Do Sex Hormones Cause, or Are They Only Associated With, Microscopic Colitis?

Microscopic colitis (MC) was first described in 1980 in patients with chronic watery diarrhea. Consisting of 2 subtypes—namely, collagenous colitis and lymphocytic colitis—the reported incidence of this disease increased steadily after its initial description, but has stabilized recently in the United States. Older age and increased steadily after its initial description, but has lymphocytic colitis nonspecific effects. Exogenous estrogen and progesterone have been shown to have high or intermediate levels of association with MC, resulting in an increase in the risk of ulcerative colitis, but not Crohn’s disease. Another study employing the NHS cohort reported an increase in the risk of ulcerative colitis, but not Crohn’s disease with MHT.

Although not intended to assess the relationship between those with MC and those without disease, a previous case control study from Sweden attempting to identify differences between phenotypes of MC did note that OCP use was positively associated with MC, but actually showed an inverse relationship with exposure to MHT. The current article by Burke et al calculated hazard ratios of 2.60–2.64 for developing MC in patients currently using MHT after adjusting for other reproductive factors, smoking, body mass index, and other medications commonly associated with the development of MC. Significant results were also seen for OCP use; however, the results were more modest, with multivariate-adjusted hazard ratios of 1.56–1.57. Additionally, the authors demonstrated that the hazard increases with duration of use and decreases with time since discontinuation. These trends are highly suggestive but not proof of causality.

Several medications have been shown to have high or intermediate levels of association with MC including nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, and proton pump inhibitors. Multivariate odds ratios assessing the risk of MC based on exposure to these medications have previously been derived from both retrospective cohort and case control studies and are between 1.76 and 3.37 (Table 1). The current study
Table 1. Effect Sizes of Potentially Modifiable Risk Factors for Microscopic Colitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women’s Health Study, Multivariate HR</th>
<th>Previous Studies, Multivariate OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of MHT</td>
<td>2.64 (1.78-3.90)</td>
<td>0.42 (0.33-0.83)</td>
</tr>
<tr>
<td>Any use of OCP</td>
<td>1.57 (1.16-2.13)</td>
<td>7.49 (4.66-12.43)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.02 (1.59-4.00)</td>
<td>2.67 (1.38-5.17)</td>
</tr>
<tr>
<td>Current use of SSRIs</td>
<td>1.68 (1.15-2.48)</td>
<td>2.34 (1.33-4.12)</td>
</tr>
<tr>
<td>Current use of NSAIDs</td>
<td>1.96 (1.46-2.62)</td>
<td>2.03 (1.58-2.61)</td>
</tr>
<tr>
<td>Current use of PPIs</td>
<td>1.25 (0.89-1.77)</td>
<td>1.76 (1.03-3.02)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; MHT, menopausal hormone therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; OCP, oral contraceptive; OR, odds ratio; PPIs, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitor.

aRisk estimates reflect data representative of the duration of the study.
bEstimates based on analysis restricted to follow-up after 2000 when ascertainment of these medicines was reliably obtained.
cIncludes both SSRIs and serotonin-norepinephrine reuptake inhibitors.

estimated hazard ratios of similar and significant magnitude for nonsteroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors, but not for proton pump inhibitors. In a prior publication, the NHS reported a hazard ratio for tobacco smoking of 2.52 (1.59–4.00). This result was similar to a previous odds ratio calculated for current tobacco use of 2.67 (1.38–5.17). The similarity of these risk estimates from different studies again suggests but does not prove causality for MC.

In interpreting the results of this study, it is important to remember lessons from past epidemiologic studies. Despite the authors’ efforts to control for various confounding factors that may bias their findings, the cohort design of the current study limits our ability to determine causation. Importantly, data from the NHS were previously used to advocate for the use of MHT with early epidemiologic evidence demonstrating a decreased risk of major coronary disease, which was not borne out in later randomized clinical trials. Although the results of the current study suggest that sex hormones may play an important role in the development of this inflammatory condition, they do not prove causation or even that withdrawal of the medication will lead to an improvement in symptoms. The best clinical use for these data are in the context of the ongoing review of each patient’s active medication list. As always, patients should only be on medications necessary for the control of symptoms and/or prevention or treatment of a disease process. The potential harm of medications, such as MHT or OCPs in MC, must be weighed against their potential benefit. If a medication is thought necessary, the dosage should be limited to the lowest effective dosage for that patient.

The current study by the NHS, strongly suggests a possible harmful association between exogenous reproductive hormones and the development of MC. Whether or not these or any medications are causative for MC remains to be proven. Nevertheless, these findings align with previously published data in terms of the effect size conferred by the medications and suggest plausible mechanisms by which MC might arise. Further work regarding the exact mechanisms of how these hormones affect mucosal immunity and why this disease is predominantly observed in older women is needed.

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Even When You Know Everything, There Is Still More to Learn About Hirschsprung Disease

Hirschsprung disease (HSCR) is a life-threatening birth defect where the enteric nervous system (ENS) is absent from the distal bowel (called “aganglionosis”). Because the ENS controls bowel motility, blood flow, epithelial and immune functions, and even the short segment aganglionosis (S-HSCR) causes profound symptoms including severe constipation, growth failure, and predisposition to inflammation and sepsis (“enterocolitis”). In 1886, Hirschsprung described this disorder and hypothesized that intrauterine developmental defects caused symptoms. In 1949, Swenson et al demonstrated distal bowel aganglionosis in HSCR causes functional obstruction. Later, Yntema et al showed that ENS ganglia derive primarily from the “vagal” neural crest although more recent data suggest additional sources of ENS precursors (Figure 1A). In 1990, Badner et al highlighting a >1% sibling recurrence (compared with an approximately 1:5000 incidence), 4:1 male predominance, increased HSCR risk with Down syndrome, and many HSCR-associated anomalies. They hypothesized that many genes influence HSCR occurrence and that environmental factors could impact risk. In 1993, RET kinase was the first HSCR-linked gene followed shortly by a report that endothelin receptor B (EDNRB) mutations were present in syndromic HSCR with hearing loss and pigmentation defects. McCallion et al later demonstrated multigenic inheritance for HSCR-like disease, combining hypomorphic Ret and EDNRB mutations to cause highly penetrant aganglionosis. In 2010, we demonstrated that vitamin A deficiency causes HSCR-like disease and Ret heterozygosity exacerbates bowel aganglionosis. Some medicines also slow ENS precursor bowel colonization, suggesting that gene–environment interactions impact HSCR occurrence. Dozens of additional HSCR-associated genes are now known, confirming multigenic inheritance. This complex HSCR etiology occurs because many proteins cooperate to facilitate bowel colonization by ENS precursors. The abundance and activity of these proteins is influenced by genetic, epigenetic and nongenetic factors. In this issue of Gastroenterology, Tang et al pursued whole genome sequencing for 443 people with S-HSCR and 493 controls providing deep insight into disease mechanisms. Their remarkable analyses highlight spectacular breakthroughs and remaining challenges in human genetics. They

See “Identification of genes associated with Hirschsprung disease, based on whole-genome sequence analysis, and potential effects on enteric nervous system development,” by Tang CS, Li P, Lai FP-L, et al, on page 1908.