Ital J Gender-Specific Med 2017; 3(1): 23-28

Inflammatory bowel disease: gender difference

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Summary. Inflammatory bowel diseases (IBDs) are chronic, relapsing inflammatory diseases characterized by exacerbations and remissions of the gastrointestinal tract, clinically manifested as Crohn's disease and ulcerative colitis. The etiology of IBDs is considered to be multifactorial, comprising environmental, immune, microbial and genetic factors. Clinical signs may include abdominal pain, frequent bloody diarrheas, mucorrhea, vomiting, fever, fatigue or weight loss. Males and females have a different predisposition for the development of intestinal disorders, like the inflammatory bowel disease. This review paper discusses the difference of gender in inflammatory bowel disease. Gender medicine has allowed, in recent years, to solve many diagnostic and therapeutic problems of female and male health.

Key words: gender difference, inflammatory bowel disease, immune system.

Le differenze di genere nelle malattie infiammatorie croniche intestinali

Riassunto. Le malattie infiammatorie croniche intestinali (MICI), rappresentate dalla colite ulcerosa e dalla malattia di Crohn, sono caratterizzate da periodi di remissione alternati a recidive. L'eziologia è multifattoriale e include fattori ambientali, immunitari, genetici e alterazioni della flora batterica. La sintomatologia è caratterizzata da dolori addominali, diarrea muco sanguinolenta, vomito, febbre, astenia e perdita di peso. I due sessi hanno una differente predisposizione allo sviluppo di alcuni disordini intestinali come le malattie infiammatorie croniche. Questa review affronta le problematiche relative alle differenze di genere nelle MICI. La medicina di genere, negli ultimi anni, ha permesso di risolvere molti problemi diagnostici e terapeutici della salute della donna e dell'uomo.

Parole chiave: differenze di genere, malattie infiammatorie croniche intestinali, sistema immunitario.

Introduction

Inflammatory bowel disease (IBD) is a multifactorial disorder encompassing two major diseases, ulcerative colitis (UC) and Crohn's disease (CD)[1]. An imbalance of the interaction among immune system, enteric antigens and intestinal mucosa results in a chronic, immune-mediated inflammation[2].

IBDs are associated with several gastrointestinal (GI) symptoms that can differ widely in severity of presentation and can include the following: abdominal pain, diarrhea, GI bleeding, intestinal fistula, intra-abdominal abscess and anal disease[3]. IBDs can also present a large number of extra intestinal manifestations (EIMs) with involvement of the musculoskeletal, cutaneous, hepatobiliary and ocular systems[4]. Diagnosis of IBDs is based on the correlation of clinical, radiological, endoscopic and histopathological findings[5].

Estimated incidence is 10-15 new cases/100,000 inhabitants/year (9-12%) and prevalence is about 0.2 to 0.4%. Crohn's disease and Ulcerative colitis have a peak incidence between the second and third decade of life and more rarely around the sixth decade[6]. IBDs generally occur with similar frequency in men and women and can be a debilitating illness with significant impact on the quality of life[7]. Susceptibility to develop inflammatory bowel disease (IBD), such as Crohn's disease, could depend on factors related to gender differences. In Asian countries, men have a higher incidence of the disease (considering data from studies conducted in Asia and Middle East) whereas in European countries there is a moderate female predominance[8,9,10].

Although IBDs have been traditionally considered characteristic of Western industrialized countries, their incidence and prevalence have increased rapidly across Asia in the last two decades[11]. The change in the epidemiology seems to be related to westernization of lifestyle and environmental factors. However, different genetic factors may be involved in the pathogenesis with the NOD2/CARD15 mutations, characteristics of White and Jewish population, being less common. Instead, variations in the tumor necrosis factor superfamily member 15 (TNFSF15) seems to be associated with Asian populations[12]. TNFSF15 is a member of the TNF cytokines family and is expressed in endothelial cells but its role is not completely understood. Some studies demonstrated that TNFSF15 polymorphism is associated with CD in Japanese and Koreans[13,14].

Male predominance in the incidence of Crohn's disease in Asian countries is not completely understood; it

could be partly explained by the differential rates of cigarette smoking in this group of patients. This data is highlighted in a population-based study conducted by members of the Korean Association for the Study of Intestinal Diseases (KASID) in a district of Seoul, Korea, from 1986 to 2005[15]. During this period, 138 new cases of CD were diagnosed, 102 men and 36 women. The male predominance was observed for CD but not for UC (341 patients, 170 men and 171 women). These findings have been observed also in Japan and Hong Kong[16,17]. The difference in the smoking rates might justify this data but it is not sufficient to completely explain it; since in the KASID study the male-to-female ratio for UC was 1:1, other factors could be involved. Sex-related differences or predisposing factors should be investigated for a better comprehension of IBD etiology[15].

Despite other diseases, such as cardiovascular diseases, autoimmune connective tissue disorders, diabetes and cancer, data about gender-related differences in the management of IBD are lacking[18].

Immune system

The immune system seems to play an important role in the development and progression of IBDs[19]. Numerous epidemiological, clinical and experimental studies have shown significant differences between women and men in the immune response.

Females have a higher risk of developing autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus than males[20]. Differences in peripheral immune responses can explain the increased risk of autoimmune diseases[21]. Females generally have a more vigorous adaptive immune response, whereas males have increased innate immune response[22]. It was hypothesized that sex differences in IBD may be due to a different intestinal immune response[23]. The intestinal immune system, defined as gut-associated lymphoid tissue (GALT), is in close contact with intestinal microbes and dietary antigens, and work in a different manner with respect to the peripheral immune system[24]. The main challenge of the GALT is to distinguish harmless from harmful antigens and to respond appropriately. The GALT consists of immune cells scattered throughout the lamina propria and organized lymph structures like the Peyer's patches (PP) and mesenteric lymph nodes (MLN)[25]. Dendritic cells (DCs) in the PP that express integrin sub-unit CD103 are able to differentiate T helper (Th) cells into FoxP3$^+$ T regulatory cells (Tregs)[26,27]. Tregs can produce Il-10 and are important in controlling T helper responses and in preventing inflammation. Both CD103$^+$ DCs and Tregs play an important role in intestinal homeostasis and tolerance and in the prevention of IBD[28]. Other immune cells that play a role in intestinal homeostasis are natural killer (NK) cells. NKp46$^+$ NK cells co-expressing transcription factor RORγt in the intestine can produce interleukin 22 (IL-22)[29], which is involved in regulating mucosal barrier homeostasis and antimicrobial host defense[30]. Whether these intestinal immune cell subsets are sex dependent is still to be determined.

Gender issues

Different aspects have been addressed regarding the impact of gender on characteristics, phenotypes, management and outcome of IBD patients, since sexual differences could influence disease presentation, prognosis and treatment. As far as the natural history is concerned, male gender seems to be associated with a more severe disease, but data are still controversial[8]. The same consideration should be applied for surgery. While observational studies report an increased risk for surgery in men, in a retrospective study a higher rate of ileo-colocecal resection in female patient with CD[31] was noted. The risk of colon-rectal cancer (CRC), as long-term complication, is higher in male IBD patients due to biological and behavioral factors; however the exact mechanisms are not fully understood. Indeed increased mortality from CRC has been observed in men[8].

In addition, the association between IBD and extra intestinal manifestations (EIMs) is well established, in particular musculoskeletal, mucocutaneous and ocular. The prevalence ranges from 16% to 40% of patients with IBD but this value depends on the definition considered. The pathogenesis is largely unknown, but environmental factors such as smoking, autoimmune disorders and genetic mutations are thought to be involved. Patients can experiment EIMs during the course of CD or UC but the development of these disorders can also precede IBD diagnosis by several years. Data on epidemiology, risk factors and gender differences are limited. A recent Greek multicenter study on a large cohort of IBD patients highlighted a positive association between active disease and EIMs (61.1% of patients) and a female prevalence; indeed the latter resulted statistically significant in multivariate analysis[32]. Other studies described this increased prevalence in females[33] due to altered hormone and autoimmune patterns[34], however the results are controversial[35]. In general, the female gender is associated with eye and skin disorders, meanwhile in men primary sclerosing cholangitis and ankylosing spondylitis are more frequent[8].

Some aspects are related to the experience of a bad perception of body image and sexuality.

Women with IBD, who use tobacco, are immunosuppressed and those which were diagnosed with IBD at an early age may be at an increased risk for cervical dysplasia and should be screened[36,37].

Men and women with IBD generally have preserved fertility but have fewer children due to voluntary childlessness. However, certain subgroups of men and women may be at a higher risk for infertility. Men on therapy with certain immunosuppressive medications and women after ileal pouch-anal anastomosis (IPAA) can have infertility[38]. Despite reports of sexual dysfunction in men and women after IPAA, both sexes report improved sexual satisfaction postoperatively. Pregnancy in women with IBD should be planned, and contraceptive choice should be individualized. Women with IBD reach menopause at similar rates as those of the general population and do not experience change in post menopause disease activities[39,40].

Low bone mineral density (BMD) is more common in both men and women with IBD compared with the general population, and most patients with IBD should be screened with dual-energy X-ray absorptiometry (DEXA) scans[41].

As more is learned regarding the physical and psychosocial effects of IBD and its treatment, it has become clear that men and women face unique challenges. IBD may affect patients' physical appearance due to fistulae, surgical scarring, and/or ostomy placement. In addition, patients with IBD often suffer from abdominal pain, diarrhea, and fecal incontinence, which have the potential to affect both body image and sexuality. Some patients, especially women and postoperative patients, may be at a greater risk for impaired body image. In a survey-based study of more than 200 patients with IBD, almost 70% of patients reported impaired body image, and this appeared to affect women more than men (75% vs 51% prevalence of impaired body image in women and men, respectively) and operated patients more than non operated patients (81% vs 51%, respectively). Female gender and operated condition are also associated with impaired sexuality. In the same study, women and operated patients reported significantly decreased sexual activity due to IBD than their male and non operated counterparts (66% vs 41% prevalence of decreased sexual activity in women and men, respectively, and 69% vs 50% prevalence of decreased sexual activity in operated vs non operated patients, respectively). A second interview-based study further investigated the origins of impaired sexual function in women with CD. When women were asked why they avoided intercourse, the most common reasons were abdominal pain, diarrhea and fear of fecal incontinence. A significant proportion of women also reported dyspareunia.

Psychosocial factors are also a significant contributor to impaired sexuality; research has shown that a depressed mood is the strongest and most consistent risk factor for low sexual function in IBD patients[42].

Effect of smoking on genders in Crohn's disease

In 1982 the relation between smoking and IBD was highlighted for the first time thanks to a British case control study performed by Harris: among the patients affected by UC it was noticed that there was only a low percentage of smokers. Later several studies well established that cigarette smoking is a crucial environmental factor in the course of IBD, however it has two opposite effects on UC and Crohn's disease[43]. The reasons underlying this divergent impact remain largely obscure but probably depend on several factors including the direct effects of tobacco components on the immune system (innate and acquired), microvasculature and microbiota[44].

In ulcerative colitis, tobacco seems to have a beneficial and protective effect: the risk of development of the disease is lower in smoking patients compared with lifetime non smokers[45], the corticosteroid utilization is reduced as well as the risk of colectomy (smoking is associated with higher disease-related costs and lower health-related quality of life in IBD) and in general the course is more benign. Moreover, stopping smoking leads to an increased risk of developing UC and it is associated with a worse disease activity, both in men and women without any sex differences[43].

On the contrary, smoking has a deleterious effect on the course of the CD. The smoke exposure appears to be one of the environmental factors that contribute to gender differences in CD. It also appears that smoking could determine the location of the disease, with a higher prevalence of ileal disease and a lower prevalence of colonic involvement[43]. The females who smoke would develop an early onset disease and a more severe form compared with men. The precise mechanism responsible for the gender differences in the CD is not yet known. It is believed that cigarette smoking strongly influences the humoral and cell-mediation, even leading to the release and inhibition of various pro- and anti-inflammatory mediators[46]. It seems that the molecular mechanism is at least partially responsible for the immunomodulatory properties of smoking, involving the activation of the kinase inhibitor IκB (IKK), phosphorylation of IκB (inhibitor of nuclear factor NF-κB), NF-κB nuclear translocation and histone acetylation[47]. NF-κB is a key transcription factor regulating the expression of various proinflammatory cytokines and numerous studies have linked its activation to elevated cytokine expression in smokers[48]. Other transcriptional factors related to smoking have been identified so far, including GATA, PAX5, Smad 3/4, AP-1, ISRE, ICSBP[46, 47].

There is evidence to support the idea that women are more vulnerable to the effects of smoking with an easier rupture of immune balance, which results in a significant increase in the production of IFN-γ, not accompanied by the release of Th2 cytokines[47,49]. Some possible explanations for this phenomenon are the negative

effects of estrogens on proinflammatory cytokine gene regulation and interactions of immune cells[50] or the differences between genders in smoking habits, since females use more filter cigarettes and lighter cigarettes, resulting in a relatively greater exposure to nicotine[51].

Therapy

There is little information in the literature on the use of sulfasalazine in the treatment of IBD that prove its negative effect on fertility in men, but not women[52]. The effects of sulfasalazine on sperm count, motility, and morphology are reversible after drug withdrawal.

In rat models, corticosteroids have been shown to decrease fertility in men, but not in women, while 5-aminosalicylic acid agents, 6-mercaptopurine, azathioprine, and biologic agents have not been shown to affect fertility in men or women, although it should be noted that researches on fertility and biologic agents have been limited to animal studies[53].

Currently there are not many studies on the differences in the treatment of IBD in the two sexes, often because they are women of child bearing age and/or pregnancy; indeed the results are contradictory.

A cohort study carried out in a metropolitan area of Germany showed that women had an infrequent use of immunosuppressive agents compared to men. This finding is probably related to the lower rate of remission in women than men, especially in patients with UC[54]. In men there is an increased risk of developing a more serious illness and, as they have lower adherence to treatment with corticosteroids and/or aminosalicylates, the use of these drugs takes place earlier. In women of childbearing age there is a low tendency to use these drugs. According to the current "step-up" approach in the medical management of IBD, these results could explain the more common use of immunosuppressive drugs in males. So, as immunosuppressive drugs are more effective than aminosalicylates, remission rates appear higher among male patients[55].

Furthermore, it appears to be unreasonable to believe that gender-related adherence to various drugs utilized in IBD may be different. In favor of the latter assumption Mantzaris et al. reported that male gender was associated with non-adherence of treatment with AZA in patients with CD in long-term remission[56]. However these patients showed a short term remission of the disease and a quality of life that did not differ significantly from patients who were adherent to treatment. So, if there was female predominance in medical adherence to treatments, this appears not to be influencing the better outcome of women compared to men. Other studies need to clarify this relationship among adherence, gender and outcome of the disease.

As already pointed out, the lower use of immunosuppressive therapy in females could also be explained by the uncertainties in the prescription for women of childbearing age. However, an age-related analysis (women age 18–42 vs >42 years) did not reveal any difference in the treatment of women in either CD or UC between both age groups. A therapy with AZA/6-MP, the most commonly used immunosuppressive drug in IBD, is generally considered to be of low risk during pregnancy[57, 58].

AZA and 6MP may have effects on the fetus when used by men within three months from conception, while the metrotrexate (MTX) is an absolute contraindication for men and for women before conception and during pregnancy. Zelinkova et al. in a study of a cohort of 61 IBD patients (51 females, 40 with CD, 21 with UC) showed that about one-third changed the medication due to active reproductive plans[59]. In a review article that analyzes reproduction in IBD the authors underline that the risk of complications during pregnancy seems to be primarily related to disease activity and not to specific medications, but the argument remains controversial because the literature comes from retrospective studies[60].

Regarding biological agents, Lesuis et al performed an observational study to analyze gender differences in biological treatments in three different immune-mediated diseases: IBD, psoriasis and rheumatoid arthritis. 131 IBD patients were included and received anti-TNF-α (infliximab) as their first biologic; disease characteristics and activity were examined at the beginning of the treatment at a single time point, according to clinical and laboratory parameters. Men and women presented similar disease severity at the treatment start but female patients experienced more symptoms. Women showed higher scores than men on subjective, but not objective, disease activity measures, therefore it is assumed that the disease has a greater effect in women[61].

In conclusion, few data regarding the influences of gender on IBD are available in the literature. To get more information, it will be necessary to carry out further trials that include an equal number of men and women. Data from genetic and metabolic studies need to clarify some aspects, however the efficacy of drugs should also be explored in some physiological conditions, such as fertility period and pregnancy.

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Key messages

- Several studies showed that females have a higher risk of developing autoimmune diseases. Gender can influence immune response in IBD.
- Smoking has a deleterious effect on the course of Crohn disease. The females who smoke would develop an early onset of the disease and a more severe form compared to men. Exposure to smoke appears to be one of the environmental factors that contribute to gender differences in Crohn disease.
- Men and women with IBD generally have preserved fertility but have fewer children due to voluntary childlessness.
- Men on therapy with certain immunosuppressive medications and women after ileal pouch-anal anastomosis can have infertility often related to impaired sexual function.
- Complications of IBD during pregnancy seem to be primarily related to disease activity and not to a specific medication.

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Conflict of interest statement: the Authors declare no potential conflits of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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