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Literature Review of Inflammatory Bowel Disease in South Asian Populations

Muhammad Waqar[1], Tharshika Raguraj[2], Raguraj Chandradevan[1*]

[1]Medical College of Georgia, Augusta University Medical Center, Augusta, USA
[2]Faculty of Medicine, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka
Email: *craguraj@gmail.com

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Abstract

Background: South Asians have been recently identified as having rapidly rising incidence of inflammatory bowel disease (IBD). There is a paucity of data regarding the phenotypic and genotypic associations of IBD among the patients of this region. Due to the rising disease prevalence, a study on South Asian population can disclose more information about the etiopathogenetic causes of the disease. **Methods:** Here we did a review article of IBD among South Asians. In order to get a correct sense of factors associated with the disease, we have reviewed approximately 150 articles through the PubMed search and google scholar. **Results:** We attempted to find temporal trends of IBD among south Asian population, compared phenotype and genotype of IBD among South Asians and western patients and looked at the patterns of IBD presentation in different countries of South Asia. We have also reviewed the differences in the incidence of IBD among South Asian immigrants and discussed the treatment challenges of IBD among this special population. **Conclusion:** We identified that both patients in South Asia as well as South Asian patients living in Western countries are at greater risk for all types of IBD. This geographical region provides an opportunity for revealing possible etiopathogenetic factors. Further population-based studies, comparison of studies in South Asians and immigrants from South Asian countries, and large-scale biologic treatment models need to be accelerated to control the disease burden in South Asians, as well as to achieve reduced burden globally.

Keywords

Inflammatory Bowel Disease, South Asians, Phenotype and Genotype

1. Introduction and Background

Due to global industrialization in recent decades, multiple diseases have in-

creased dramatically in many populations. The exponential rise of inflammatory bowel disease (IBD) in industrialized countries and the emergence of IBD in countries with a traditionally low prevalence, highlight the importance of environmental triggers in the pathogenesis of this disease [1]. In addition, the high incidence of IBD observed in the South Asian immigrant population in Canada and the United Kingdom further reinforces the contribution of environmental triggers [2] [3] [4].

Crohn's disease (CD) and ulcerative colitis (UC) are two clinicopathological subtypes of IBD related to mucosal immune responses of the digestive tract in genetically susceptible individuals. IBD has multifactorial etiologies, including intestinal dysbiosis, altered immune responses, and environmental triggers. Recent additional findings related to the disease include epigenetic changes, inflammasome, and damage-associated molecular patterns [5] [6] [7].

As the two clinicopathological subtypes of IBD have multiple underlying factors and environmental triggers contributing to the disease pathogenesis, this literature review seeks to explain these factors in context of the South Asian population. We first discuss the temporal trends and patterns of IBD in various countries of South Asia and then compare phenotypic differences in IBD between the South Asian and the Western populations. We compared various genetic factors, differences in the treatment approaches, and the effectiveness of biological agents among South Asian and non-South Asian patients. Finally, we have reviewed the pattern of IBD in the South Asian immigrant population and how do they differ from the local population of that region. Through this review, we intend to identify the impact of environmental factors in the pathogenesis of IBD, the challenges present in the treatment of IBD, and to identify a specific area of research which could improve our understanding of IBD.

2. Epidemiology: Incidence and Prevalence Rates and Temporal Trends

South Asia is a term used to represent the southern region of the Asian continent, which includes the territories of the sub-Himalayan countries that are a part of the South Asian Association for Regional Cooperation. South Asia is surrounded by other subcategories of the Asian continent including West Asia, Central Asia, Southeast Asia, and East Asia. It is also confined by the Indian Ocean on the south. The countries of this region include Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, India, Pakistan, and Sri Lanka, which cover a total of 5.2 million km^2 of land. South Asia is a home of 1.75 billion people, accounting for about one-fourth of the world's population, which makes it the most densely populated region globally. Since the turn of the 21st century, IBD has become a global disease with accelerating incidence in industrializing countries, especially of South Asia [8]. The prevalence of IBD in westernized countries appears to have stabilized [9]. Yet, many studies in South Asia show evidence of a rising incidence of IBD in the last two decades [10]. Increasing

awareness and improved diagnostic methods have resulted in a higher rate of IBD prevalence in South Asia. However, population studies demonstrate the emerging trend of the disease incidence every year [11]. The overall estimated prevalence of IBD in India was 1.4 million in 2010, making it the second country with the highest IBD prevalence after the USA with 1.64 million.

Although the prevalence of IBD in India is less compared to the Western countries, but the total population in India is more than 120 million which makes the total patients of IBD in India to be the highest in the world [12]. Two epidemiological studies on UC have been conducted in northern India. In the first study, a house-to-house survey conducted in the State of Haryana revealed a UC prevalence of $45.5/10^5$ in 1980 [13]. The second study, conducted in the neighboring State Punjab in 2010, revealed a crude incidence of $6.02/10^5$ and a prevalence of $44.8/10^5$. Although the incidence and prevalence found are the highest in Asia, they are lower than across North America and Europe [14]. As the population-based studies have not been conducted which could better determine the burden of CD, the data collected from the hospital is used to determine the prevalence of CD in the population. A multicenter study from northern and eastern India demonstrated a rise in the total number of patients with CD from being less than 5000 in 1987 to 21,061 in 2001. This indicates the increase in IBD cases as well as its prevalence over the years in a newly industrializing country of South Asia [15].

A hospital-based survey performed in two districts of Sri Lanka revealed a prevalence rate of Ulcerative colitis was $5.3/10^5$ and Crohn disease was $1.2/10^5$. The incidence rate was $0.69/10^5$ for Ulcerative colitis and $0.09/10^5$ for Crohn disease. The survey also showed the prevalence of Ulcerative colitis in females more predominantly [16]. In a recent retrospective tertiary care-based multicentric study in Sri Lanka, revealed a pattern of increase in CD prevalence overtime, compared to UC [17]. Another study published from a tertiary care center in eastern Nepal revealed IBD is not a rare disease, and there is evidence of increased detection of IBD cases which is attributed to their increased awareness and establishment of specialty services [18]. A study published on UC in Bangladesh revealed that more than 50% of patients who had diarrhea without an apparent cause actually fulfilled the diagnostic criteria of UC [19]. Studies have shown that varying clinical presentations of CD and UC [20] exist in Pakistan and should be considered in differential diagnosis; however, no data is available for the prevalence or the burden of the disease. The lack of a national IBD registry and few tertiary care referral centers for the specialist care of IBD patients may be the reason for the deficiency of data from the other regions.

3. Varying Patterns of Inflammatory Bowel Disease Subtypes by Geographic Region and Subpopulation

The IBD survey published in India in 2012 revealed the presence of patients with IBD in all geographic parts of North and South India [21]. However, a later

study published in 2020 identified South India as the most common region for patients with CD. Those suffering from UC were more likely to originate from West, Central, or North India than those with CD [22]. Likelihood of CD and UC was equal in the patients from the cities while patients from smaller towns were more likely to have CD, and those from villages were more likely to have UC [22]. Epidemiological studies in Western countries have shown that an increase of UC incidence preceded an increase in CD incidence by around 15 - 20 years [23]. This observation of an increased incidence and prevalence of IBD which occurred 50 years ago in the West, mirrors the current pattern of the disease in South Asian countries, as evidenced by various studies. However, as the disease load in the West has been stable for some time [24] [25], the gap between the rise of CD initially and UC later, has decreased; a shift that could be experienced in South Asian countries in future decades. A hospital-based study in Sri Lanka in 2018 revealed the burden of IBD is lower in the central province of Sri Lanka when compared to other Asian and Western countries. Lack of population-based studies and nature of hospital-based data from most of the South Asian countries (except India) are the hurdles to compare the prevalence and geographic differences in the pattern of IBD between the different regions.

4. Phenotypic Differences of Inflammatory Bowel Disease in South Asian versus Western Patients

The pattern of UC in South Asia was almost similar to the pattern of the disease found in Western countries. Data from an IBD survey of 714 patients with UC in India in 2020 indicated that the disease extent was pancolitis in 42%, left-sided colitis in 38.8%, and proctitis in 18.3% [21]. Another study also reported similar patterns in the extent of the disease in Asians as well as in Australians [26]. Hospital-based data in Sri Lanka revealed that among patients diagnosed with UC, the percentages of extensive disease, left-sided colitis, and proctitis were 15%, 24.3%, and 60.7%, respectively [16]. A recent study on different groups in Sri Lanka revealed no significant change in the disease phenotype of UC [17].

The phenotypic location of CD in South Asia also resembles to that found in Western countries. A multicenter study on 182 patients in India revealed L1 in 32%, L2 in 41%, L3 in 23%, and L4 in 4%. The perianal disease was seen in 19% of the patients [15]. An IBD survey of 394 CD patients in India also reported similar disease locations with 29% having L1, 31% having L2, 40% having L3, and 6% having L4 phenotype [21]. Two more studies done in India including one study on 178 patients from Mumbai [27] and another study done in Vellore [28], also reported a similar disease location. A study also reported similarity in disease location between Asians and Australians, with L1, L2, L3, and L4 phenotypes in 31%, 24%, 45%, and 5% of all patients, respectively [26]. This pattern was also observed in a recent study from Sri Lanka, where the L3 pattern predominated [17]. The behavior of CD in South Asia was also found to be similar to the behavior of the disease in western world. Inflammatory disease is the most

common pattern found in both Western and Indian studies [21]. A similar pattern was seen in Sri Lankan studies as well [17]. Temporal changes in phenotypic behavior are explained in patients with CD in 2016 by Kalarie and colleagues. Their retrospective analysis revealed similarity in the gender distribution and predominant ileocolonic location of the disease compared to earlier Asian reports. However, while one-fourth of Indian patients had an aggressive disease at diagnosis, the tendency to progress towards aggressive disease over time was less pronounced than in Western patients [27].

5. Genetic Determinants of Inflammatory Bowel Disease in South Asian versus Western Populations

IBD is a complex genetic disease instigated and amplified by the confluence of multiple genetic and environmental variables that perturb the immune-microbiome axis. Over the past decades, significant advances in understanding the genetic contributions to IBD have been made. Genetic testing and DNA sequencing allowed for genome-wide association studies that identified new single nucleotide polymorphisms (SNPs) [29]. Nucleotide-binding oligomerization domain containing 2 (NOD2) was the first susceptibility gene for CD discovered in 2001. From the various single nucleotide polymorphisms associated with IBD in White patients which are detected by metanalysis of genome-wide association studies, only 5 of 59 index ones studied in North India were found significant, showing limited replication in Indian patients [30]. Also, studies done more recently assessing the NOD2 polymorphisms in Indian patients were not able to find any similar association, and none of the three common CD-associated NOD2 polymorphism were found [31] [32] [33]. This raises the question of what impairs the common causative genes in the White population are non-causal in the Indian population, which could be due to differing environmental exposures, secondary factors, or immunological interactions.

However, two studies found a weak association of rs2066842 (Pro268Ser) with UC [31] [34]. Few studies have demonstrated a relation to the UC phenotype. UC response to steroids, early age (<29 years) of disease onset and left-sided disease are few of the characteristics found to be very well associated with some haplotypes of MDR1 (ABC B1) gene [35]. TNF alpha 863 AA genotype increased the risk of both UC and CD, especially for pancolitis related to UC. IL4 B2 carrier state was less in left-sided colitis than proctosigmoiditis and absent in colonic CD [36]. One study showed that the ancestral origin of North Indians from Indo-Aryans can explain the association with UC as well as the phenotypic and genotypic similarities [37].

Mahurkar and colleagues also reported that in Indian population, the protective allele of the Il23 gene (R381Q) called NOD2, was not associated with CD [21]. Another study conducted in India showed that TNFSF15 (tumor necrosis factor superfamily) gene polymorphisms were protective against IBD in the Indian population [38]. Studies done in Japan and UK have also demonstrated an

association between TNFSF15 and IBD risk [39]. The association of an autophagy-related gene as well as IRGM gene with CD in Indian population was also reported by the same group. This association had previously been reported in many European studies [40].

A Sri Lankan case-control study published in 2018 concluded heterogenicity of allelic mutations in South Asian patients when compared to White patients [41]. Surprisingly, most SNPs and disease associations reported in this study have not been reported previously in South Asian populations. The observed genetic heterogenicity across divergent populations at several risk loci can be explained by differences in risk allele frequency (NOD2), the effect size of TNFSF15, or a combination of these factors (IL23R or IRGM).

6. Clinical Presentations and Diagnosis of Inflammatory Bowel Disease

Despite a decrease in diagnostic delays in Western countries over the last decades, there is still a delay of one to two years and more larger delays in CD in western countries, despite widely available resources in health care [42]. This could result in a poorer medical outcome [43]. The major challenge related to the accurate and timely diagnosis of IBD is due to high prevalence of infectious enteritis and intestinal tuberculosis. Infections with chronic diarrhea can delay the diagnosis of IBD and sometimes cause complications for existing IBD. A scarcity of medical experts and advanced diagnostic facilities in South Asian communities' results in 37% of IBD patients receiving antituberculosis drugs [21]. CD and mycobacterium tuberculosis (MTB) are chronic granulomatous diseases with overlapping clinical, pathological, radiographic, and endoscopic findings. Additionally, the lack of sensitive and specific laboratory markers led to a 50% - 70% misdiagnosis rate [44]. Importantly, seven susceptibility loci including NOD2, IL23R, RIPK2, and TNFSF15 for Mycobacterium leprae infection, have also been associated with CD [45]. This raises the question of the coexistence of CD and MTB or a causal relationship of mycobacterium tuberculosis initiating CD by producing the altered gut mucosal immunity. Recent findings indicate that the disease can be exacerbated in patients on immunosuppressive therapy. Thus, large-scale studies exploring the association between CD and MTB are needed to identify the presence of association further. In addition to MTB infectious colitis, various other microbes can lead to gut involvement which can mimic the presentation of IBD such as ileitis due to Salmonella and Yersinia, colitis due to various other bacterial and parasitic organisms, and ileocolonic ulcers which due to amebiasis. As mentioned above, these infections can also complicate the course of IBD.

7. Differing Treatment Modalities of Inflammatory Bowel Disease in South Asia

According to an IBD survey from India, steroids were given to two-thirds of all

UC patients, Azathioprine (AZA) was given to 30% of the patients, and biologics were used as a treatment for less than even 1% of the patients [21]. This decreased use of biologics in Indians indicates the lack of insurance coverage and affordability, in the Indian healthcare system. In a recent retrospective analysis of 179 patients with a diagnosis of acute severe UC, followed from discharge to a median of 56 months, the rate of colectomy at admission was lower than that reported in Western countries but matched other similar Asian studies [46]. In the Leicestershire cohort, although all ethnic groups showed a similar disease extent, South Asian patients required less surgery and experienced fewer complications than European patients [47]. The overall colectomy rate was 12% in the diagnosed UC cohort from Oxford, UK [48]. These data indicate that overall colectomy rates are lower in Indian patients when compared to patients in Western countries, indicating a slightly milder disease severity in India. Other variables accounting for the lower rate of colectomy in India could include social factors or fewer Indian patients being receptive to a colectomy. One study from three different centers in India reported that surgery was required by 37% of all patients with CD [15].

The medication used in 78% of patients was 5-aminosalicylic acid (5-ASA) compounds, 42% of all patients were given steroids, 29% of all patients received Azathioprine, and 2% of all patients were given methotrexate. The IBD survey from India revealed 5-ASA was used only for 64% of patients, steroids for 69% of all patients, AZA for 63% of patients, and biologics were used in 2% of all patients [21]. In a study done on a cohort from Mumbai, 55% of patients required surgery within 15 years [27].

Medical treatment-induced remission in UC in a hospital-based study from Sri Lanka in 2018, showed positive results with 5-ASA in 99% of patients, while 68% of patients achieved remission with a combined treatment of oral steroids and 5-ASA. AZA was also used for 15% of the patients [49]. Biologic therapy (infliximab) was given as an induction treatment for almost 6% of nine UC patients, however, combination of other medications such as AZA, 5-ASA and steroids were used initially as a treatment for all these patients. For maintenance, oral 5-ASA was used for 71% patients of UC and combination therapy consisting of both oral 5-ASA and azathioprine was used for 24% of patients. In the said study, 40% of CD patients achieved remission with a combined treatment of 5-ASA drugs, systemic steroids, and azathioprine. Infliximab was used for induction in 23% patients of CD who did not achieve remission with the above-mentioned treatment. Maintenance of remission was achieved in 96% of CD patients with either a single or a combination of 5-ASA and AZA. Only two (3%) CD patients were on infliximab maintenance [49].

Importantly, there is a scarcity of data regarding treatment modalities for IBD in South Asian countries. This is due to diverse medical practices employed in these countries including alternative and complementary medicine such as Ayurveda and homeopathy. It can also be assumed that there must be a high number of unidentified patients with IBD who only present to these South Asian

traditional and modern alternative health practitioners, and therefore, data from these patients is not available.

8. Impact of Migration on Inflammatory Bowel Disease among South Asian Patients

Migration is associated with changes in the incidence, new environmental exposures, or movement away from such exposures. Studies to date done in different time and duration, as well as differences in second and third generations, complicate the outcome [50]. However, recent studies revealed different phenotypic characteristics among South Asians immigrants. One retrospective study conducted between 2000 and 2016 at two tertiary centers in the US randomly matched 171 South Asians with IBD to White controls. This revealed a more penetrating disease in those with CD, less proctitis among patients with UC, and altered medication use patterns [51]. A population-based cohort study in Canada showed that a younger age of migrating to Canada increased the risk of IBD. At the same time, Canadian-born children of immigrants from some regions especially from middle east/North Africa, South Asia and Sub-Saharan Africa assumed the high Canadian incidence of IBD, indicating that an underlying risk is activated with earlier life exposure to the Canadian environment [52]. Therefore, environmental exposure and a South Asian genetic profile could be contributing factors to this increasing incidence and variable phenotype among South Asian immigrants.

9. Discussion

Epidemiologic trends document an increasing incidence of IBD in South Asia, where the phenotypic expressions of their disease are like those in the Western societies. It is also worth noting that the emergence of various diagnostic modalities and lack of availability of specialists in South Asia cause difficulty in recognizing the trends and masking the disease burden. However, population studies, hospital-based reports, and other genetic studies indicate that the incidence of IBD is rising every year. Population-based data from all parts of South Asia remain scarce, which hinders any comparison of epidemiology, risk factors, phenotypic expression, and treatment modalities of IBD in South Asia to what is seen in the West. This highlights a need for future population-based prospective studies in a traditionally low-prevalence region like South Asia.

Current findings suggest that genetic susceptibility and environmental triggers differ between populations in South Asia and the West. Ongoing urbanization, industrialization, changing lifestyle and dietary patterns, increasing stress, pollution, unidentifiable environmental influences, and alteration of gut microbiota likely play a role in the rising incidence of IBD in South Asia. South Asian immigrants to the West showing a more severe initial presentation in their disease behavior and increased incidence compared to the western population of those regions, suggests that in addition to genetics alone, unique environmental exposures and a potentially unique genetic profile of South Asian patients may deli-

berate this variable phenotypic expression which consequently will influence the management of IBD in this population. The increase in incidence in this population also provides a unique opportunity to examine the multifactorial contributors of IBD.

Considering the current findings, future studies in South Asia should not only seek to replicate studies of environmental and genetic risk factors in the West but also attempt to detect novel associations which might specifically apply to the local populations. Epigenetic changes, modulation of the transcriptome and post-transcriptional events, as well as host-gut microbiota interactions also appear to contribute to the risk of IBD and should be considered alongside genetic and environmental risk factors. With a deeper understanding of the differences in the etiologic background and natural disease course of IBD in South Asia versus the West, we will be better equipped to stem the global rise of IBD.

IBD can no longer be considered a disease with a lower burden in South Asia. IBD affects individuals in their most productive years and is associated with significant morbidity and loss of functional capacity. It also increases the financial burden on the patients due to its prolonged treatment course. IBD in South Asia and IBD among South Asian migrants show an aggressive nature, like what can be observed in the West or in some cases even worse than what is seen in the Western population, therefore, it requires an equally aggressive treatment approach. Challenges in treating IBD include the expense of therapy, the lack of medical insurance coverage, and poor acceptance rates of patients for surgery. Moreover, most of the clinical trials, genetic studies, and biological treatment catered to the Western population in White or African Americans are unlikely to reproduce a comparable effect in South Asian populations. Further challenges may arise due to this during the escalation of therapy and in predicting the response in South Asians.

10. Conclusion

Concluding, this review identified that both patients in South Asia as well as South Asian patients living in Western countries are at greater risk for all types of IBD. Due to this increasing disease prevalence, this geographical region provides an opportunity for revealing possible etiopathogenetic factors. Further population-based studies, comparison of studies in South Asians and immigrants from South Asian countries, and large-scale biologic treatment models need to be accelerated to control the disease burden in South Asians, as well as to achieve reduced burden globally.

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The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest

There are no financial conflicts of interest to disclose.

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