THE INVISIBLE PRESENCE OF MICROSCOPIC COLITIS

Ph.D. Thesis Booklet

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1 INTRODUCTION

1.1 Overview of the topic

Microscopic colitis (MC) presents a rising incidence in Western countries, with 11.4 cases per 100,000 person-years. But still, it is assumed that diagnosis may take years.

1.2 What is the problem to solve?

First, MC's risk factors remain debated, as a vast amount of contradictory data exists on MC's risk factors.
Second, MC's risk factors might overlap with those of low bone density (LBD), and few publications report the potential loss of bone mineral density (BMD) in MC.

1.3 What is the importance of the topic?

Chronic watery diarrhea, which is the leading symptom of the disease, is a huge burden for individuals who suffer from MC; it not only limits the person's physical abilities but can also have a psychological and emotional impact, not to mention the social and occupational limitations. Therefore, addressing the underlying cause as soon as

possible is one of the biggest challenges for both the patients and practitioners.

1.4 What would be the impact of the results?

First, identifying and acknowledging the clinically relevant risk factors for MC would help practitioners in the early diagnosis of MC.

Second, ascertaining if MC extraintestinal manifestations include BMD loss could point out the need for early screening and prevention of potential osteopenia. It is especially crucial to detect bone mass reduction and bone architecture remodeling that result in skeletal fragility and peaks in fracture risk.

2 OBJECTIVES

2.1 Study I – Microscopic colitis is a risk factor for low bone density: a systematic review and meta-analysis

In the first study, we aimed to investigate the relationship between MC and LBD by assessing whether MC is a risk factor for LBD development.

2.2 Study II – Risk Factors for Microscopic Colitis: A Systematic Review and Meta-Analysis

In the second study, we aimed to investigate MC's risk factors to diagnose it as early as possible, comparing MC patients with distinct histologically verified and population-based, random controls, taking into consideration MC's primary histological diagnosis.

3 METHODS

Both studies had a prospectively registered protocol on the International Prospective Register of Systematic Reviews (PROSPERO), with the following identifiers: CRD42022286624, CRD42021283392 for the first and second studies, respectively.

Both studies were conducted with full adherence to the Cochrane Handbook and to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.

3.1 Information sources and search strategy

3.1.1 Study I

We conducted a literature search from inception to October 16, 2021, among five databases: MEDLINE (via PubMed), Embase, Scopus, Web of Science, and Cochrane Library (CENTRAL).

3.1.2 Study II

A primary systematic search was performed on December 18, 2021, that was supplemented on January 6, 2025, in the databases of MEDLINE (via PubMed), Embase, and

Cochrane Central Register of Controlled Trials (CENTRAL); in plus, a backward and forward reference search of the eligible articles on January 28, 2023, and then January 9, 2025.

3.2 Data synthesis and analysis

In both studies, the following steps were applied: a meta-analysis was performed using a minimum of three studies. Forest plots displayed the findings of the meta-analytical calculations. A random-effect model was used with an anticipated substantial between-study heterogeneity to calculate pooled effect sizes. We used the Mantel-Haenszel Method (based on raw data) to calculate the pooled event rate for categorical variables and the ORs with 95% confidence intervals (CIs). To pool the calculated ORs with the extracted ORs (where the raw data were not published), the inverse variance weighting method was applied. We applied the random intercept logistic regression model method to compile the proportions for events with 95% CIs. Results were considered statistically significant if $p < 0.05$. Since the

number of studies was low (fewer than five), the Hartung-Knapp adjustment was not applied.

4 RESULTS

4.1 Search and selection

4.1.1 Study I

From the total of 3046 records, only three full-text articles and one conference abstract were eligible for analysis.

4.1.2 Study II

From the total of 6,493 that were yielded from the second and final round of systematic search, an additional 2,922 records were found via the backward and forward citation chases of the suitable studies; 45 were eligible for meta-analysis.

4.2 Quantitative analysis

4.2.1 Study I

4.2.1.1 MC as a risk factor for LBD

We included all four articles in our quantitative synthesis. Each of them used age- and sex-matched controls to evaluate LBD occurrence in patients with MC. The odds of detection of LBD were increased two times (OR=2.13, CI: 1.42–3.20) in the presence of MC. The I^2 was 37%

(CI: 0–78), suggesting moderate heterogeneity across the studies.

The odds of detecting osteopenia were 2,4 times higher (OR=2.45, CI: 1.11–5.41) in the presence of MC with moderate heterogeneity (I^2=35%, CI: 0–79), while osteoporosis occurrence showed an increased tendency (OR=1.42, CI: 0.65–3.12); however, statistical significance was not confirmed, and the I^2 was 0% (CI: 0–90).

4.2.2 Study II

The female sex among MC patients compared to histological controls was given in 13 studies. A mean age difference of 5.93 years (CI: 2.08–9.77; I^2=94%, CI: 91–96) was between the MC patients and their controls.

The female cases among MC patients compared to histological controls were reported in 15 studies. This analysis resulted in a 1.48-fold increase in odds for developing MC (CI: 1.13–1.95; I^2=80%, CI: 69–88) in female patients.

The number of NSAID user MC patients compared to histological and random controls was investigated in 14 and 13 studies. Both cases resulted in two-and-a-half-fold higher odds (OR=2.57, CI: 1.45–4.53; I^2=69%, CI: 46–82; OR=2.56, CI: 1.13–5.79; I^2=99%, CI: 98–99) for having MC.

Six and eight articles reported on statin use among MC cases in comparison to histological and random controls. Both analyses showed an increase in the odds for having MC if one is taking statin (OR=2.15, CI: 1.14–4.05; I^2=75%, CI: 43–89; OR=1.84, CI: 0.58–5.80; I^2=98%, CI: 98–99), but only the first comparison reached statistical significance.

5 CONCLUSIONS

5.1 Study I

In conclusion, our findings suggest that MC is a risk factor for LBD, doubling the odds for it and its mild form, osteopenia.

5.2 Study II

Our data confirm that female sex, increased age, NSAID, and statin therapy are risk factors for MC when compared to histological controls.

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