



World Journal of Current Medical and Pharmaceutical Research

Content available at www.wjcmpr.com

ISSN: 2582-0222



Factors that Increase the Risk of Inflammatory Bowel Disease

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Article History	Abstract
Received on: 19-02-2024 Revised on: 16-03-2024 Accepted on: 29-04-2024	Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract. It comprises Crohn's disease (CD) and ulcerative colitis (UC). The disorder begins in young adulthood. It is characterised by remission and relapse. IBD significantly affects a person's life more so, their productivity and ability to perform activities of daily living. Although IBD is prevalent in Western countries, the recent epidemiology data shows a rising global prevalence and incidence. Addressing IBD is important. Although it is not significantly associated with high morbidity rates, it is a significant burden to healthcare. Identifying the risk factors of IBD can help in improving preventative measures. Since IBD does not have a known cure, controlling for these factors can minimize the impact of the disease. Some of the risk factors that increase the risk of IBD are genetics, environmental factors such as smoking, diet, lifestyle changes, medications, and intestinal microbiome. Identifying the factors that contribute to the risk of developing IBD can help in creating effective measures that can prevent the pathogenesis of the disease.
	Keywords: Inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), environmental factors, microbiota.

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DOI: <https://doi.org/10.37022/wjcmpr.v6i1.322>

Introduction

Inflammatory bowel disease (IBD) is a chronic disorder that causes the inflammation of the gastrointestinal tract. IBD comprises Crohn's disease (CD) and ulcerative colitis (UC). The disorders begin in young adulthood and are characterised by remission and relapse [1]. The disorders are debilitating to patients causing abdominal pain, diarrhoea, and rectal bleeding [2]. IBD adversely affects all aspects of a person's life. Because it is a disease characterised by remission and relapse, it can significantly affect one's productivity and make it difficult to perform daily activities. IBD is mainly present in developed Western countries, but the epidemiological pattern has been shifting over recent years. The recent data on the global burden of IBD suggests that over 2 million people in Europe and North America suffer from the disease [2, 3]. In the US approximately 3.1 million people have been diagnosed with IBD at one point in their lives [4].

The burden of IBD continues to rise across the world. Previously predominant in Western countries, newer studies indicate a rising prevalence and incidence of the disease in Eastern Europe, Asia, South America, and Asia [2, 3, 5]. Several factors are attributed to the rise of IBD in non-Western

countries. These factors include urbanization, environmental factors, and a Westernized lifestyle [6, 7, 8]. Addressing IBD is vital because of its associated morbidity and mortality. IBD is also a significant burden to healthcare with approximate costs for treating the disease averaging \$23,000.9. Addressing IBD is vital to ensure patients lead a productive life. At the moment, IBD does not have a known cure with most interventions in place aimed at managing the symptoms. Considering there is no cure for IBD, prevention is crucial. Identifying the risk factors for the disease is essential in putting effective prevention measures in place to address the disease. Identifying risk factors can help to put effective preventative measures in place to reduce the occurrence of IBD.

This review aims to provide an overview of factors that increase the risk of developing IBD. The review begins by giving data on global prevalence and incidence before delving into factors that make an individual more susceptible to the disease. The review also provides an overview of the measures that can be put in place to control for risk factors of IBD.

IBD Prevalence and Incidence

The prevalence and incidence of IBD varies by geographic region. However, one factor that is constant is that IBD is more prevalent in Western countries more so among people of European descent [11]. IBD tends to disproportionately affect people in North America, Europe, Australia and New Zealand [5]. Globally, approximately 6.9 million people are living with IBD with females tending to be more affected at 3.9 million and males at 3.0 million [2]. This number is an increase from 3.7 million cases reported in 1990.2 North America contributed the

highest number of these cases. The USA for example reported a prevalence of between 252 to 429 cases per 100,000. Similar to the US, a high prevalence was reported in the UK. Approximately, there 373 per 100,000 population.² The findings from this epidemiological study were similar to those of Ananthakrishnan.¹ The study established a high incidence rate of both UC and CD in North America and Europe. The incidence rate in North America was 0-19.2 per 100,000 while in Europe it was 0.6-24.3 per 100,000.¹ For Crohn's disease, the incidence rate was 0-20.2 per 100,000 in the North American region, and 0.3-12.7 per 100,000 in the European region.¹ The prevalence of IBD was also linked to the social demographic index (SDI). Countries that had higher SDI such as the US, UK, Canada, and Australia reported a higher prevalence rate of IBD than countries with a lower SDI prevalence [2,3].

Although IBD has a higher occurrence rate in Western countries, recent epidemiological data shows an increasing incidence in countries that are becoming more industrialized in regions like Asia, South America, the Middle East, and Africa [3,12]. The rising cases of IBD can be attributed to various factors including lifestyle changes more so changes in diet, environmental factors, and urbanization [7]. Improvement in socioeconomic factors can also be a factor that is contributing to the increase in IBD in these countries [2]. Change in socioeconomic status comes with changes in diet and lifestyle. In most instances, diet changes to become one that is low in dietary fibre and meat. A diet that is rich in fibres has been shown to have a protective effect on IBD [13]. However, as countries become more industrialized and urbanized, the intake of a diet that is high in fibre tends to reduce. This could explain why the newly industrialized countries are reporting an increase in the rates of IBD. The increasing incidence in developing countries could also be attributed to an increase in diagnosis and surveillance due to an increase in access to healthcare systems [2]. Other factors that are increasing the occurrences of the disorder in these countries are also at play as will be discussed below.

Factors that Increase the Risk of IBD

Genetic Factors

One of the factors that increase the risk of developing IBD is genetics. The role that genetics plays in IBD is supported by family aggregation studies with twin studies linking IBD to hereditary components [14-17]. The risk of developing IBD was established to be up to five times higher if patients had a first-degree relative with IBD [15, 18]. The risk was up to 30% in siblings that had two parents who had IBD. The genetic component of IBD is greater in patients that have CD than UC.¹⁸ As such, patients who have a family history of CD had a greater likelihood of developing the disease than those with a family history of UC [14]. The risk with CD was up to 30% to 58% compared to 10 to 15% in UC.¹⁹ Another study established the risk to be between 20% to 50% for CD in monozygotic twins compared to 15% for UC [20].

The genetic loci that contribute to the risk of developing IBD have been identified through linkage analysis. Based on the analysis, the NOD2 gene was found to increase the patient's susceptibility to CD [21, 22]. Specifically, homozygosity at the NOD2 locus increased the risk of developing CD by up to 20 to 40 times.²² Heterozygosity was

found to have a more moderate risk of 2 to 4 folds.²² The association between genetic loci and IBD have also been established in other studies with more genetic variants being identified. One study found 163 distinctive loci that increased the likelihood of IBD.²³ Other studies show that there are more than 200 genetic loci that increase the risk of getting IBD with most of the loci being shared between both CD and UC.¹¹ The different genetic variants that are shown to have a role in developing IBD are an indication that alterations in innate immunity and an individual's response to bacteria contribute to the likelihood of developing the disease [11]. Anantha krishnan also established that different genetic variants associated with IBD can be divided into those that influence autophagy, immune responses, adaptive immune responses, those that maintain the integrity of epithelial cells, those involved in restitution and injury repair, and those that influence antimicrobial activity [1].

However, it is important to note that though genetic loci are associated with IBD, the risk among different population groups is different and varies. For instance, people of European descent have a higher familial risk for IBD than people of Asian or African-American ancestry [11]. Most genetic risk loci though were shared among the diverse ancestry groups with few risk loci being specific to certain populations [11]. Despite the link between genetics and IBD, the risk of developing IBD because of genetic association still remains low.¹ This means that other factors play a crucial role when it comes to developing IBD. Environmental factors, for example, play a strong role in increasing the risk of IBD in different studies.

Environmental Factors

Diet

Diet is one of the factors that is constantly mentioned when it comes to the likelihood of developing IBD. The link between diet and IBD has been demonstrated in different studies with different dietary factors coming to play when it comes to the risk of developing the disorder.^{24,25,26} One of the most common dietary patterns that is constantly mentioned and which has been to be a contributing factor to IBD is taking a diet that is low in fibre.^{5,20} According to Amre et al [26]. Paediatric patients who received a recent diagnosis of CD were more likely to be on a diet that was low in fibre more so one that was low in fruits and vegetables. The risk of receiving a CD diagnosis was higher than in the control group.²⁶ The findings were similar to another prospective study that showed people who consumed fibre on a long-term basis had a reduced risk of developing CD. The reduction in risk was significant up to 40% [27]. The reduction in risk was mostly associated with fibre drawn from fruits. Fibre drawn from legumes, cereals, and grains did not modify the risk. In addition to dietary fibre, dietary fat was also linked to IBD. Specifically, a diet that is high in n-6 polyunsaturated fatty acids (omega-6 PUFA) and low consumption of n-3 PUFA (or a high n-6:n-3 ratio) was shown to contribute to the likelihood of developing both UC and CD [1]. Other dietary factors such as the consumption of a diet that is high in vitamin D, zinc, and iron were also shown to lower the risk. Higher consumption of foods high in vitamin D reduced the risk of CD significantly.²⁸ Moderate reduction in risk of UC was also established.²⁸ The association between vitamin D and IBD is supported by the fact that patients who are newly

diagnosed with the disorder have a vitamin D deficiency than healthy individuals [1]. Zinc is important in autophagy and bacterial clearance in CD. It also helps to reduce intestinal permeability hence reducing the likelihood of CD relapse [1]. Controlling for dietary intake can help to lower the risk of getting IBD. From the reviewed studies, certain dietary nutrients affect intestinal microbiota and increase the risk of inflammation. The contribution of dietary intake to the risk of IBD could explain why Western countries have a high incidence and prevalence. For instance, consumption of packaged and fast food in these countries tends to be high [29]. Such foods are high in processed sugar and dietary fat and low in fibre. This could explain why the prevalence and incidence of IBD in these countries are high. The rising cases of IBD in industrializing nations also support this hypothesis. With industrialization, comes change in diet and in most cases, there is a reduction in intake of food that is high in fibre.²This could explain the changing trajectory of IBD with more cases being reported in countries that are becoming more industrialized.

Smoking

Smoking is an additional factor that is constantly mentioned when it comes to the likelihood of developing IBD. Different studies show an association between smoking and CD^{30,31}The association between smoking and UC is lower [31]. Current smoking was particularly found to play a big role when it came to developing CD [32]. Individuals who were currently smoking had a higher risk of developing CD than individuals who were not smoking [32]. On the contrary, the risk of UC was high in past smokers.³³ Current smoking had a protective effect.³²For patients that have CD, smoking increased the aggressiveness of the disease with recurrence likely even after ileocecal resection and the need for immunosuppression and surgery [33]. For patients with UC, stopping smoking was associated with increased flares [1]. One of the reasons why smoking increases the risk of developing CD is because it affects the intestinal microbiota [5]. A study by Benjamin et al [34]. showed that patients who had CD were more likely to have intestinal dysbiosis in their gastrointestinal microbiota. However, the data is inconsistent with different pathways being hypothesized on why smoking increases the risk of IBD. Some of these hypotheses include impaired autophagy, toxicity to immune and mucus-producing cells, and changes in the microbiome [19].

Medications

Using some medications, particularly antibiotics also increases the risk of IBD. The reason why antibiotic use increases the risk of IBD is because of the disturbance in gut microbiota leading to the development of microbial dysbiosis [35]. Gut microbiota in early childhood is diverse and unstable. Certain medications such as antibiotics can alter this microbiota significantly affecting how the gut responds to diseases such as IBD [1]. Altering this microbiota can affect how an individual responds to diseases which increases susceptibility to IBD. For instance, a case study showed that paediatric patients who were given an antibiotic in the first year of life had a 58% likelihood of developing IBD compared to 39% in patients who did not receive antibiotics [36]. However, the link between using antibiotics and the risk of IBD is not conclusive because most studies have been done in Western populations. A study done

in Asia for instance showed different effects of antibiotic exposure associated with a protective effect on CD and UC [37]. In addition to antibiotics, other medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, statins, and postmenopausal hormone therapy drugs also increase the risk of IBD.^{1,19}NSAIDs in particular were found to have a stronger association with the risk increasing with the duration of usage [1].

Hygiene

Hygiene is an additional environmental risk factor that increases the likelihood of getting IBD. The link between IBD and hygiene can be traced to the "hygiene hypothesis [38,39]. The aim of this hypothesis was to explain why there was a significant increase in allergic diseases in the UK after the Industrial Revolution. According to this hypothesis, introducing an infection in early childhood can prevent autoimmune disease. Having unhygienic contact with older siblings can facilitate this transmission. Similar to autoimmune diseases, the risk of developing IBD can also be linked to hygiene factors. Some factors that come into play when it comes to IBD are exposure to pets in childhood, drinking unpasteurized milk, living on a farm, and having a large family [11]. Individuals who are exposed to these factors have a lower risk of IBD. The association between IBD and improved hygiene is also supported by the recent epidemiological studies that show an association between increasing incidence and prevalence of IBD and increased industrialization [2]. Industrialization tends to be linked with hygiene because of the increased need for improved sanitation.

Lifestyle changes

The recent epidemiological data shows an increasing prevalence and incidence of IBD in developing countries could explain the role of lifestyle changes in the pathogenesis of IBD [2, 3]. Lifestyle changes, more so lifestyle that contributes to increased stress levels, less sleep, and less exercise have been shown to contribute to gut inflammation and increased risk of IBD [1,40]. Stress reduces bacterial diversity which could explain why lifestyle changes are attributed to increased risk of IBD [41-43]. Leading a sedentary lifestyle is a risk factor for IBD [1, 44, 45]. Based on this data, IBD rates are increasing in newly industrialized countries. Industrialization has often been linked to a sedentary lifestyle as more occupations that require large amounts of physical labor become replaced with office work which does not require a lot of physical labour [46]. This explains why lifestyle changes increase the likelihood of developing IBD.

The Intestinal Microbiome

The intestinal microbiome is an additional factor that plays a role in developing IBD. Research has established a correlation between changes in intestinal microbiota and a higher risk of developing IBD [19, 47, 48]. Microbial dysbiosis is commonly present in people with IBD. It results from a decrease in the diversity of the microbiome. In particular, people with IBD tend to have fewer bacteria that have anti-inflammatory capacity such as Firmicutes, Faecalibacterium prausnitzii, and Roseburia hominis. On the contrary, bacteria that have inflammatory capacities tend to be higher in people with IBD than in healthy individuals. Such bacteria include Fusobacterium, Proteus,

Escherichia coli [11]. The change in the intestinal microbiome could explain the increased risk of IBD.

Controlling for Risk Factors

The global prevalence and incidence of IBD is rising. As a result, it is important to have a better understanding of the mechanisms that increase the risk of IBD to put better risk mitigation measures in place to reduce the incidence and prevalence. Controlling for risk factors is one of the measures that can help to reduce the increasing prevalence of IBD. Environmental factors are some of the most known contributors to the increased risk of IBD. Moderating for several environmental factors can reduce incidence. For instance, smoking increases the risk for CD [1]. Encouraging people to quit smoking can reduce the risk of Crohn's disease [49,50]. Encouraging an increase in the uptake of a diet that is high in fibre can also help. Reducing antibiotic prescription in children in the first year of life can also help. Other factors that can help are lifestyle modifications such as increasing physical activity, reducing interaction with factors that increase stress levels, and getting more hours of sleep.

Conclusion

The incidence and prevalence of inflammatory bowel disease is increasing globally. Previously predominant in the Western world, the disease is increasing in developing countries. IBD is linked to a number of factors. Genetics, environmental factors, and intestinal microbiome are the main risk factors associated with IBD. Environmental factors tend to be the common denominator when it comes to IBD. Although the other factors are involved, there are no substantial studies to establish the association. Some of the environmental factors linked to IBD are smoking, consumption of a diet that is low in fibre, high intake of a diet that is high in fat, hygiene, certain medications, and lifestyle changes. The association between these factors and IBD is evident from recent epidemiological studies that show that IBD incidence is rising in countries other than the West. Identifying and controlling for risk factors that increase the risk of IBD is vital to improved disease outcomes. Considering the disease has no known cure, controlling for risk factors is the best preventative measure that can reduce prevalence and incidence.

List of Abbreviations

IBD: Inflammatory bowel disease

CD: Crohn's disease

UC: Ulcerative colitis

PUFA: Polyunsaturated fatty acids

NSAIDs: Nonsteroidal anti-inflammatory drugs

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