Sex-Specific Issues in Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) affects approximately 1 in 500 people living in the United States and generally occurs with equal frequency in men and women. However, despite equal sex distribution of the disease, men and women face unique challenges that can significantly impact quality of life. As more is discovered regarding the pathogenesis, clinical manifestations, and treatment of IBD, physiologic and psychological differences between men and women with IBD have become increasingly apparent. It is important to understand these differences, as they have the potential to affect patient care and outcomes. This article will review sex-specific issues in IBD, such as impaired body image and sexuality, increased risk of cervical cancer, altered menstrual cycles, reduced fertility, and low bone mineral density.

Keywords
Ulcerative colitis, Crohn's disease, fertility, contraception, sexuality

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of unknown etiology that affects approximately 1 in 500 people living in the United States. IBD generally occurs with equal frequency in men and women and can be a debilitating illness with significant impact on quality of life.[1] In addition to experiencing difficulty with body image and sexuality, women with IBD—particularly those who use tobacco, are immunosuppressed, or were diagnosed with IBD at an early age—may be at an increased risk for cervical dysplasia and should be screened. 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, including men on certain immunosuppressive medications, women over 30 years, and women after ileal pouch-anal anastomosis (IPAA). 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 disease activity postmenopause. 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. 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.

Body Image and Sexuality

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 nonoperated patients (81% vs 51%, respectively).[2]

Female sex and operated state 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 nonoperated 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 nonoperated patients, respectively).[2] 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.[3] 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.[4]

Although impaired body image and sexual function are common in patients with IBD, these issues are rarely brought up by physicians during appointments. In a survey administered to women with IBD attending an educational seminar, less than 20% reported that their gastroenterologist addressed issues of body image or sexual function, and even fewer reported that these issues were brought up by a primary care provider or obstetrician/gynecologist. Of the patients who did report having discussions about body image or sexuality, most of these conversations were initiated by the patient.[5] The above data underscore the importance of physicians taking the initiative to ask patients about body image, sexuality, and mood. In addition to managing physical symptoms that may interfere with body image and sexuality, physicians should have a low threshold for referring patients with psychosocial challenges for further support.

Cervical Cancer

The immunocompromised states of systemic lupus erythematosus (SLE), HIV, and posttransplantation are associated with an increased risk of cervical abnormalities and cancer,[6-8] and it has been speculated that women with IBD may also be at an increased risk. There are conflicting data regarding the risk of abnormal Papanicolaou (Pap) smears and cervical cancer in women with IBD. Initial retrospective case-control studies suggested an association of IBD with abnormal cervical histology. In one study, 18% of IBD patients were found to have abnormal Pap smears compared with 5% of controls, although the type of IBD and exposure to immunosuppressive medications were not associated with abnormal Pap smears.[9] In another study, 42% of women with IBD were found to have abnormal Pap smears vs 7% of controls. Women with IBD were also more likely to develop high-grade lesions than controls. In this study, immunosuppression was associated with the risk of abnormal Pap smear, and all abnormal Pap smears were positive for human papilloma virus (HPV) 16 or 18.[10]

Subsequent research has not found an association between IBD and abnormal Pap smears and has criticized the above studies, noting that they were underpowered and that they disagreed regarding the potential role of immunosuppression in the development of abnormal Pap smears. In a Scottish retrospective case-controlled study of more than 400 women with IBD, no difference was found in the rates of abnormal Pap smears compared with controls, and no association was found between cervical abnormalities and immunosuppression. However, a statistically significant increase in cervical abnormalities was found in women with IBD who smoked compared with nonsmokers, and there was also a nonsignificant trend toward higher rates of cervical abnormalities in women who were diagnosed with IBD at a younger age.[11] In a population-nested, case-control study in Canada of nearly 20,000 women with cervical abnormalities matched with controls who had normal Pap smears, no association was found between UC and cervical abnormalities, although there was an increased risk in the subgroup of patients with CD who had received at least 10 prescriptions for oral contraceptive pills. Regardless of IBD status, combined corticosteroid and immunosuppressant exposure was associated with an increased risk of cervical abnormalities.[12] A recent population-based nationwide cohort study of almost 30,000 women with IBD supported an increased risk for cervical dysplasia and cancer in women

with IBD; when compared with controls, patients with UC were found to have an increased risk for cervical dysplasia, and patients with CD were found to have an increased risk for cervical dysplasia and cervical cancer. This increased risk was not explained by differences in screening activity.[13]

Given the above conflicting data, it is a challenge to develop generalized recommendations to guide cervical cancer screening in women with IBD. The American Congress of Obstetricians and Gynecologists' practice bulletin for screening for cervical cancer acknowledges the lack of guidelines for screening non–HIV-positive, immunocompromised women and reports that it is reasonable to obtain an annual cytology screening starting at 21 years in this population.[14] In the setting of conflicting data and major studies not supporting an association between IBD and cervical cancer, it is also reasonable to pursue screening with the same approach used in the general population (ie, cytology screening every 3 years starting at 21 years), with special considerations made for patients using tobacco, receiving an early diagnosis of IBD, using oral contraceptive pills, or receiving significant immunosuppression. Given the clear association between smoking and cervical cancer, all patients—including IBD patients—should be counseled regarding tobacco cessation. Because the sexually transmitted HPV is the most important risk factor for cervical neoplasia, women should also be counseled regarding safe sexual practices, and appropriate populations should receive the HPV vaccine.[15]

The Menstrual Cycle

Patients with IBD may experience delayed menarche and menstrual cycle irregularity.[16] Malnutrition and inflammation may play a role, but the complex interaction between IBD and hormones is not well understood.

Not only can IBD affect the onset and regularity of menstruation, but menstrual-related hormonal fluctuations can also influence gastrointestinal (GI) symptoms in IBD. Estrogens have both suppressive and stimulatory effects on autoimmune diseases, with promotion of B-cell activation and survival as well as interference with monocyte proliferation.[17,18] It is also well established that hormones play a significant role in the cyclical alteration of GI symptoms during the menstrual cycle in healthy women.[16] It is, therefore, not surprising that women with IBD may also experience a cyclical alteration of their IBD symptoms during the menstrual cycle. This was first examined in 1998 by Kane and colleagues, who studied premenstrual and menstrual symptoms in women with irritable bowel syndrome (IBS), IBD, and controls through a retrospective interview-based approach.[19] It was found that, although there was no difference between the disease groups and controls in non-GI premenstrual symptoms, women with IBD and IBS reported a cyclical pattern of their GI symptoms significantly more than controls. Specifically, women with IBS/IBD tended to experience more diarrhea during menstruation but also noted cyclical changes in abdominal pain and constipation.[19-21]

A more recent prospective study by Parlak and colleagues also revealed a cyclical pattern of IBD symptoms through the menstrual cycle and found that this cyclical pattern could be influenced by disease activity.[20] Women with UC, CD, and their healthy counterparts were asked to keep GI- and non–GI-related symptom diaries through 3 menstrual cycles. While controls, patients with UC, and patients with CD in remission experienced cyclical fluctuations of GI symptoms during the menstrual cycle, this pattern did not occur in women with active CD. This suggested that inflammation related to IBD may counterbalance the mechanism through which cyclical GI symptoms occur.[20] Thus, it is helpful to consider GI symptoms in the context of a woman's menstrual cycle to better distinguish between cyclical fluctuations of GI symptoms vs a true IBD flare.

Many healthy women seek hormonal contraception to treat menstrual-related GI symptoms. Given the complex role of hormones on the immune system, questions have been raised regarding whether hormonal contraception may improve or worsen GI symptoms in women with IBD. In 2014, Gawron and colleagues published the results of a cross-sectional phone survey of 129 women with IBD, 88% of whom reported current or past hormonal contraceptive use and 60% of whom reported cyclical IBD symptoms.[21] Symptomatic improvement of cyclical IBD symptoms (ie, improvement in diarrhea, cramping, and/or pain) was described by 19% of estrogen-based contraceptive users and 47% of levonorgestrel intrauterine device (LNG-IUD) users. Only 5% of patients using the hormonal method reported symptomatic worsening.[21] Although this small survey-based study of a very specific cohort of educated women is limited, it suggests that hormonal contraception may be beneficial to treat cyclical symptoms in women with IBD.

Endometriosis

Endometriosis, the presence of endometrial tissue outside of the uterus, is thought to result from retrograde menstruation and subsequent ectopic implantation of endometrium-like tissue that fails to be cleared by the immune system.[22,23] Endometriosis has been increasingly associated with autoimmune diseases, including IBD,[23] and women with endometriosis have altered immune surveillance with findings of depressed cell-mediated immunity and heightened humoral immune response that are similar to

those commonly seen in other autoimmune diseases.[24] In a retrospective study based on the clinical records of more than 37,000 Danish women with endometriosis, women with endometriosis had a 50% increased risk of developing IBD when compared with women in the general Danish population. This risk was even greater in women with surgically verified endometriosis.[22] It is still unclear whether this association is related to a shared immunologic predisposition or to endometriosis treatments (eg, nonsteroidal anti-inflammatory drugs and oral contraceptive pills) that may play a role in the development of IBD.[22] Regardless, it is important for physicians to consider endometriosis in women with IBD who have cyclical abdominal pain, dyspareunia, and/or infertility.

Fertility

Most women are affected by IBD during their childbearing years; thus, fertility is an important but unfortunately misunderstood clinical consideration.[25] Although there are subgroups of IBD patients with decreased fertility, men and women with IBD generally have a reproductive capacity that is similar to that of the general population, with decreases in reproduction often related to voluntary childlessness.[25,26] In a systematic review of fertility in non-surgically treated IBD patients, there was a 17% to 44% reduction in fertility in women with CD as compared with controls, but this was linked to voluntary childlessness and not involuntary infertility. Similar trends were seen in men with CD, who had an 18% to 50% reduction in fertility without any difference in reproductive capacity.[27] Voluntary childlessness is at least in part driven by misconceptions about the outcomes of pregnancy in IBD.[26]

In general, large population-based studies have revealed that the infertility rate of IBD patients is 5% to 14%,[25,28,29] which is similar to the infertility rate of the general population. Normal fertility in IBD patients is also suggested by hormonal studies of ovarian reserve; in a retrospective case-control study of 50 women with CD and 160 controls, no difference was found between the 2 groups in terms of mean serum anti–Mullerian hormone levels. Interestingly, after 30 years of age, anti–Mullerian hormone levels were significantly lower in women with CD vs controls, and there was a stronger negative correlation between age and anti–Mullerian hormone levels in patients with CD. This suggests that women with IBD may be at risk for accelerated loss of fertility with age. This same study suggested that women with disease located in the colon may be at a higher risk for infertility, although the mechanism for this finding is unclear.[30]

Although the general IBD patient population has normal fertility, subgroups of patients may be at risk for reduced reproductive capacity due to medications, nutritional deficiency, weight loss, surgery, and underlying adhesions or fistulae that can result in impaired ovulation and tubal function.

Table. The Effect of Inflammatory Bowel Disease Treatment on Fertility in Men and Women

Inflammatory Bowel Disease Treatment	Effect on Fertility	
	Men	Women
Sulfasalazine	Reduces	Has no effect
5-aminosalicylic acid	Has no effect	
Methotrexate	Reduces	N/A (teratogenic)
Corticosteroids	Reduces	Has no effect
6-mercaptopurine/ azathioprine	Has no effect	
Biologic agents	Unknown (but unlikely)	
Ileal pouch-anal anastomosis	Reduces	

Adapted from Heetun ZS et al.[31]

Medications and Fertility

Sulfasalazine is often used for treatment of IBD and has been shown to affect fertility in men, but not women.[31,32] In men, sulfasalazine has a reversible effect on sperm count, motility, and morphology.[33] This was first studied in the 1970s as a case series of 4 men with UC and infertility, with improvement of semen analysis after withdrawal of the drug.[34] Methotrexate has also been shown to cause reversible sterility in men[35,36] and should be avoided in women due to significant teratogenicity.[37] In rat models, corticosteroids have been shown to decrease fertility in men, but not in women.[31,38] 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 studies of fertility and biologic agents have been limited to animal studies[32,39-42] (Table).

Surgery and Fertility

There are little data available regarding the effect of small or limited large bowel resection on fertility in men and women. However, there have been numerous studies investigating the effect of IPAA (the surgical treatment of choice for patients with UC who require colectomy) on fertility. Studies of fertility in men after IPAA suggest overall satisfaction with the surgery but conflicting results regarding resultant sexual dysfunction.[43] One prospective study of 18 patients undergoing IPAA revealed a small (<5%) risk of loss of ejaculation.[44] A retrospective review of 111 men found that almost 20% reported some sexual dysfunction postoperatively.[45] Regardless, it should be noted that even with sexual dysfunction, patients often reported overall improved sexual satisfaction. In a ques-

tionnaire-based study of men after IPAA, despite 15% of men reporting erectile function issues and 2% reporting retrograde ejaculation, sexual satisfaction improved due to overall improvement in general health.[43] Other studies actually suggested improvement in sexual function; in a survey-based investigation of 122 men before and after IPAA, a statistically significant improvement was seen in erectile function, sexual desire, intercourse satisfaction, and overall satisfaction. No change was found in orgasm function.[46]

Most literature regarding the effect of IPAA in women suggests some loss of fertility postoperatively. In a systematic review of women undergoing IPAA for UC that totaled 22 studies of almost 2000 patients, the overall infertility rate rose from 12% to 26% after restorative proctocolectomy.[47] This is likely related to pelvic adhesions and obstruction of fallopian tubes, which suggests that a laparoscopic surgical approach may result in improved fertility outcomes.[48] There was also an increase in dyspareunia and an increase in the prevalence of sexual dysfunction, from 8% preoperatively to 25% postoperatively.[47] Despite the above result, many individual studies found an overall improvement in sexual satisfaction postoperatively with maintenance of orgasm function.[43,48] Women who desire pregnancy after IPAA are often advised to undergo Cesarean section to prevent damage to the anal sphincter and pouch, although data for vaginal vs Cesarean delivery are limited.[48]

Contraception

Women with IBD should be reassured that pregnancy can be safe but should be planned. Planned pregnancy ensures disease control at the time of pregnancy and avoids harmful medication exposure to a fetus. Interestingly, despite the importance of contraception in this population, women with IBD use contraception less frequently than women in the general population and often choose less effective methods.[49]

Most available information regarding contraceptive use in IBD patients is limited and comes from surveys targeting educated, white populations. In 2014, Gawron and colleagues published a cross-sectional, survey-based study investigating the factors associated with contraceptive use and selection in women with IBD.[49] Of the 162 respondents, almost 25% of women at risk for pregnancy were not using any form of contraception, approximately 20% used highly effective methods, and 60% used either short-term hormonal methods or barrier/behavioral methods. Low educational attainment was associated with lower rates of contraceptive use, which suggests that this survey may actually have underestimated the prevalence of women who are not using contraception.[49] Unfortunately, contraception is not consistently brought up or documented during primary care and gastroenterology clinic visits, and this discussion should be encouraged.[50]

Choosing a Contraceptive

The choice of birth control method should be tailored to each patient, with emphasis placed on the effectiveness of the method. In 2010, the Centers for Disease Control and Prevention published guidelines for contraceptive use by patients with IBD that were based on a 2010 systematic review by Zapata and colleagues.[51,52] Unrestricted contraceptives for IBD patients include implants, the copper intrauterine device (IUD), and the LNG-IUD. In general, the advantages generally outweigh the risks for progestin-only pills or depot medroxyprogesterone acetate. The decision to use combined oral contraceptives, a combined hormonal contraceptive patch, or a combined hormonal vaginal ring should be made on a case-by-case basis. In general, these contraceptives are safe in women with mild IBD and no other risk factors for venous thromboembolism, but the risks generally outweigh the benefits in women with more severe IBD or with risk factors for venous thromboembolism.[51,52]

Intrauterine Devices

As suggested by the above guidelines, IUDs are generally safe and highly effective contraceptives for women with IBD. However, it is still important to closely monitor these patients because known complications of IUD use (ie, pelvic inflammatory disease, abdominal pain) may be confused with an IBD flare (and vice versa).[53] The influence of IUD use on IBD symptoms and relapse is largely unknown and has not been formally studied. The current available literature is limited to 2 case reports noting women to have IBD exacerbations following LNG-IUD placement.[51,54,55] Questions have been raised regarding the risk of pelvic infection in immunosuppressed IBD patients with IUDs. Although there have been no studies investigating the risk of IUD-related infection in immunosuppressed IBD patients, reviews of IUD use in patients with HIV and SLE have suggested that there is no greater risk for IUD-related pelvic infections.[56]

Oral Contraceptives

Oral contraceptives are an appropriate method of birth control for women with mild IBD who do not have risk factors for venous thromboembolism. Despite initial concerns that hormonal contraceptives might increase the risk of IBD relapse, there is literature to the contrary.[51] One of the most convincing studies was a prospective cohort study by Costnes and colleagues that included more than 300 women and did not find a difference in CD relapse between oral contraceptive users and nonuser controls.[57]

No studies have investigated the influence of hormonal therapy on thrombosis in IBD patients. The recommendation that women who have moderate to severe IBD or an increased risk for venous thromboembolism should avoid oral contraceptives is based on the established association between oral contraceptives and venous thromboembolism in the general population and the known increased thrombosis risk in patients with severe IBD.[58,59]

The absorption of oral contraceptives occurs primarily in the small intestine and may be compromised in patients with active inflammation and in those who have undergone bowel resection. This is a potentially serious issue, as decreased absorption may result in subtherapeutic drug delivery and unplanned pregnancy. There have been no pharmacokinetic studies examining the absorption of oral contraceptives in patients with CD, the population theoretically at highest risk for malabsorption. Interestingly, in a study by Nilsson and colleagues, women with larger bowel resections had the lowest drug levels of levonorgestrel, but these levels were still considered to be therapeutic.[60] It is important to note that these studies were performed in the 1980s with higher doses of ethinyl estradiol and levonorgestrel than typically used in oral contraceptives today.[60]

Hormonal Therapy and the Risk of Developing Inflammatory Bowel Disease

The factors influencing susceptibility and development of IBD are still being elucidated, but research has supported that oral contraceptive users may have a small but measurable increased risk of developing CD and UC.[51,61] In a meta-analysis of 14 studies conducted between 1980 and 2007, Cornish and colleagues found that oral contraceptive users had a relative risk of 1.28 for developing UC and 1.46 for developing CD.[61] Critics have questioned the clinical relevance of this study given the lower doses currently used in oral contraceptive pills. However, a more recent prospective cohort study of more than 100,000 healthy women using hormonal therapy for menopause also found a relative risk of 1.71 for UC among patients on hormonal therapy. No increased risk was found for the development of CD.[62] The potential role of oral contraceptives in the development of IBD is not fully understood but may be related to thrombogenic effects of oral contraceptives on the intestinal microvasculature.[51]

Menopause and Hormone Replacement Therapy

Menopause, the cessation of spontaneous menses for 12 months, is a hormonal transition in a woman's life characterized by decreasing estradiol levels.[63] As a result of this hormonal transition, women often experience hot flashes, menstrual irregularity, and genitourinary symptoms. Menopause usually occurs around 50 years of age. Earlier menopause is associated with a lower body mass index and nulliparity, both of which occur more commonly in women with IBD.[63] It has thus been suggested that women with IBD may experience menopause at an earlier age, but research has been conflicting. A small, survey-based study in Wales suggested that premature menopause might be associated with CD; of the 48 women with CD surveyed who had undergone physiologic menopause, the median age of menopause was 47.6 years compared with 49.6 years in a group of healthy women from the same area.[64] This result was not supported in a subsequent retrospective study by Kane and colleagues investigating the effect of menopause on IBD disease activity. Of the 65 women with UC or CD followed at a single IBD clinic in Chicago, the median age of menopause was similar to that of historical controls.[65] Both of the above studies were limited by small sample sizes and very specific population cohorts.

Given the complex role of estrogens in both the stimulation and suppression of the immune system, questions have been raised regarding whether the hormonal change during menopause may affect IBD disease activity and whether this could be modified by hormone replacement therapy (HRT). In a retrospective study, Kane and colleagues sought to investigate whether women with IBD had a change in symptoms pre- vs postmenopause.[65] Disease activity was measured using clinical scoring systems during the pre- and postmenopausal states of 65 women with IBD. No difference in disease activity was found in pre- vs postmenopausal states, but, interestingly, the use of HRT seemed to have a protective effect on IBD disease activity. Specifically, postmenopausal women taking HRT were 80% less likely to have a flare of IBD than their postmenopausal counterparts not on HRT. Although this study was limited by the small number of study subjects, it was strengthened by the fact that women were followed through both pre- and postmenopausal periods, and, thus, each served as her own control.[65] Although this study did suggest a protective role for HRT in IBD, HRT use is associated with an increased risk for certain cancers, thrombosis, stroke, and coronary artery disease.[66] Therefore, initiating HRT is a complex decision and should be individualized based on each patient's medical problems and risk factors.

Osteoporosis

Low BMD is more common in patients with IBD regardless of sex, and the potential for increased fracture risk may have significant impact on quality of life and potentially on mortality. Unfortunately, most of the current research that associates BMD with fractures and morbidity/mortality has

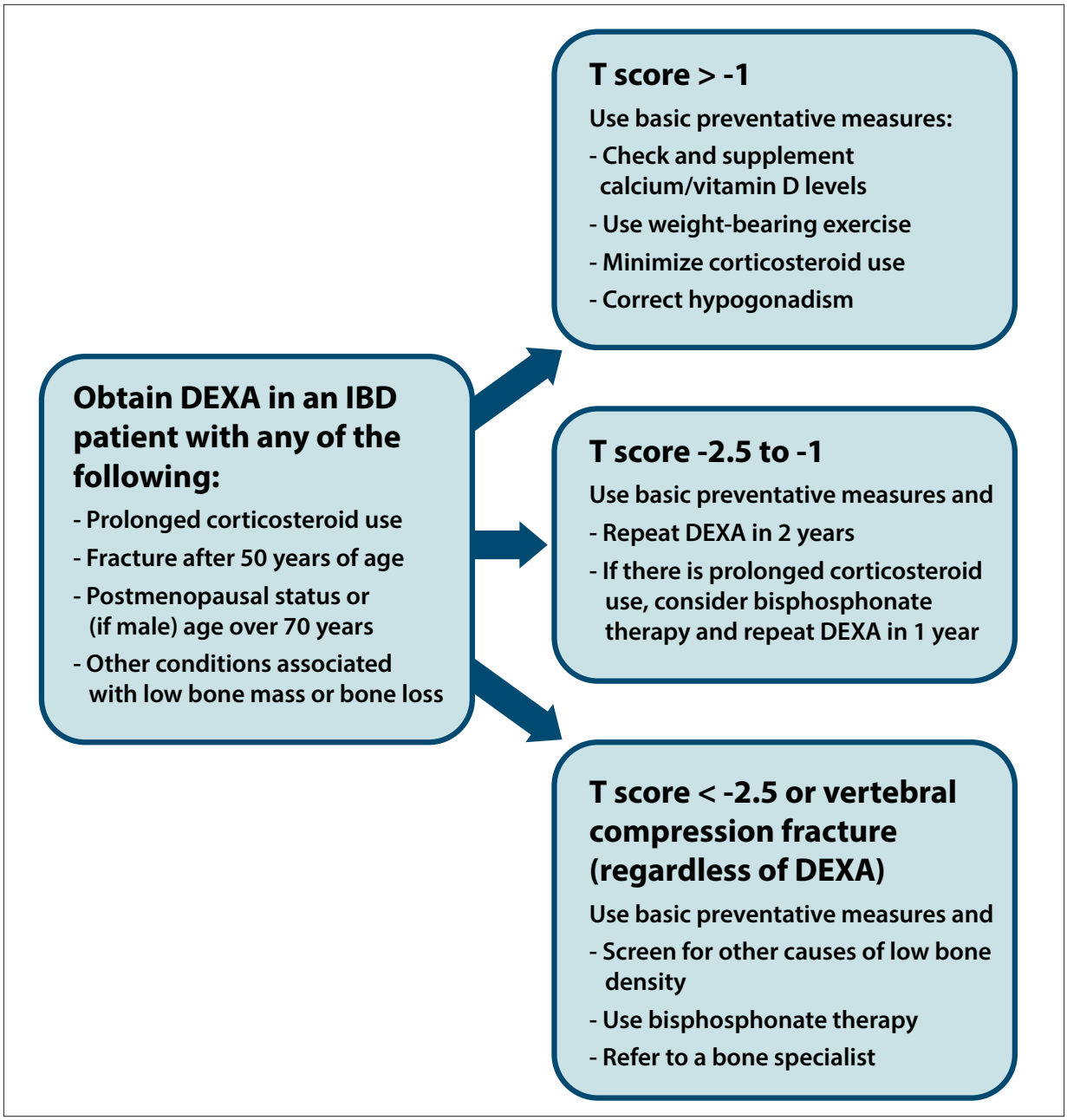

Figure. A management approach for low bone mineral density in patients with IBD.

DEXA, dual-energy X-ray absorptiometry; IBD, inflammatory bowel disease.

Adapted from Bernstein CN et al.[68]

been performed in postmenopausal patients without IBD, which limits the applicability of these data.[67]

The prevalence of osteoporosis in IBD has been estimated at 18% to 42% in uncontrolled studies and 2% to 16% when only larger studies are included.[68] Interestingly, patients newly diagnosed with IBD have similar rates of bone demineralization as their age-matched counterparts and also seem to have a similar decline in BMD.[69] However, IBD has a measurable but modest effect on BMD with a pooled Z score of -0.5 and a relative risk of fractures that is 40% greater than that of the general population. This increased risk for fractures was demonstrated in a population-based retrospective Canadian study of more than 6000 IBD patients with a matched control group of more than 60,000 persons. The fracture rate for IBD patients was found to be 1 per 100 patient-years, with most

fractures of the spine and hip occurring in patients over 60 years.[69] In general, vertebral fractures are found in 7% and other fractures in 24% to 27% of IBD patients.[70,71]

There are multiple contributing factors to the development of decreased BMD and fractures. In the general population, it is well established that age, female sex, body weight, family history, and personal history of fractures are associated with an increased risk of osteoporosis and fractures.[67,72-74] Other modifiable risk factors in the general population include low calcium and vitamin D levels (either from dietary deficiency or malabsorption), low body weight, and menopause. The above factors should be taken into account for IBD patients when considering screening and management of low BMD.[67]

Interestingly, within the IBD population, most research supports similar risk of osteoporosis and fracture regardless of sex or IBD subtype. One study, however, has shown a trend toward lower BMD in CD when compared with UC.[69] Overall, in IBD patients, the most strongly associated variable with osteoporosis is corticosteroid use, although it is challenging to distinguish between the effect of corticosteroids and the effect of increased inflammatory disease activity on BMD.[69] It is likely that both corticosteroid use and inflammatory disease contribute to the development of osteoporosis. The contribution of corticosteroids to the development of osteoporosis is well known and related to increasing the balance of osteoclast vs osteoblast activity.[75] Inflammatory activity may also contribute by stimulating cytokines (including tumor necrosis factor-alpha) that in turn activate the protein RANK-L, which is responsible for bone turnover.[76] The role of inflammatory activity in BMD is supported by research suggesting that BMD may improve after colectomy in patients with UC.[77-79]

Increased inflammatory activity may also lead to decreased absorption and resultant low BMD, although research has been conflicting. In general, disease site and disease activity have not been shown to have an association with low BMD, but a single study did indicate lower BMD in CD patients with jejunal disease.[69,80-84] Interestingly, most research has also not supported an association with bowel resection and BMD,[71,77,82,83] although one study did find that patients with ileal resection had decreased BMD compared with nonoperated patients.[85]

The American Gastroenterological Association (AGA) recognizes the general paucity of data for therapeutic interventions to prevent and treat bone loss in IBD patients. The AGA has suggested that patients with IBD be screened for low BMD in the same way as the general population. Specifically, the National Osteoporosis Foundation and the AGA recommend DEXA scan for postmenopausal women 65 years and older, men 70 years and older, and persons at increased risk for low BMD (including all postmenopausal women, women in the postmenopausal transition, adults with fracture after 50 years, adults taking glucocorticoids at least 5 mg for at least 3 months, or adults with conditions associated with low bone mass or bone loss).[69,86] Fracture risk assessment tools can be used to help guide management and may be helpful in assessing patients with IBD who are at low risk of fracture and may not require a DEXA scan[69] (Figure).

In general, the AGA also suggests common sense approaches, including exercise, nutritional maintenance/supplementation, and bisphosphonate therapy, and/or HRT when appropriate.[69] Vitamin D levels should be checked and supplemented as necessary. As in the general population, dietary intake of calcium 1000 to 1200 mg and vitamin D 600 to 800 IU daily is suggested for all adults.[87] In patients at high risk for osteoporosis and on high-dose glucocorticoids, bisphosphonates are sometimes given to increase BMD.[88] The British Society of Gastroenterology has guidelines regarding the management of osteoporosis and suggests bisphosphonate therapy for patients less than 65 years with a T score of less than 1.5 on DEXA scan as well as patients over 65 years on corticosteroids. A recent meta-analysis of medical therapy for low BMD in IBD found no evidence that calcium or vitamin D increased BMD, but did find that the pooled effect of bisphosphonates was significantly greater than that of controls to increase BMD at the lumbar spine and hip with resultant decreased risk of vertebral fracture.[89]

Conclusion

In the past, sex-specific issues in IBD focused only on pregnancy and childbirth. It has become apparent that there are several other physiologic and psychological differences between men and women with IBD that affect patient care and potentially therapeutic choices and even outcomes. The observation that tobacco smoke has a greater impact on disease course in women vs men was the first indication that perhaps sex did make a difference and that counseling did have to take this factor into consideration. More recently, the finding that clearance of biologic agents is different based on sex has further emphasized this point. Clinicians must be cognizant of these physiologic differences and manage patients with these issues in mind. As the field of IBD continues to evolve into individualized management, sex is one of the variables that should be factored into decision-making.

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