the results of the complete analysis in each subgroup (Supplement files 4 and 5).

DISCUSSION

Understanding the co-existence of IBD and T1DM is important for clinical practice, since the presence of other autoimmune diseases in patients with IBD can increase disease severity and lead to further need for anti-TNF therapy and intestinal surgery [10]. To the best of our knowledge, this is the first meta-analysis to determine the association between IBD and T1DM. The complete estimates suggested that there was no association between CD/UC and T1DM. However, a subgroup analysis stratified by study country/region was performed and the ORs recalculated; results indicated that patients with CD in Northern Europe and patients with UC in Israel were at a higher risk of developing T1DM.

Previously, a strong linkage between IBD and T1DM was supported by genetic research. A genome-wide association study identified that IBD and T1DM shared risk variants at 20 loci, which is 10 times higher than that expected by chance [30]. Most of the overlap genes, including *PTPN2, IL2*, and *IL21*, were related to the inflammatory response, which strongly indicated that the two diseases shared similar immune-mediated pathogenesis [19, 30]. However, several

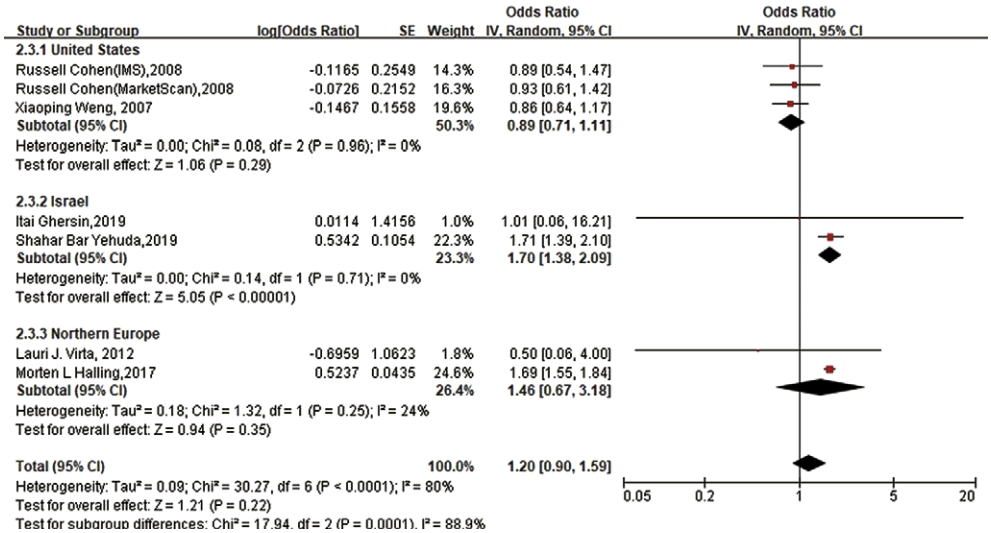

Fig. 4. Forest plot and pooled estimates evaluating the association between T1DM and UC stratified by study region. UC: ulcerative colitis, T1DM: type 1 diabetes mellitus.

variants residing in genes *IL10, PTPN22, IL18RAP*, and *IL27* were reported to play opposite roles in the development of IBD and T1DM [20, 30]. In addition, clinical research has identified altered composition and decreased diversity of gut microbes in patients with both T1DM and IBD compared with healthy controls [31-34]. Microbes exert profound effects on the development and function of the host immune system, and abnormalities in gut microbes can result in a dysregulated inflammatory response. For instance, the short-chain fatty acids (SCFA) secreted by the gut microbes are important anti-inflammatory factors [35, 36]. Insufficiency of SCFA accelerates the development of IBD and T1DM. Clinical research has reported the decreased production of SCFAs in patients with IBD, which was predicted to cause epithelial cell damage and abnormalities in intestinal homeostasis [37]. In addition, non-obese diabetic mice fed with a SCFA-free diet showed a higher incidence of T1DM and stronger inflammation in islets than those fed with a SCFA-yielding diet [38, 39].

Taken together, IBD and T1DM may share a similar pathogenesis. It is plausible that patients with IBD are more susceptible to T1DM. However, epidemiological studies have yielded inconsistent results. In addition to the articles included in this meta-analysis, several observational studies have assessed the association between the two diseases. Kappelman et al. [7] reported that type 1 and type 2 diabetes were more common among patients with UC than among controls in an American pediatric cohort. A previous retrospective nationwide cohort study conducted in South Korea showed that the incidence of diabetes significantly increased in patients with CD compared with the general population after adjusting for age, sex, life risk factors, and medicine used [23]. However, two cross-sectional studies performed in the USA and Switzerland revealed no association between diabetes and IBD [40, 41]. A critical limitation of the above studies is that type 1 and type 2 diabetes could not be distinguished.

In the present meta-analysis, we collected studies that assessed the epidemiologic connection between T1DM and IBD. Most of the studies were population based and of high quality. A large sample of 45,103 CD and 76,046 participants with UC was included. After combining all the available data, the complete analysis showed no association between the two diseases. However, the significant statistical heterogeneity was an important limitation for the complete analysis, which indicated that studies may be too heterogeneous to combine.

As widely reported, there are substantial variations in the prevalence of T1DM or IBD between different areas around the world [3, 4, 14, 15, 42]. Therefore, the differences in the study region could contribute to the heterogeneity in the complete analysis. A subgroup analysis based on the study region was then conducted. As expected, heterogeneity was dramatically reduced in each subgroup (I^2=0% or 24%). Interestingly, compared with matched controls, the prevalence of T1DM was significantly higher in the patients with CD from Northern Europe and patients with UC from Israel. The results of the subgroup analysis suggest that the association between the two diseases varies among different areas, and patients with IBD from specific countries/regions may be at a higher risk of developing T1DM than healthy controls from the same countries/regions. However, as confounding factors were lacking in the included studies, we could not identify any specific factors that could explain these regional differences. As described above, one plausible explanation is that genetic risk variants of T1DM and IBD co-related genes (*PTPN2, IL2*, and *IL21*) may appear more frequently in the residents from Northern Europe/Israel, thus leading to a significant association between T1DM and IBD in these regions. Further studies are required to verify this hypothesis.

There are some limitations in our study: (1) unknown temporal relationship between the two diseases due to the observational nature of cross-sectional studies, (2) a small number of included studies, (3) lack of confounding factors except for age and sex, and (4) clinical heterogeneities caused by unknown diagnosis criteria in each study.

CONCLUSIONS

The complete meta-analysis showed no epidemiologic association between IBD and T1DM. However, the results

of subgroup analysis stratified by study region indicated that patients with IBD from specific regions may have a higher risk of developing T1DM. Several limitations of our study are mentioned, suggesting that the conclusions should be addressed with caution. Considering the strong linkage in the pathogenetic mechanism of the two diseases, more epidemiologic studies should be performed in different areas to further evaluate the association between the two diseases.

Conflicts of interest: None to declare.

Authors' contributions: Y.T. and D.L. conceived the study. J.G., S.L. and Y.T. literature search, study selection, data extraction and quality assessment, statistical analysis. J.G.: drafted the article. All authors critically revised the paper, approved the final version and agreed to be accountable for all aspects of the work.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-798

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