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Gender and Inflammatory Bowel Disease

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Abstract

Men and women differ in susceptibility and exposure to environmental risk factors for inflammatory bowel disease (IBD) but various endogenous sex-determined differences in immune reactions might play a role in IBD pathogenesis as well. There is a sex-specific pattern of extra-intestinal manifestation and men and women suffer from different long-term complications of the disease. This review focuses on the gender and sex dimorphic disease profile and outlines the potential mechanisms of sex-specific pathogenesis in the view of current understanding of sex-specific immunity.

Keywords: Gender; Sex; Inflammatory bowel disease; Sex hormones; X-chromosome

Epidemiology

In contrast to some female-specific autoimmune diseases, female predominance in inflammatory bowel disease (IBD) is not a general feature and when present, it is subject to great geographical variation. Asian populations are rather consistently characterized by male predominance in both, paediatric and adult populations [1-4]. In European and North-American populations female:male ratio varies from equal distribution to 2.5:1 in different study populations [5-13] (Table 1). Explanation for these geographical differences is currently lacking but gender-specific cultural habits resulting in differential exposure of men and women to recognized environmental risk factors for IBD might, at least, partially account for these findings.

Rapid increase of IBD incidence observed in Asian countries [14], a region with typically observed male predominance in IBD, is more likely to be caused by changes in environmental factors than by genetic factors. Several environmental factors that were found to be associated with IBD in observational studies indeed seem to affect males and females differentially. In one pediatric IBD cohort, the association of antibiotics and Crohn`s disease development was stronger in boys than girls [15]. Furthermore, in another pediatric IBD population that showed association of antibiotics use and IBD development, antibiotics were found to be significantly more frequently prescribed to boys than girls [16]. Another factor possibly related to increased risk of Crohn`s disease, appendectomy, has been shown to confer higher risk in females than males [17] and the same was observed for smoking [18,19].

In addition to differential susceptibility to some environmental factors, across different cultures men and women are also likely to differ in dietary habits, socio-economic status as well as exposure to infectious agents, all factors implicated in IBD pathogenesis [14]. Furthermore, one typically female factor increasing the risk for IBD, the use of oral contraceptives [20] has presumably high geographical variation depending on cultural habits.

Thus, men and women are not equally susceptible to at least some environmental factors associated with IBD. Furthermore, both genders possibly differ in the exposure to these factors, depending on the cultural background which might explain the geographical differences in the female:male ratio observed across different IBD populations.

Phenotype

Concerning IBD phenotype, the only difference between the two genders that was consistently reported thus far is a dimorphic profile of extra-intestinal manifestations. There is higher prevalence of eye and skin involvement in females and higher prevalence of primary sclerosing cholangitis and ankylosing spondylitis in males [5,21-23] (Table 1). Female gender has also been associated with higher risk of perianal findings other than fistula [24]. The underlying mechanism of these differences is unclear but it is tempting to speculate that general differences in male and female immune reactions [25] may be implicated in sex-specific disease pathogenesis.

Pathogenetic Considerations

General differences in male and female immune reactions have long been recognized in observational studies but the underlying mechanism of these differences is still unclear. On one hand, the sex dimorphic features of immune reactions are reflected by increased susceptibility and complicated course of viral, bacterial, parasitic and fungal infections in males [26,27]. On the other hand, autoimmunity seems to be a female feature, although the magnitude of female predominance varies across the spectrum of autoimmune diseases and show important geographical differences [28].Thus, epidemiological data suggest that male and female immune reactions might differ substantially. However, given important geographical differences in female:male ratio in autoimmune disorders, it is more likely that female sex acts as a modifier rather than an independent trigger that would set out the aberrant autoimmune reaction.

From different factors possibly underlying sex-specific immunity, sex hormones have long been recognized to influence immune reactions. Upon immunization, the antibody production and T cell

activation is more pronounced in female mice [29,30] and the T_H1 cytokines production after immunization is higher in female mice [31]. In human, higher absolute numbers of $CD4^+$ lymphocytes are observed in women compared to men [31]. Cytokine secretion *in vitro* is enhanced by estrogens, whilst it decreases upon stimulation with androgens [32,33]. In addition, sex hormones, especially estrogens seem to influence the cytokine production by T_H lymphocytes in a dose dependent manner *in vitro* [33,34] which may explain the immunomodulatory effect pregnancy has on several autoimmune diseases including IBD.

The specific immunomodulatory properties of sex hormones have been implicated in the pathogenesis of some autoimmune conditions such as multiple sclerosis [35] whilst in others, like primary biliary cirrhosis and autoimmune thyroid disease, X-chromosome abnormalities are more likely to play a role [36-38]. In IBD, studies on the role of sex hormones in the mediation of an aberrant immune response are scarce and data available are limited to animal models. It has been shown that estrogen decreases while progesterone increases macrophage migration inhibitor factor production in a female rat with trinitrobenzene sulfonic acid-induced colitis [39]. In HLA-B27 transgenic rat IBD model, estrogen treatment improved the stool frequency, histological score and reduced the levels of myeloperoxidase activity [40]. In another study, using two different murine models of colitis, treatment with estrogens had beneficial effect on dinitrobenzene sulfonic acid-induced colitis in contrast to dextran sodium sulfate-induced colitis where estradiol increased the macroscopic and histological scores compared to placebo [41]. Interestingly, a prospective multi-national case-control study on the course of IBD during pregnancy showed a disease-specific effect with similar course of Crohn`s disease in pregnant and non-pregnant patients but increased rate of flares in pregnant ulcerative colitis patients [42]. Thus, estrogens may have differential immunomodulatory effect on intestinal mucosal immune response, depending on the type or site of inflammation.

In addition to immunomodulatory effect, sex hormones may differentially influence IBD pathogenesis in males and females through their influence on intestinal permeability. In animal models, estrogens seem to decrease intestinal permeability [43] and this effect follows the cyclic changes of estrogen-progesterone shift. Interestingly, women with IBD and IBS experience fluctuations in their gastrointestinal symptoms across the menstrual cycle [44] which may be related to these cyclic changes of the intestinal permeability. Thus, taking these observational human data and studies with different animal IBD models together, sex hormones, especially estrogens, seem to have important modulatory effects on intestinal mucosal immunity and permeability. These effects that are probably interrelated might be dichotomic in Crohn`s disease and ulcerative colitis.

With regards to androgens and their putative role in the disease pathogenesis, the data available are very limited. Overall in autoimmune disease, including IBD, decreased levels of testosterone have been described in both, male and female patients [45,46]. It is, however, unclear whether these differences are secondary to underlying disease or whether the androgens-deficiency plays a specific pathogenetic role in IBD.

Another thus far unexplored signal of sexually dimorphic pathogenesis of IBD comes from several genetic studies reporting differential risk of some susceptibility gene variants for men and women, respectively. In CD, the R30Q DLG5 variant confers a male-specific risk in various independent populations [47-50]. On the other

hand, a variant of IL-23 receptor (L310P) seems to protect women but not men from the development of ulcerative colitis [51]. In addition, two functional single nucleotide polymorphisms (SNP) in the promotor region of IL-10 were associated with ulcerative colitis in females exclusively [52]. In addition to these sex-specific SNP, a phenomenon of maternal imprinting in familial IBD has been reported [53]. In a recent analysis of the 286 families with IBD we also observed maternal imprinting with a specific female-to-female transmission [54]. Thus, gender seems to have a modulatory effect on the translation of some susceptibility genes but the mechanistic explanation of this phenomenon is currently lacking.

Last mechanism that has been suggested to be involved in female-specific pathogenesis of autoimmune disorders implicates X-chromosome abnormalities. In the past years, increasing understanding of the role of X-chromosome in the sexual dimorphism of immune responses has turned the focus towards the mechanisms that would directly (i.e. not through the effect of sex hormones) involve the X-chromosome anomalies in autoimmunity. Thus far, three mechanisms of X-linked pathogenesis of female autoimmune disorders have been proposed: loss of mosaicism, reactivation of silenced X-chromosome and loss of X-chromosome [55]. From these three mechanisms, only loss of X-chromosome has been thus far confirmed to be linked to a specific autoimmune disorder. In patients with primary biliary cirrhosis, autoimmune thyroid disease, Reynolds sydrome and systemic sclerosis, significantly higher rates of X-monosomy were found in peripheral T- and B-lymphocytes [37,56]. The mechanism by which the loss of X-chromosome would lead to autoimmunity is not clear but it has been proposed that this loss of specific X-linked genes in T- and B-cells might results in an enhanced antibody production [37]. X-chromosome abnormalities have not been studied in IBD thus far, but some observations of increased incidence of IBD in patients with Turner syndrome [57] might indicate that this mechanism could be implicated in IBD pathogenesis as well. Interestingly, more than half of the patients with concomittant IBD and Turner syndrom, a female disorder characterized by the abscence of all or part of the second X-chromosome, have the same karyotype [58]. Thus, hypothetically, loss of specific immunoregulatory genes located on the X-chromosome might be implicated in the pathogenesis of IBD associated with Turner syndrome. On the other hand, it is tempting to speculate that the same mechanisms could play a role in the pathogenesis of female IBD in acquired X-chromosome haploinsufficiency.

Taken together, in the IBD pathogenesis, the basic immunological differences between males and females may underlie sex-specific disease pathogenesis. The data currently available are, however, very limited and the subject has not been studied in depth. Sex hormones influence the systemic and mucosal immunity as well as intestinal permeability which may be reflected in specificities of the IBD course during pregnancy and variable symptoms during menstrual cycle. Some genetic variants carry differential risk for men and women, respectively, but the mechanistic explanation for these differences is lacking. There are indications that X-chromosome abnormalities, more specifically loss of X-chromosome, might hypothetically be implicated in IBD pathogenesis in (some) female patients but this has not been studied thus far.

Disease Course and Long Term Outcomes

The impact of gender on disease course remains a controversial issue due to the limited data providing conflicting observations on this

subject thus far. The results of studies analysing the gender-specific risk for complicated disease course vary from negative findings with sex not being a prognostic factor for complicated disease course [59] to opposing results of one longitudinal cohort study showing male gender as an independent risk factor for complicated disease course (OR 2.6017, 95% CI: 1.17 to 5.75) [60], contrasting to higher remission rate among male IBD patients found in another study with cross-sectional design [61]. The findings of the latter study were related to the fact that in the same cohort, female IBD patients were treated significantly less frequently with thiopurines, regardless of their childbearing potential. This unequal clinical approach towards both genders might be under-recognized and is likely to be present with different magnitude in all studies focussing on the sexual dimorphism of the disease course and outcomes. Separating the effects of unintentional gender-biased approach in clinical practice from the real biological differences in the disease course is methodologically difficult since many of the potential confounding factors remains unknown.

The same methodological concern applies for the interpretations of the sex-specific risk for surgery in IBD. In one population-based cohort of CD patients, male gender was shown to be a risk factor for major abdominal surgery (HR 1.6); [62]. Yet, another retrospective study found significantly higher rate of ileocoecal resection in female CD patients compared with males (44% vs. 32%, p=0.004]. In addition, this same retrospective study showed shorter time to second surgical resection in females [22], in contrast to another retrospective study that found significantly shorter time to post-operative recurrence in male CD patients [63]. In one large, population-based cohort of CD patients, female gender was found to slightly increase the risk for postoperative recurrence in females (RR 1.2; 95% CI 1.01-1.4) [64]. The findings are more consistent in ulcerative colitis (UC) with two retrospective studies, both in a population-based cohort documenting higher risk of colectomy in male patients (respective HR, 2.1; 95% CI, 1.3-3.5 and 2.63, 95% CI: 1.58-4.36) [65,66]. With regards to other types of surgery, female patients were found to be at higher risk for long term complications after ileo-anal pouch anastomosis such as bowel obstruction, pouch related fistula and pouch failure [67].

1	**Epidemiology** Male predominance in Asian countries Equal distribution to female predominance in Europe and North America
2	**Enviromental factors** Reported • *Antibiotics* more frequently used by male patients* stronger association with Crohn`s disease in males than in females* • *Smoking* associated with higher risk for Crohn`s disease in females • *Appendectomy* associated with higher risk for Crohn`s disease in females Hypothetical • Dietary habits • Socio-economic status • Exposure to infectious agents
3	**Disease phenotype** • Higher prevalence of eye and skin involvement in females • Higher prevalence of primary sclerosing cholangitis and ankylosing spondylitis in males
4	**Disease course** • Conflicting data
5	**Long term complications** • Higher risk and mortality of colorectal cancer in males • Higher mortality from pulmonary complications in females
*pediatric population	

Table 1: Summary of sex-dimorphic features of IBD.

These conflicting results with regard to gender as one of determinants of the disease course may result from classical methodological differences between the studies with limited size studies failing to detect a modest risk. On the other hand, as discussed earlier, due to the observational nature of all these studies, they are all prone to produce results biased by gender-specific factors that may have influenced the clinical care in particular studies. This bias may be of different nature and magnitude depending on cultural differences, although this has not been evaluated. With regards to risk of surgery, documented gender-related differences in drug use with females being under-treated [61] but also less adherent to treatment [68,69] might be partially at origin of the increased risk of surgery in females documented in some studies. Furthermore, the indication for surgery does not necessarily reflect a complicated disease course but might

represent for some patients an alternative for drugs tried to be avoided by female patients with reproductive plans. In addition, the discrepant results of gender-related difference in time to second surgery might as well reflect regional differences in the screening for postoperative recurrence. Female patients have more side-effects from bowel preparation [70,71] which may influence the quality of preparation with impact on the completeness and accuracy of endoscopic findings and may act as a demotivating factor for the patient to agree with a postoperative recurrence surveillance colonoscopy. One study documented lower rate of colonoscopies in female IBD patients performed during the disease follow-up compared to their male counterparts [72] which may also account for the differences between the two genders in the diagnosis of postoperative recurrence. Thus, several potential biases may underlie the conflicting results regarding the sex-specific disease course and currently available data are not sufficient to create a comprehensive view on this subject.

Sex-stratified analysis of long term complications of IBD show consistently higher risk of colorectal cancer (CRC) in male IBD patients compared to female IBD patients [73]. Several biological as well as behavioral factors have been suggested to account for this sex-specific increase in risk in IBD-related CRC [74,75] but none of them has been confirmed thus far. Compared to general population, the risk of CRC is increased for both, males and females with IBD, but the risk is higher in male IBD patients. Male IBD patients have also increased mortality from CRC, as shown in a recently published meta-analysis [76]. Overall mortality analysis in this meta-analysis showed a trend to higher mortality in females with significantly higher mortality from pulmonary complications (Table 1). Thus, there is sexual dimorphism in long term outcomes with differential mortality rates and causes in both genders. The reasons for this dimorphic mortality remain speculative covering a broad range of factors from biological to socio-behavioral ones.

In conclusion, several clinical features of sexual dimorphism in IBD have been documented thus far but the underlying mechanism by which gender contributes to the specific disease presentation, prognosis, and therapy success remains to be unravelled. Men and women differ in susceptibility and exposure to various environmental risk factors for IBD but various endogenous sex-determined differences in immune reactions might play a role in IBD pathogenesis as well. In order to articulate research questions to be answered by basic research, the extent of the problem must first be determined through well-designed epidemiological and observational studies.

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