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Review Article

A Review on Prevalence of Inflammatory Bowel Disease in India

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Abstract

Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) was believed to be a Western disease, but are now increasingly being reported from India and other Asian countries where IBD was almost unheard of 30 years ago. Now India is projected to have one of the highest IBD burden across the world. There is rising incidence and prevalence of IBD in India topping the Southeast Asian countries. The clinical presentation of IBD in India is similar to other South East Asian countries. IBD is considered as a result of the complex interaction between the environment, diet, certain medications, genetic variables and a severe autoimmune response against normal bacteria in the gut. However exact cause is still unknown. Also there exists a gender distribution in IBD. In India IBD is more prevalent in males compared to females. This review summarizes the prevalence of IBD in India and some possible risk factors contributing to it.

Keywords: Inflammatory bowel disease, prevalence, India

Introduction

Inflammatory bowel disease (IBD) include two main disease categories Crohn's disease (CD) and ulcerative colitis (UC) and are idiopathic chronic inflammatory intestinal conditions. They have both overlapping and distinct clinical and pathological features. The pathogenesis of IBD is still not completely known however it is known to be as a result of interaction between genes, the immune system, and some environmental factors such as altered luminal bacteria and enhanced intestinal permeability. [1] CD can affect any part of the Gastro Intestinal tract, especially at the end of the small intestine and the beginning of the large intestine. Ulcerative colitis is characterized by the inflammation of large intestine especially colon and the rectum. [2]The most common symptoms for CD and UC are frequent bowel movements, diarrhoea, bloody stool, abdominal pain and cramping. Patients may also report symptoms such as fatigue, lack of appetite and weight loss. [3]When come to the prevalence of IBD, once it was thought to be a Western disease but now common in Asian countries including India. In 2010 the overall estimated IBD population in India came out to be 1.4 million, indicates the second-highest number after the USA (with 1.64 million).[4] In India IBD started gaining special attention only after mid 1980s that is after wider availability of colonoscopy. Before 1985, these diseases were difficult distinguish from more prevalent infectious colitis and even the existence of these diseases were questioned. [5]The incidence of ulcerative colitis in Indians migrating to countries with a higher prevalence is higher when compared to Indians residing in India. Apart from the major factors like immunity, genetic, environmental and familial factors some drugs may also trigger IBD.[6] According to recent reports more than 6.8 million people are living with IBD worldwide.[7] In India the burden of UC is more than CD when compared to West.

Disease burden and prevalence of IBD in India

There were few population based studies carried out in India to determine its prevalence among Indian population. First study was conducted by Khosla et al. [8] in 1984 in Haryana. The study included 21,971 participants and found a prevalence of 42.8 UC patients per 100,000 people. [4] The second study, conducted in Panjab in 1999 by Sood et al. and it was the first study that provided evidence of the dynamic epidemiology of ulcerative colitis in India. From this study, they found an incidence of 6.02/105 per year and a crude prevalence rate of 44.3/105 inhabitants. [9] A comparison of prevalence of IBD among Asian countries indicated a highest disease burden in India compared to other Asian countries. UC was found to be more predominant than CD in Asian countries when compared to Western countries and the prevalence of UC was 24.4 cases per 100000 and those for CD was 7.84 cases per 100000[10] . Another study conducted in Himachal Pradesh in 2017 also found a predominance of UC rather than CD. [11] A latest study from Kerala which was the largest state-wide survey of IBD in India. The study showed that the ratio of UC to CD was 1.1 to 1.0 and concluded that UC and CD were seen in equal proportion in Kerala. [12] A study conducted by Sathiyasekaran et al [13] concluded that paediatric inflammatory bowel disease in India shares similarities with adult-onset IBD.

An IBD survey published in 2012 revealed that IBD is prevalent in all parts of India and does not follow any North-South gradient as observed in other Asian countries. [14, 15] Another study conducted in South India suggested that gluten-rich diet and out- side food are important factors contributing to the increased prevalence of disease. [16] From studies performed on immigrants from South Asia (largely from India and Bangladesh) to the United Kingdom indicated that the incidence of ulcerative colitis in Indians migrating to countries with a higher prevalence was higher as compared to Indians residing in India. [17]

Age and gender distribution of IBD

IBD in the West was characterised by a bimodal age distribution pattern, with a peak at age between 20-39 years and a second smaller peak at 60-79 years unlikely from the surveys of IBD conducted in India. The mean age at diagnosis of UC and CD was found to be 38.5 and 35.9 years respectively in India and was not associated with a bimodal age distribution. [15] But the IBD onset age in India is similar to that in the West. CD occurs at a younger age than UC which was also similar to the West. According to the observations from different studies the prevalence of IBD increases with age. Studies were carried out on paediatric populations also. A retrospective analysis of the case records of children, aged 1 year to 18 years was conducted on Kolkata found an incidence of 13.9/1000 children with IBD in the year 2017. [18] Epidemiological studies highlighted that, 25-30% cases of paediatric IBD associated with familial aggregation.

Studies from India indicated that UC is associated with a slight male predominance similar to West and CD also associated with male predominance with a higher male: female ratio (>1) which is different from West where, CD is more found in female. [15] This male preponderance in studies from India may either due to low incidence of IBD in Indian females compared to west or may be due to the underrepresentation of females in receiving medical care.

Risk factors associated with IBD

Genetics

Genetic factors considered important cause of both CD and UC, with stronger effects in CD. Previous studies suggested that genetic factors are found to be major contributors to familial aggregation and familial aggregation of IBD was significantly lower in Asia than that in the West. [19] A genome-wide association study (GWAS), conducted in north India in 2015 concluded that UC susceptibility genes were shared at a certain rate between north Indians and Europeans, the study identified three novel HLA-independent risk loci for UC containing, BAT2 (Branched Chain Amino Acid Transaminase), MSH5 (MutSHomolog5), HSPA1L (Heart Shock Protien), SLC44A4 (Solute Carrier gene), CFB (Compliment Factor B) and NOTCH4 (Neurogenic Locus Notch Homolog Protein4). It was the first GWAS on UC in a genetically distinct north Indian population and they highlighted the importance of performing GWASs in non-Caucasians [20] More than 200 IBD-specific genetic loci were identified globally by GWAS, 110 of which were common to both CD and UC, 30 were specific to CD and 23 were specific to UC. Studies from West revealed that NOD2 gene has the strongest association with IBD especially with CD but, NOD2 (Nucleotide-Binding Oligomerization Domain-containing protein 2) polymorphisms did not play any major role in CD in Indian patients but two were weakly associated with UC, this study also confirmed the association of rs2066842 with UC in Indian population. [21] Another observation was that the development of IBD may be associated with defects in the main pathway involved in immune cell activation. A study conducted in Indian population revealed strong protective associations between TNFSF15 (Tumor Necrosis Factor Superfamily15) polymorphisms and IBD. [22] Another study reported the association of the TLR4 (Toll Like Receptor) D299G polymorphism with both UC and CD and the association of T399I polymorphisms only in UC. [23]

Colonic Microbiota

The gut microbiota mainly comprises bacteria, fungi, viruses, and other microorganisms. Among these, the bacterial microbiome play important role in etiopathogenesis of IBD. The bacterial community present in gut performs important functions in the host, such as educating the immune system, secreting enzymes for digesting substrates [24] and suppressing harmful microorganisms. The predominant constituents in the healthy gut microbiota are phyla *Firmicutes, Bacteroidetes, Actinobacteria* and *Verrucomicrobia*. [25] Factors such as age, genetics, diet and drugs were shown to alter this beneficial colonic microbiome.

IBD was found to be associated with microbial imbalance. The microbial signature in the Indian IBD population was found similar to that of patients in the West. A reduction in biodiversity of beneficial bacterial taxa was found in IBD patients when compared with a healthy person. Studies shown that some adherent and invasive species such as *Escherichia coli* and *Fusobacterium* which potentiate the colonic inflammation were present at a higher abundance in the colonic mucosa of patients with UC compared to healthy controls [26, 27] Another study conducted in North India found a decreased abundance of predominant butyrate producers like *R. intestinalis* and *F. prausnitzii* belonging to clostridial clusters in the UC disease condition. [28] Concluding that the compositional imbalance or dysbiosis of gut microbiota is an aggravating factor of IBD. In addition, dysbiosis provides a therapeutic approach which aims to restore the normal microbial balance.

Medications

Many drugs such as NSAIDs, Oral contraceptives, Antibiotics and some immune modifiers were found to trigger IBD. All types of antibiotics were significantly associated with IBD except clindamycin. The weakest association was observed with penicillin and the strongest with metronidazole. Antibiotics alter the gut microbiota, intake of antibiotics lead to overgrowth of opportunistic, toxin producing bacteria *Clostridioides difficile* and causing more inflammation. A recent study conducted on paediatric population reported that antibiotic use in first year of life associated with later development of IBD. [29] NSAIDs inhibit cyclooxygenase and decrease prostaglandins production leading to variation in the mucosal protection and microcirculation and cause injuries to mucosa which can initiate nonspecific inflammation, disrupt the epithelial barrier and activate innate immune responses.[30] Previous studies concluded that regular use of NSAIDs may increase risk of IBD, also cause relapse of IBD. [31] Majority of studies reported a stronger association of oral contraceptives with CD. A meta-analysis conducted by Wang et al. showed that use of oral contraceptives associated with increased risk of IBD. [32] An immune modifier, Mycophenolate mofetil caused the release of TNF and interleukin 6 and produce local inflammatory reactions. It also inhibited the proliferation of intestinal epithelium [30]

Smoking

Smoking may cause disruption of epithelial barrier and intestinal inflammation. Previous studies from West observed that smoking is associated with a higher prevalence of CD and risk of development of CD also increased by smoking, but it was negatively associated with UC [33, 34]. Few intervention

studies found that smoking cessation in CD may decrease risk of flare compared to active smokers however, some nicotine preparations found effective in UC. [35, 36] The CD risk for former smokers did not differ from the risk in non-smokers. Studies observed that smoking is not an initiator of CD but rather a promoting factor. [37] Latest study conducted in India concluded that oral tobacco use and smoking has no significant effect on disease presentation. However, current tobacco use in any form was associated with hospitalization during follow up. [38] A case control study conducted by Wang et al in 2018 reported that current or former smoking is not associated with risk of CD in the USA but, former smokers found affected with UC than control and in India, smoking status of patients to control at diagnosis was similar to both CD and UC cases. [39] At last, there found heterogeneity in association of smoking and IBD risk between different countries.

Psychological factors and sleep

Risk of UC and CD found increased with depression and stress. Disease relapse and failure of immunosuppressive therapy were also associated with these impaired psychological conditions. Stress causes vagus nerve inhibition, production of proinflammatory cytokine, modification of the gut microbiota and increase in intestinal permeability. [40] Antidepressants, stress management therapy and psychological counselling like stress management interventions increased the quality of life and reduced disease flare in small number of patients only.

The quality and duration of sleep were found to be reduced in IBD patients and reduced sleep increased the risk of relapse of IBD. A prospective cohort study observed that CD patients who had disturbed sleep even during clinical remission had nearly two-fold increase in the risk of active disease compared to those with unimpaired sleep, both having fewer than 6 hours of sleep per day and having more than 9 hours of sleep per day. [41] Another study reported that less than 6 hours sleep per day and more than 9 hours sleep per day are associated with an increased risk of UC, indicated that both short and long duration of sleep associated with increased risk of IBD. [42]

Diet

Diet is considered as an important factor in pathogenesis of IBD. Diet influences the gut microbiome and some food derivatives can alter the intestinal permeability. Epidemiological studies indicated that adopting Western diet which is low in fruits and vegetables, rich in fats, ω-6 fatty acids, red meat, and processed foods contributes to the increasing incidence of inflammatory bowel disease in developing countries. Various studies demonstrated that dietary constituents like maltodextrins could alter the gut microbiome, in addition food additives such as emulsifiers alter the intestinal permeability, these all results in the development of inflammatory bowel disease. [43]

However, patients with inflammatory bowel disease are advised to include adequate amounts of calories, proteins, and fats in their diet. The calorie and protein requirement of a patient with IBD in remission is similar to that of a healthy individual. But, the protein requirement is more in a patient with active disease since proteins display beneficial effects in mucosal healing. [44] Vitamin D may have a protective role in pathogenesis of inflammatory bowel disease as the vitamin D supplements can reduce TNF-α and supress inflammation. [45] Alcohol consumption may worsen disease symptoms so it should be avoided. No generalized recommendation can be made on avoidance of specific food item. It should be based on individual experience.

Air pollution

One of the contributing factors to IBD is air pollution as it increased the risk of both UC and CD. Especially exposure to SO_2 and NO_2 increase the risk of early onset of UC and CD respectively. [46] Chemical pollutants can alter the gut microbiota and trigger onset of IBD. This fact was confirmed by the study conducted Kish et al. concluded that particulate matter present in the polluted air could initiate inflammatory responses in the colon and can alter the colonic microbiome. [47] A pilot study conducted in US observed that county-level criteria air pollutant emissions directly associated with the rate of IBD hospitalizations. [48]

Conclusion

In the current era of increasing prevalence of IBD in a developing country like India, it is important to find a better solution to this disease since IBD affect a person in his productive years. This could affect the economy of the country. In India disease burden is high compared to other Asian countries. The disease characteristics in Indian patients are similar to West in some aspects. Factors such as genetics, microbiota and environmental factors such as smoking, air pollution, diet play an important role in the pathogenesis of IBD. In addition psychological factors like stress, depression and some medications found aggravating the disease. Conducting more studies on IBD can provide better understanding of the disease and its risk factors. It will help in the future development of some better advanced treatment options.

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