**Review Article**

Diabetes mellitus increases the risk of enteric infections: a meta-analysis

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Received July 9, 2017; Accepted March 28, 2018; Epub June 15, 2018; Published June 30, 2018

**Abstract:** Background: In diabetes mellitus (DM), the gastrointestinal tract is one of the systems affected by hyperglycaemia. Aims: To determine the risk of enteric infections in diabetic individuals and assess the contributory factors. Methods: We searched PubMed, Embase, Web of Science, Cochrane CENTRAL, Wanfang Data, SinoMed, and CNKI Database for relevant studies about DM and enteric infections up to December 2016. Subgroup analyses were conducted based on the types of DM, study designs, development degree of the regions, diagnostic methods, and categories of pathogens. Results: Fourteen studies containing 1,841,653 subjects were included. DM was associated with a significantly increased risk of enteric infections (OR = 1.93; 95% CI 1.33-2.79). However, we found no statistical significance in either type 1 or type 2 DM subgroup. DM patients in developing countries were at a significantly higher risk of enteric infections (OR = 2.30, 95% CI 1.13-4.67). A trend towards higher risk of parasitic infection in DM was detected (OR = 2.90, 95% CI 0.96-8.74). Conclusions: DM was associated with a significantly increased risk of enteric infections. The evidence regarding the influence of that the type of DM has on enteric infections was limited. A higher risk of parasitic infection might exist among diabetics.

**Keywords:** Enteric infections, diarrhoea, diabetes mellitus, meta-analysis

**Introduction**

Enteric infections are intestinal diseases caused by any infection. Severe case with significant losses of fluid and electrolytes, and infection spreading throughout the body can be life-threatening in immunocompromised patients, such as those with diabetes mellitus (DM) [1]. Among individuals with diabetes, the physiological and barrier functions of the intestine are impaired, possibly resulting in greater susceptibility to enteric infections [2, 3]. As there is a high prevalence of DM and it requires continuous medical care and patient self-management to decrease the risk of acute or long-term complications, it is meaningful to reveal the risk of enteric infections in DM and draw adequate attention to it in clinical practice [4, 5].

However, studies investigating the risk of enteric infections in DM have drawn different conclusions. Some researchers showed that the susceptibility to enteric infections was increased in DM [6], and others reported that diabetes increased the risk of pneumonia, urinary tract infection, skin infections and sepsis, rather than enteric infections [7]. And these studies focused mainly on one specific kind of pathogen, such as Enterococcus, Clostridium difficile (C. difficile), Strongyloides, and Candida [8-12]. So far, no published systematic literature has investigated the association between DM and common enteric infections.

Therefore, the present study was conducted to determine the risk of enteric infections caused by bacteria, viruses, parasites, and fungi in patients with DM. Subgroup analyses were conducted to further investigate the association.

**Materials and methods**

**Search strategies**

We conducted this meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [13]. We searched PubMed, Embase, Web of Science, Cochrane CENTRAL, Wanfang Data, SinoMed, and CNKI Database for potentially eligible studies up to December 2016. For PubMed, we applied the
following algorithm in both the Medical Subject Headings and the text words: (“diabetes mellitus” or “Diabetes Mellitus, Type 1” or “Diabetes Mellitus, Type 2” or “diabetes” or “DM” or “T1DM” or “ T2DM” or “insulin resistance”) and (“enteric infection”* or “intestinal infection”* or “gut infection”* or “digestive tract infection”* or “colonic infection”* or “gastroenteritis” or “enterocolitis” or “diarrhoea” or “enteritis” or “escherichia” or “enterococcus” or “Clostridium difficile” or “C. difficile” or “Campylobacter” or “cholera” or “shigella” or “dysentery” or “cryptosporidiosis” or “giardia”* or “strongyloides” or “vibrio” or “amoeba”* or “entamoeba”* or “norovirus” or “rotavirus” or “adenovirus” or “enterovirus” or “ETEC” or “fungi” or “fungus” or “candida” or “parasitic” or “intestinal parasites” or “nematode” or “ascaris” or “trichuris” or “hookworm” or “pinworm” or “cyclospora”). Similar searching strategies were used in the other databases. The reference lists of the relevant articles were scrutinized to find additional literature on this topic.

Selection criteria

Studies were included if they: 1) evaluated or included the results of evaluating the risk of enteric infections in patients with DM, using individuals without DM, impaired glucose tolerance, or impaired fasting glucose as controls; 2) provided odds ratio (OR), relative risk (RR), or longitudinal prevalence ratio (LPR) and their confidence intervals (CI) or sufficient data to calculate these items; 3) were observational studies designed as case-control, cohort, or cross-sectional studies or randomized controlled trials (RCTs); and 4) clearly defined the outcomes of interest including enteric infection with either the microbial isolation of pathogens or a clinical definition.

Studies were excluded if they were: 1) duplicate publications; 2) case report, review, meta-analyses, or guidelines. If an author published more than one article using the same case series, we only referred to the article that reported the data with the largest number of cases and the most complete information.

Data extraction and quality assessment

Data were extracted by two investigators independently and were recorded in a well-designed form. The data items included the first author, publication year, age, sample size, country, study design, diagnostic method, category of pathogen, type of DM, and follow-up/study period. Disagreements were resolved by consensus including a third author. The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of each study. This measure assesses the aspects of the methodology in observational studies related to study quality [14]. A final score of more than 6 stars was considered high-quality.

Statistical analysis

The overall outcome was measured by the ORs with their corresponding 95% CIs. The significance of the pooled ORs was determined by the Z test with a P value. A P value less than 0.05 was considered statistically significant. Statistical analyses were conducted using Review Manager Software (Version 5.3 for Windows, Cochrane Collaboration, Oxford, UK). The presence of between-study heterogeneity was assessed using Q and I² statistics tests. For the Q statistic, a P value less than 0.1 was considered representative of statistically significant heterogeneity. For the I² statistic, an index of approximately 25% was considered low level of heterogeneity, 50% was medium, and 75% was high. The pooled effect measures were calculated using a random-effects model if there was heterogeneity. Otherwise, a fixed-effects model was used. We conducted further subgroup analyses based on the types of DM, study designs, diagnostic methods, development degree of the regions, and categories of pathogens, to clarify the source of heterogeneity. The influence of a single study on the overall risk estimates was estimated in sensitivity analyses by removing each study sequentially. Potential publication bias was evaluated by inspecting a funnel plot and statistically by Begg’s test and Egger’s test. The meta-analysis was considered to have significant publication bias if the Pr or P value was less than 0.05. The funnel plot was generated using Review Manager and the Begg’s test and Egger’s test were conducted using the STATA software (Version 12.0; STATA Corporation, College Station, TX, US).

Results

Literature search and study characteristics

A total of 11,539 studies were identified from PubMed, Embase, Web of Science, Cochrane
CENTRAL, Wanfang Data, SinoMed, and CNKI Database in our initial searches. After excluding duplicates, case reports, reviews, guidelines, and meta-analyses, 9,588 studies remained. Finally, 261 studies were found to be relevant after scrutiny of titles and abstracts. We closely reviewed these 261 studies and excluded 245 according to our inclusion and exclusion criteria. Two more studies were identified from the references of another article [15, 16]. Eighteen studies were recruited for further review. Among them, two studies were excluded for duplicate data. One study was excluded because it investigated intestinal fungi colonization without definite infectious symptoms [17]. One study was excluded for illustrating small intestinal bacterial overgrowth (SIBO) but providing no diagnostic evidence of enteric infections [18]. SIBO refers to abnormally large numbers of anaerobic bacteria in the small intestine. It was more common among patients with DM due to diabetic gastroparesis and neuropathic motility disorders, but it was fundamentally different from enteric infections caused by pathogenic microorganisms [19]. Eventually, a total of 14 articles including 1,841,653 subjects were included in this meta-analysis [15, 16, 20-31] (Figure 1). Thirteen were published with the fulltext in English, and one was published in Egyptian Arabic with an English abstract, which provided sufficient data for our research [22] (Table 1). According to the NOS, ten studies scored 6 stars or more and were thus considered high-quality (Table 2). But No RCTs meeting the selection criteria were found in the literature search.
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The pooled analysis of all studies indicated that DM was associated with a significantly increased risk of enteric infections (OR = 1.93; 95% CI: 1.33-2.79, P < 0.01; Figure 2A). Nevertheless, significant heterogeneity was detected across the studies (I² = 89%, P < 0.01). Sensitivity analyses by re-estimating the pooled OR while excluding each study in turn were therefore implemented. The pooled ORs ranged from 1.76 to 2.20, with all showing a statistically sig-
significant association between DM and a higher risk of enteric infection (Figure 2B).

**Subgroup analyses**

We conducted subgroup analyses based on the types of DM, study designs, diagnostic methods, development degree of the regions, and categories of pathogens to further investigate the association between DM and the risk of enteric infections and the source of heterogeneity.

**Types of DM**

No statistical significance was detected in either the T1DM subgroup with 5 studies and 197 diabetic individuals (OR = 1.72, 95% CI 0.65-4.59), or the T2DM subgroup with 5 studies and 383 diabetic individuals (OR = 1.69, 95% CI 0.70-4.11). Six studies did not specify the type of DM but showed a significantly increased risk of enteric infections (OR = 2.10, 95% CI 1.27-3.45, P < 0.01; Figure 4). The heterogeneity was reduced in the T2DM sub-
groups, but remained significant in the subgroup that did not specify the type of DM and the T1DM subgroup (T1DM, $I^2 = 73\%$, $P < 0.01$; T2DM, $I^2 = 50\%$, $P = 0.09$; DM, $I^2 = 95\%$, $P < 0.01$). Considering the high heterogeneity in the two of three subgroups, the random-effects model was used.

**Diagnostic methods**

In some studies, enteric infection was diagnosed by laboratory test such as stool tests (including microscopic examination for pathogens, stool specific pathogen antigen detection, toxin testing for enteric pathogen, pathogen culture), serologic antibody detection, or small intestine biopsy [16, 22-26, 28, 30, 31]. In the other studies, enteric infection was diagnosed by clinical symptoms, namely, diarrhoea with an acute increase in stool frequency by more than three stools per day, or symptoms of enteric infection documented in hospital records that could be searched [15, 20, 21, 27, 29]. Therefore, studies were assigned into two subgroups based on diagnostic methods. The heterogeneity was significant among studies based on laboratory tests ($I^2 = 91\%$, $P < 0.01$).
but not among those based on clinical symptoms ($I^2 = 7\%, P = 0.37$). Studies based on the clinical symptoms were conducted in different regions, with participants recruited from differ-

Figure 4. Forest plot (random-effects model): subgroup analysis based on types of DM.

Figure 5. Forest plot (random-effects model): subgroup analysis based on study designs.
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ent population. And information of the clinical symptoms for diagnosis was obtained by different ways. Subjects and interventions in these studies might differ in ways that would impact the result. So the random-effects model was generally a more plausible match for this subgroup analysis. A significantly increased risk of enteric infections in DM patients was detected in both subgroups, with ORs of 1.48 (clinical symptom, 95% CI 1.28-1.70, \( P < 0.01 \)) and 2.46 (laboratory test, 95% CI 1.22-4.96, \( P = 0.01 \)), respectively (Figure 6).

Development degree of the regions

Studies were assigned into two subgroups, developing and developed countries subgroups, according to development degree of the regions being studied. The subgroup of developing countries showed a significantly increased risk of enteric infections in DM (OR = 2.30, 95% CI 1.13-4.67, \( P = 0.02 \)). However, no statistical significance was detected in the subgroup of developed countries (Figure 7). The heterogeneity was statistically significant in both subgroups (developing countries, \( I^2 = 91\% \), \( P < 0.01 \); developed countries, \( I^2 = 69\% \), \( P < 0.01 \)).

Categories of pathogens

Our meta-analysis included studies observing various pathogens contributing to intestinal infections. Five studies were about parasites, but only two studies were about viruses, one was about fungi, and one was about C. difficile. Thus, we only investigated the association between DM and parasites. A trend towards higher risk of intestinal parasites infections in DM was detected (OR = 2.90, 95% CI 0.96-8.74, \( P = 0.06 \)). The heterogeneity was statistically significant in the parasites subgroup (\( I^2 = 89\% \), \( P < 0.01 \); Figure 8).

Publication bias

Funnel plot inspection revealed no evidence of publication bias (Figure 3A). Most of the studies were distributed symmetrically. Potential publication bias was also quantitatively demonstrated by Egger’s and Begg’s test. No significant publication bias was identified by Begg’s test (\( P = 0.76 \); Figure 3B) or Egger’s test (\( P = 0.53 \); Figure 3C).

Discussion

Our pooled analysis of 14 studies suggested that individuals with DM had an approximately 93% increased risk of developing enteric infections. We included studies on a variety of pathogens, which were more comprehensive than previous studies that were limited to just one kind of pathogen. It may not only draw more attention to diabetics, regarding personal hygiene and preventing enteric infections, but may also raise physicians’ awareness of enteric infections.

Figure 6. Forest plot (random-effects model): subgroup analysis based on diagnostic methods.
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Infections in diabetics with intestinal symptoms.

Some studies of basic science showed that there are pathophysiological alterations in DM patients that might lead to susceptibility to enteric infections. In T1DM, abnormal differentiation of the intestinal epithelium cell might impair the bactericidal function of Paneth cells [32]. T2DM was characterized by a state of systemic and local chronic low-grade inflammation in the intestine [33]. The distribution of gut microbiota was significantly altered in both T1DM and T2DM [34, 35]. Our pooled analysis of all the studies and the subgroup including studies that did not specify the types of DM, showed a significantly increased risk of enteric infections in DM, consistent with the findings mentioned above. However, we found no statistical significance in either the T1DM or T2DM subgroups, which might result from the small sample sizes of these two subgroups. More robust studies are still needed to determine the clinical difference between T1DM and T2DM in terms of the risk of enteric infections.

The present study showed a significant association between DM and a higher risk of enteric infections in case-control studies, but not in cohort studies. However, the follow-up years of cohort studies ranged from 6 weeks to 1 year, which might be insufficient to reveal the risk of
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gut infections in DM [15, 20, 27, 29, 30]. By contrast, the study period of most case-control studies ranged from 1 year to 5 years [16, 26, 28, 31]. On the other hand, only 3 cohort studies and, however, all the case-control studies were based on laboratory diagnosis [23, 24, 30]. In general, we considered that the results of this meta-analysis were creditable.

For the diagnostic methods, studies based on clinical diagnosis might have a risk of overestimating the infection rate in DM because some of the symptomatic diseases could be non-infectious. However, there was no significant heterogeneity in the subgroups based on the clinical diagnosis, thus making the result creditable. The present study suggested a significant association between DM and enteric infections in subgroups based on either clinical or laboratory diagnosis, which minimized the potential bias and further enhanced the reliability of this meta-analysis.

For development degree of the regions, we found that the diabetic-enteric infections relationship might be stronger in developing countries. Due to the poor economic conditions and defective sanitary facilities, DM patients in developing countries are probably unable to receive adequate treatment and glucose control or to manage diabetic complications well. Subgroup analysis regarding intestinal parasitic infections in DM showed a trend towards higher risk. There might be a higher success rate for parasites in intestine among diabetics owing to their impaired gut barrier function. However, the numbers of studies on viral, fungal, and C. difficile infections in DM were limited, so we could not analyze their association. This reinforces the need for more studies on enteric infections by different kinds of pathogens in DM.

Last but not least, there were several limitations in our study. First, there was significant heterogeneity among the included studies. Sensitivity analyses still showed a significantly higher risk of enteric infections in DM after omitting each individual study in turn. There was clinical heterogeneity in the studies as follows: 1) differences in types of DM, as the heterogeneity reduced in subgroup of one specific type of DM, and 2) different diagnostic methods. The heterogeneity reduced in subgroup based on clinical diagnosis but remained significant in the subgroup based on laboratory diagnosis, which included different detection methods. This underlined that studies on enteric infections in DM must consider both clinical and laboratory diagnoses. Moreover, subgroup analyses based on other factors such as age, gender, and the duration of DM could not be performed due to insufficient data. Second, we noticed that sample size of the study by Shah BR et al. was more than 100 times larger than those of the other studies, and possibly driving the evidence towards a positive conclusion [27]. However, the diabetics-enteric infections association was still statistically significant after removing this study from the overall analysis. We then removed this study from subgroups to investigate how it affected the results. Statistical significance was no longer apparent in the subgroup of studies based on clinical diagnosis. This subgroup had no more than 350 diabetic individuals after removing the study. Considering its high quality according to NOS, we supposed that its influence should not be neglected and that it should not be excluded from our analysis.

In summary, our meta-analysis revealed that DM is associated with a significantly increased risk of enteric infections. The diabetic-enteric infection relationship might be stronger in developing countries. Among all the enteric infections, a trend towards higher risk of parasitic infection was found in DM.

Acknowledgements

There is no conflict of interest to be declared. All authors read and approved the final manuscript. This study was supported by National Natural Science Foundation of China (No. 812-70442 and No. 81370475).

Disclosure of conflict of interest

None.

Abbreviations

DM, diabetes mellitus; T2DM, type 2 DM; T1DM, type 1 DM; C. difficile, Clostridium difficile; NOS, Newcastle-Ottawa scale; OR, odds ratio; RR, relative risk; LPR, longitudinal prevalence ratio; CI, confidence interval; SIBO, small intestinal bacterial overgrowth; RCTs, randomized controlled trials.
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