

Statin Use and Risk of Acute Diverticulitis: A Population-Based Case-control Study

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Abstract

Objective: To examine the association between statin use and the development of acute diverticulitis requiring hospital admission.

Methods: A retrospective, population-based, case-control study was carried out on a cohort of adults, resident in Canterbury, New Zealand between 1-1-2003 and 31-1-2008, identified from the National Census; all identified cases were admitted to hospital and had CT confirmed diverticulitis. The positive control group comprised patients on non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), and the negative control group were patients on selective serotonin reuptake inhibitors (SSRIs). Medicine exposure was obtained from the Pharmaceutical Management Agency of New Zealand. Subgroup analysis was done by age and for complicated diverticulitis and recurrent diverticulitis.

Results: During the study period, there were 381,792 adult's residents in Canterbury. The annual incidence of diverticulitis requiring hospital presentation was 18.6 (<65 years, 13.1;>64 years, 41.3) per 100,000 per year. Complicated disease was seen in 37.4% (158) of patients, and 14.7 % (62) had recurrent disease. Statins were not found to affect the risk of developing acute diverticulitis, nor the risk of complicated or recurrent diverticulitis. Subgroup analysis suggested statin use was associated with a decreased risk of acute diverticulitis in the elderly (age>64 years). NSAIDs were associated with a decreased risk of acute diverticulitis (RR=0.65, CI: 0.26-0.46, p<0.001), as were SSRIs (RR=0.37, CI: 0.26 - 0.54, p<0.001).

Conclusion: This population-based study does not support the hypothesis that statins have a preventative effect on the development of diverticulitis, including complicated disease.

We also found a decreased risk of diverticulitis associated with NSAID and SSRI use.

Keywords: Diverticulitis; Statins; Non-steroid anti-inflammatory drugs (NSAID); Selective serotonin re-uptake inhibitors (SSRI); Complicated diverticulitis; Recurrent diverticulitis

Introduction

Diverticulitis is a common, costly and usually acutely presenting gastrointestinal disorder, with approximately 20% of people requiring surgery on their first presentation. Although the incidence of diverticulitis is increasing, particularly among younger age groups, its pathophysiology and modifiable risk factors are incompletely understood, and are of increasing research interest.

The classical pathogenesis of diverticulitis was traditionally considered a process initiated by obstruction and trauma to a diverticulum, with subsequent ischemia and bacterial overgrowth. This theory has been challenged with new research indicating a multifactorial pathway involving genetic and environmental predisposition, alteration in the colonic microbiome and chronic inflammation through dysregulated immune response.

Statins have been shown to affect the inflammatory response. Statins decrease T-cell activation by inhibiting antigen presentation,

reducing the production of pro-inflammatory cytokines (IFN γ and TNF α), and increasing the production of anti-inflammatory molecules (IL-10). Statins may also affect intestinal permeability, impacting leucocyte migration and bacterial translocation, and promote the growth of anti-inflammatory luminal bacteria. As such, they may have a role in modifying an episode of acute diverticulitis. Further evidence on the possible effects of statins on acute diverticulitis would be of benefit in helping both to understand the pathophysiology, and to quantify the potential for risk reduction of acute diverticulitis.

The aim of this study is to examine the association between statin use and the development of acute diverticulitis requiring hospital admission, including complicated and recurrent disease.

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Received date: December 31, 2019; Accepted date: January 15, 2019; Published date: January 22, 2020

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Methods

Study design

This was a retrospective, population-based, case–control study. The source population was a cohort of adults, resident in Canterbury, New Zealand between 1-1-2003 and 31-1-2008, identified from the National Census.

Case identification

Cases of diverticulitis were identified from a prospectively maintained database containing all adult patients aged 20 years or over assessed at Christchurch Hospital, with computed tomography (CT)-proven acute diverticulitis between July 2003 and December 2008. CT was readily available during this period, and routinely carried out in the work-up of patients with suspected diverticulitis. Christchurch Hospital is the only provider of acute general surgical services within Canterbury, including both public and private sectors. Therefore, all patients within the Canterbury population, with diverticulitis severe enough to warrant hospital presentation, were captured.

Control identification

Positive and negative controls were used. The positive control group comprised patients on non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), as previous studies have reported this as a risk factor for acute diverticulitis, and there is a high prevalence of NSAID use in the population.

The negative control group were patients on selective serotonin reuptake inhibitors (SSRIs), as we did not expect SSRIs to influence the rate or severity of diverticulitis, and it is a class of medicine commonly used in the general population.

Drug exposure

Data on drug exposures was obtained from the Pharmaceutical Management Agency of New Zealand (PHARMAC), which is a national body that funds prescribed medicines in New Zealand. A database containing information on all of the prescriptions filled in the Canterbury region, between January 2003 and December 2008, was searched to identify all prescriptions of statins, SSRIs, and NSAIDs by adults during that period.

For patients in the diverticulitis database, 'statin users' were defined as those who had a prescription filled for atorvastatin, simvastatin or pravastatin within the six months prior to the CT diagnosis date. NSAID and SSRI users were defined in the same manner.

Case definitions

Uncomplicated diverticulitis was defined as the presence of colonic diverticulae with localized wall thickening and/or stranding of pericolic fat on CT scan. Complicated diverticulitis was defined as the presence of abscess, perforation (including any pericolic or extraluminal gas), obstruction, fistula formation, or an associated mass lesion. Recurrent disease was defined as a second CT-proven episode occurring at least three months after the initial presentation.

In this study, adults were defined as aged 20 years or over, and elderly patients were those aged 65 years or over. These groupings were chosen to allow comparison with population data from the New Zealand census report.

Outcome measures

The primary outcome measure was the rate of CT-proven diverticulitis. Secondary outcome measures were the rates of complicated disease and recurrent diverticulitis.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp, 2015). Two subgroups were analysed: patients aged 65 or over, and those aged 20–64 years. Pearson's chi-squared test was used for categorical variables. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for the risk of diverticulitis, and for the subgroups of complicated and recurrent disease, for each medicine. Significance was set at $p < 0.05$.

Ethics

Ethical approval was obtained for this study from the Upper South B Regional Ethics Committee of New Zealand (reference 15/STH/160).

Results

During the study period, there were 381,792 adult's resident in Canterbury, of which 309,180 were aged 20 to 64 years and 72,612 were 65 years or older.

Demographic, diverticular disease and medicine use data are shown in Table 1. There were 423 patients with diverticulitis, of which 243 (57%) were under 65 years of age, and 180 (43%) were 65 years or older.

Table 1: Demographic, pathology and medicine use.

	Acute diverticulitis	Complicated diverticulitis	Recurrent diverticulitis
Total	423	158	62
Age			
<65	243	89	36
>65	180	69	26
Gender			
Female	213	79	29
Male	210	85	33
Medication use			
Statin	69	24	9
NSAID	56	35	8

SSRI	29	10	4
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The annual incidence of diverticulitis requiring hospital presentation was 18.6 per 100,000 per year. When subdivided by age, the annual incidence was 13.1 and 41.3 per 100,000 per year in the under 65 years and 65 years and older subgroups, respectively.

Of those diagnosed with diverticulitis, 158 (37.4%) were complicated, and 62 (14.7%) had recurrent disease. There were 69 statin users, 56 NSAID users, and 29 SSRI users.

The relative risks for diverticulitis associated with each medicine are shown in Table 2 and are further stratified by age. Statins were not found to affect the risk of developing diverticulitis, nor the risk of complicated or recurrent diverticulitis. In subgroup analysis there was a decreased risk of acute diverticulitis in the 65 years and older age group (RR=0.47, CI: 0.34–0.67, $p<0.001$), including for complicated (RR=0.35, CI: 0.19–0.64, $p=0.006$) and recurrent disease (RR=0.36 CI: 0.14–0.95, $p=0.031$).

Table 2: Relative risk for diverticulitis, including complicated and recurrent, associated with medicine use.

Primary outcome: Relative risk of diverticulitis associated with medicine exposure			
	All adults	Age<65 years	Age ≥ 65 years
Statin	0.97 (0.75-1.26) $p=0.817$	0.96 (0.65-1.44) $p=0.857$	0.47 (0.34-0.67) $p<0.001$
NSAIDs	0.35 (0.26-0.46) $p<0.001$	0.33 (0.22-0.48) $p<0.001$	0.31 (0.21-0.47) $p<0.001$
SSRIs	0.37 (0.26-0.54) $p<0.001$	0.35 (0.21-0.58) $p<0.001$	0.41 (0.23-0.72) $p=0.002$
Secondary outcome: Relative risk of complicated diverticulitis associated with medicine exposure			
	All adults	Age<65 years	Age ≥ 65 years
Statin	0.89 (0.58-1.38) $p=0.603$	1.11 (0.059-2.08) $p=0.750$	0.35 (0.19-0.64) $p=0.006$
NSAIDs	0.65 (0.45-0.95) $p=0.025$	0.67 (0.40-1.11) $p=0.119$	0.52 (0.29-0.90) $p=0.019$
SSRIs	0.34 (0.18-0.65) $p<0.001$	0.24 (0.09-0.65) $p=0.002$	0.49 (0.21-1.14) $p=0.090$
Secondary outcome: Relative risk of recurrent diverticulitis associated with medicine exposure			
	All adults	Age<65 years	Age ≥ 65 years
Statin	0.85 (0.42-1.71) $p=0.640$	0.98 (0.35-2.77) $p=0.970$	0.36 (0.14-0.95) $p=0.031$
NSAIDs	0.34 (0.16-0.71) $p=0.003$	0.32 (0.11-0.90) $p=0.023$	0.30 (0.10-0.86) $p=0.018$
SSRIs	0.35 (0.13-0.96) $p=0.033$	0.44 (0.14-1.45) $p=0.166$	0.22 (0.03-1.59) $p=0.097$

NSAIDs were associated with a decreased risk of acute diverticulitis (RR=0.65, CI: 0.26–0.46, $p<0.001$), complicated diverticulitis (RR=0.65, CI: 0.45–0.95, $p=0.025$) and recurrent diverticulitis (RR=0.34, CI: 0.16–0.71, $p=0.003$).

SSRIs were also associated with a decreased risk of acute diverticulitis (RR=0.37, CI: 0.26–0.54, $p<0.001$), complicated diverticulitis (RR=0.34, CI: 0.18–0.65, $p<0.001$) and recurrent diverticulitis (RR=0.35, CI: 0.13–0.96, $p=0.033$).

Discussion

Diverticulitis is a common and costly health problem that is increasing in incidence. If an effective prophylactic treatment could be identified, this would represent disease altering progress. This study did not show any association between statin use and the risk of developing acute diverticulitis, including complicated or recurrent disease. We found two unexpected results with the decreased risk of acute diverticulitis in those exposed to NSAIDs and SSRIs.

There is no proven effective prophylactic medical treatment for acute diverticulitis, though studies have examined the roles of a wide

array of medications including rifaximin, mesalazine, calcium channel blockers, metformin, statins and more recently probiotics.

The prevention of diverticulitis with rifaximin was investigated in a meta-analysis comprising data from four studies that included 1,660 patients with symptomatic uncomplicated diverticular disease, and concluded that rifaximin improves self-reported symptoms, but does not prevent diverticulitis. This meta-analysis was limited by the scientific quality of the included studies, for example, only one study was placebo controlled.

Mesalamine has predominantly been studied in the prevention of recurrent diverticulitis. A meta-analysis including 1,423 patients in four placebo-controlled randomized controlled trials (RCT) found no evidence to support a role for mesalamine in the prevention of recurrent diverticulitis, and two subsequently published RCTs found the same results.

Calcium channel blockers (CCB) and metformin were both associated with decreased risk of diverticulitis in small retrospective studies; CCB were examined in a case-control study of 120 patients with perforated diverticulitis, and metformin in a cohort of 175 diabetic

patients with acute diverticulitis. Both studies were at risk of bias and confounding and further studies are needed to further clarify these associations.

Recently several small studies have examined the role of probiotics in the prevention of diverticulitis. One study with 15 participants investigated symptoms and recurrence rates associated with treatment with *Escherichia coli* Nissle, following uncomplicated diverticulitis. Patients treated with *E. coli* Nissle had a longer recurrence-free interval by 2.4 months. The effect of *Lactobacillus casei* in addition to a therapy with mesalazine was investigated in 90 patients with acute uncomplicated diverticulitis. The authors concluded that both substances may have some effect on symptom relief and prevent recurrence. However, the small number of patients studied, the lack of placebo control, and the short follow-up time limited the conclusions that could be drawn from this study.

Two observational studies have previously looked at the use of statins and risk of diverticulitis. A study from the UK General Practice Database by Humes et al, reported an odds ratio (OR) of 0.44 (95% CI 0.20–0.95) for diverticular perforation in regular statin users. A Swedish population-based study by Sköldberg et al. found an OR for current statin use of 0.70 (95% CI 0.55–0.89) for acute diverticulitis requiring surgical treatment. However, neither study found any effect on the risk of uncomplicated diverticulitis.

The main finding of our study is in agreement with Sköldberg et al. suggesting no association between statin use and risk of acute diverticulitis. However, in contrast to the findings of Sköldberg et al and Humes et al, that identified a decreased risk for complicated disease in those taking statins, we found no association between statin use and complicated diverticulitis. This may be due to the differing definitions of complicated disease used in the studies – in our study, complicated disease was diagnosed on CT as any abscess, perforation, obstruction, fistula formation, or associated mass lesion. Some of these cases would have been managed conservatively without surgery, and, therefore, would not be captured in the definition of complicated disease defined in the study by Sköldberg et al. This may account for the lower rates of complicated diverticulitis reported in that study compared to our study (7% v 37%). Humes et al. reported only on those patients with perforated diverticulitis, and excluded other forms of complicated disease. Statin use of 16.3% in the current study is similar to the rate reported in the study by Sköldberg et al. (14.9%) but considerably higher than that in the study by Humes et al (0.78%), likely reflecting increasing population statin use in the last 20 years

An unexpected finding from our study was a decreased risk of acute diverticulitis associated with prescription NSAID use. Numerous observational studies have reported on the risk of diverticulitis with NSAID exposure. Most report an increased risk, particularly in relation to complicated disease, while one large study reported no association. The current study is susceptible to bias from ascertainment of NSAID medication exposure – in addition to prescribed usage, NSAIDs are available “over the counter” in New Zealand and this is not captured in PHARMAC data used in our study, which implies an underestimation of NSAID use in our cohort. Furthermore, patients with mild diverticulitis may be prescribed NSAIDs by their general practitioner with or without oral antibiotics, resolving their symptoms and avoiding the need for hospital presentation, and thereby avoiding capture in our database.

Our finding of a decreased risk of diverticulitis associated with SSRI exposure was also unexpected. This observation has not been previously reported and may be an area for future research. The gut-brain axis is an emerging area of research, and several groups have reported the interaction of SSRIs with the gut microbiome. As the microbiome has also been postulated to be involved in diverticulitis, medications that interfere with gut-brain signalling may also have an effect on gut diseases, such as diverticulitis.

Recurrent diverticulitis is likely to become an increasing problem, with increasing overall incidence of diverticulitis, and particularly among younger individuals. In our study the absolute numbers of recurrent diverticulitis in each medication group were small, leading to wide confidence intervals, and hence we were not able to draw any conclusions about the effect of these medications on recurrent disease.

The strengths of the study are the population-based design and the complete coverage of prescription data, reducing the risk of recall bias. Our prospective database and the use of CT to confirm and stage disease minimises the risk of misdiagnosis or under-staging of disease severity. The main limitation of this study, and other observational studies, is that medicines are prescribed because of disease and this introduces unmeasured confounders that could not be accounted for, which may have influenced our results. Other limitations of this study include the assumption of a fixed population and the exclusion of diverticulitis managed in the community.

Conclusion

This population-based study does not support the hypothesis that statins have a preventative effect on the development of diverticulitis, including complicated disease, but found that NSAID and SSRI use is associated with a lower risk of diverticulitis in our population.

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How to cite this article: Michael O'Grady, Louise Clarke, Gregory Turner and Matt Doogue et al. "Statin Use and Risk of Acute Diverticulitis: A Population-Based Case-control Study". *Clin Gastroenterology J* 5 (2020) doi: 10.37421/Clin Gastro J.2020.5.122