

Irritable bowel syndrome: An overview on risk factors and microorganisms role; a critical review

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Irritable bowel syndrome is characterized by gut pain and altered bowel habits and known to be a functional bowel syndrome. It has been identified as one of the most extremely prevalent and significant healthcare clinical challenge. Many risk factors have been shown to predispose and increase the prevalence of this disorder.

The following review tries to give an overview on the responsibility of microorganisms, which has been demonstrated as a key risk factor in the etiology of this gastrointestinal disorder together with other risk factors. A momentary look on the diagnostic criteria, treatment, and management approaches are also discussed.

Keywords Irritable bowel syndrome, gastrointestinal disorder, bowel disorder, Rome II criteria, role of microorganisms in IBS

Introduction

Irritable bowel syndrome (IBS) is a functional bowel syndrome with discomfort and changed bowel habits in the absence of obvious structural abnormalities.¹ IBS symptoms and etiology are traditionally thought to be with unknown underlying pathological explanation. It has been known that many physical, behavioral, and psychological factors contributed to IBS's pathogenesis. Patient's conditions are exacerbated by stress, anxiety, and abnormal attitudes towards illness which are related to IBS's pathogenesis.²

IBS is known to be as one of the most highly predominant and costly gastrointestinal (GIT) syndrome that has an undeniable impact on the healthcare and patients' life quality. However, and according to the main stool pattern, IBS is divided into two subgroups: Constipation-IBS (IBS-C) and Diarrhea-IBS (IBS-D), therefore, it is considered to be a heterogeneous disorder.³ This review was conducted to cover some aspects about the IBS. It also talks over the risk factors with a focus on the role of microorganisms in the pathogenesis of this disorder. A glance on the diagnostic criteria together with the treatment and management approaches are given.

Prevalence of irritable bowel syndrome

The worldwide distribution of IBS among general population is ranged from 5.7% to 34%. The percentage is 17%–22% in western countries, while a highly variable range of 2.3%–34% in Asian countries has been observed.² A study was done in 2013 in Jeddah, Kingdom of Saudi Arabia revealed an IBS prevalence of 31.8% in all participants.⁴ Another study in Lebanon in 2015 has reported a prevalence of 20%.⁵ Studies in Iraq revealed that IBS prevalence was common among hypertensive patients, high school students, and university medical students.^{6–8}

Risk factors for irritable bowel syndrome

Many risk factors have been implicated in the pathogenesis of IBS. These factors are either predisposing or activating, ranged in their affect. The most important factors are discussed below.

Age

The incidence of IBS has insignificant statistical association with age groups as have been reported by several studies. However, it has been demonstrated that the mean age of patients with IBS is 25 years.⁹

Gender

The association between gender and IBS prevalence is not clear. A higher prevalence of IBS among females than males with a ratio of about 2:1 have been recorded in many studies.^{2,6,10}

Higher academic grade

Epidemiological study of functional bowel disorders reported that individuals with higher educational levels have relatively increased prevalence of IBS than those with lower educational levels.^{11,12}

Live in dormitory

For those individuals who live in students' houses or in dormitories are three times more prone to have IBS than those who live with their families.^{4,5}

Sleep disorder

Studies found a significant association between severe sleeping disorder, sleeping less than 8 hours/day and the prevalence of IBS.^{13,14}

Stress, anxiety and depression as psychological and psychiatric factors

Stress is the major contributing factor to IBS etiology though the exact mechanism is not clear.⁹ A disorder of brain–gut communication is highly comorbid with anxiety and depression and then to IBS development.¹⁵ Colonic spasms result from an alteration in central nervous system responses to psychological and physical stress which in turn augment IBS symptoms.¹⁶

Diet

Eating habits and dietary balance play a critical role in controlling different aspects of IBS. A study found that nutritional factors are responsible for 15.5% of IBS symptoms.¹⁷ Moreover,

a correlation between food hypersensitivity, obesity, socioeconomic status, and IBS were revealed by other studies. These studies disclosed the fact that IBS become more prevalent in those who are allergic to certain types of food, obese individuals, and those in lower income families.^{4,13} In addition, a low fructose diet seems to improve IBS symptoms in patients with fructose malabsorption disorder.¹⁸

A significant association has been reported between vitamin D deficiency (VDD) and IBS.¹⁹ In patients with VDD, high severe IBS clinical symptoms and lower quality of life were reported.²⁰

Smoking and alcohol consumption

The known destructive outcomes of smoking and alcohol consumption are well-known. However, IBS prevalence is not found to be associated with their consumption.^{4,9}

Physical activity

IBS prevalence is higher among individuals who do not practice physical exercise in comparison with non-IBS individuals.^{4,21}

Familial factors

IBS clusters or aggregates strongly in families.²² A specific mutation has been identified in a sodium channel gene (*SCN5A*), probably explaining 2% of cases. Congenital sucrose-isomaltase deficiency may represent another explanation for familial clustering of the IBS phenotype. Forty other investigators have observed to have altered small-bowel mucosal expression of genes involved in ion transport, barrier and immune function, and mast-cell function.^{3,23}

Role of microorganisms

The advances in molecular investigation techniques over the past 10 years have established the step for screening of the IBS microbiome. Moos *et al.* have demonstrated that microbial infections and Dysbacteriosis (Dysbiosis; a term referring to the impaired or imbalance microbiota on and/or inside the body) are most commonly reported conditions in the GIT representing characteristic features of IBS.^{24,25}

Collected data, in general, described that there is a relative profusion of *Enterobacteriaceae*, with a corresponding increased and/or decreased percentage in *Lactobacillus* genus or Lactobacillales order and *Bifidobacterium* genera.^{26,27} This profusion may appear as an interaction modulating the microbiota through the secretion of bacteriocins against pathogens such as *Listeria* or *Salmonella* species,²⁸ and the host immunity (via a response through dendritic cells with the aid of CD209).²⁹

Escherichia coli, particularly adherent-invasive *E. coli* strains (invade epithelial cells, can replicate within macrophages and induce granuloma formation *in vitro*), has been detected in biopsy samples from patients with ileal Crohn's disease, and are abundant in ulcerative colitis patients, especially in mucosal than in fecal specimens.³⁰ The applying of anti-inflammatory medications in the treatment of patients with IBS has been found to minimize the intestinal inflammation, and is related with a reduction in family *Enterobacteriaceae* members.³¹

Moreover, studies done worldwide on IBS patients between 2011 and 2017 have revealed that these patients

exhibit a difference in the bacterial population; *Clostridiales* order, *Erysipelotrichaceae* and *Ruminococcaceae* families, and *Faecalibacterium* have been found in lower proportions,^{32,33} *Veillonella* or *Ruminococcus* genera have been found in higher proportions.^{34,35} However, the *Firmicutes/Bacteroidetes* ratio appears to be an indicator of bacterial profile shifts, and both an increased and decreased ratio have been described.^{36,37} These variations may be interpreted through technical variations between 16s regions or DNA extraction procedure, small number of participants, geographic diversity, genetic factors, differences in diet, or the use of medications, contrast in predominance of either subtypes or severity of IBS.^{36,38}

An important data are the relationship between methane production and IBS.³⁹ Methane was found to have an anti-inflammatory effect and to inhibit the intestinal transit.⁴⁰ The microbial overgrowth in constipated patients may result in an increased production of methane because *Methanobacteriales* (most common methane producer in the human microbiota) detection is associated with all microbial spate, breathe out methane, existence of methane-producing bacteria proliferated with the *Clostridiales* or *Prevotella* species (also related with slower transit).^{41,42}

Regarding trends about the lumen, several studies suggest a shift in microbes attaching the intestinal mucous layer. The mucous layer is composed of secretory immunoglobulin A, mucin, and trefoil peptides.⁴³ The small intestine consists of one mucous layer, whereas the colon is consists of two mucous layers; an outer and an inner.⁴⁴ Generally, if the mucous layer is not damaged or impaired in any way and remain healthy, germs will only attach and will not access the epithelial cells. Whereas in certain conditions, such as Crohn's disease and ulcerative colitis, the percentage of bacteria attached to the colonic mucous layer becomes higher, compared with controls, and a prevalence of isolated bacteria, particularly adherent *E. coli* pathovar, is higher in specimens of ileal and mucosal biopsy compared with controls.⁴⁵ It has been documented that *E. coli* was seem to be in higher rates in granulomas related to Crohn's disease than to other granulomas not related to Crohn's disease.⁴⁶

Another invasive and adherent bacterium is the genus *Fusobacterium*. *Fusobacterium* species (Gram negative anaerobes settle in the oral cavity and gut) were found in higher rates in mucosa of ulcerative colitis patients compared with controls.⁴⁷ These isolates have the ability to both influence IBS pathology⁴⁸ and contributing to tumorigenesis in a laboratory model.^{49,50} Recently and in colorectal cancer cases, *Fusobacterium* isolates were found to be relatively higher in tumor vs. non-involved adjacent tissue,^{51,52} and thus this bacterium may have possible associate between these diseases.

Other microorganisms, including viruses, fungi, phage, and archaea may have a potential role in GIT diseases.⁵³ Most recent studies are carried out through techniques depending on 16s expression, sequencing, and analysis leading to missing and ignoring these microorganisms. Viral infections with Norovirus, in case of undamaged gut-microflora and a mutation in the Autophagy Related 16 Like 1 (*Atg16l1*) protein coding gene. Diseases related to any defect in this gene are the Crohn's disease and IBS.⁵⁴ Many studies clarified an association among fungi and IBS,⁵⁵ comprising a rise in fungal

variety in the cases of Crohn's disease and ulcerative colitis.⁵⁶ The association between these microorganisms and IBS within the future studies will be more illustrated.

Diagnostic criteria of irritable bowel syndrome

A variety of standard or criteria has been developed to identify a combination of symptoms in order to diagnose IBS, including Manning and Rome criteria. The Manning criteria state that the number of GIT symptoms need to be present to diagnose IBS is at least three positive findings I, II, and III.⁵⁷

- Rome I standard declare that a patient must appear with at least three months of either continuous and/or recurrent presentations of discomfort and/or abdominal pain (related with an alteration in consistency and/or frequency of stool or relieved with defecation), or alteration in stool passage, mucous passage, or bloating or feeling of abdominal distention.⁵⁸
- Rome II standard mentioned that a patient must presented with an abdominal pain or discomfort for at least three months that does not have to exhibit in a successive pattern for the previous year. Furthermore, an abdominal pain have to be present with at least two of the following characteristics; alterations in the consistency and/or frequency of stool and relief with defecation.⁵⁹ Rome I standard was gathered with Rome II standard and upgraded recently into Rome III standard.⁵⁷
- Rome III standard state that the patient should have frequent episodes of discomfort or abdominal pain for at least three days monthly for the previous three months, plus two or more of the following features; variation in stool frequency and/or appearance and/or relief with defecation.⁴

The Manning standard seems to overvalue the number of IBS conditions in comparison with Rome I or II standards.² Because diagnostic criteria were continuously studied and altered, both Manning and Rome I standard were no longer applied.⁵⁸ Currently, the Rome III standard are the most predominant standard because of its higher sensitivity in comparing with the other Rome diagnostic methods.¹⁶

Treatment and management of irritable bowel syndrome

IBS is a complex syndrome, so the management must depend on both pharmacological and non-pharmacological treatments, in addition to adjustment in lifestyle and dietary.⁶⁰ Different non-pharmacological therapy regimens were applied for IBS, comprising stress management and relaxation training, psychological and behavioral therapies, dietary adjustments, raising awareness, physical exercise, and medication.⁶¹

The management of stress in addition to training sessions for relaxation was found to be of a great value and a promising approach, facilitating patient's capability to reduce anxiety and to deal with stress.⁶²

IBS is a disorder that appears to be as a multifactorial, and for that, pharmacologic therapies concerns with abdominal pain and both diarrhea and/or constipation episodes.⁶³

Pharmacological management of IBS issued by the American Gastroenterological Association⁶³ discusses nine pharmaceutical medications or classes of therapies applied in the treatment of IBS, including loperamide, rifaximin, selective serotonin reuptake inhibitors, polyethylene glycol laxatives, alosetron, linaclotide, tricyclic antidepressants, lubiprostone, and antispasmodic (smooth muscle relaxants).⁶⁴

It has been demonstrated that increasing the dietary fiber supplementation intake represents the standard recommendation for patients with IBS.⁶⁵ However, the effect appears to be limited to soluble fibers only and not to the insoluble fibers because they may exacerbate the IBS symptoms.^{61,66} On the other hand, a new study revealed that using gluten-free diet could improve patients' symptoms of IBS.⁶⁷

A study done in Iraq in 2013 revealed that 50% of the patients with IBS have turned to complementary and alternative herbal medicines to treat their IBS.⁶⁰ It was shown that the consumption of essential oils, such as peppermint oil (*Menta piperita*) might minimize the frequency of feces and can described as an adjunctive treatment for IBS with very low side effects.⁶⁸ A peppermint oil is usually used to treat IBS which is found to be significantly a reducer for abdominal pain, discomfort, and IBS severity.⁶⁹ A recent study comes to the fact that supplementation of soy isoflavones (phytochemical agents) can improve IBS symptoms in women.¹⁹ Traditional Chinese medicine might act as an alternative therapy for IBS, involving the use of certain kinds of empiric diagnosis, including pulse and tongue diagnosis.⁷⁰

The Conclusion

Being one of the most common GIT disorder, many studies tried to investigate the risk factors and the genetic and the microorganisms' role in IBS pathogenesis. IBS found not to be associated with patients' age but the syndrome is more common among females than males. The higher educational levels, living in dormitories, sleeping disorder, stress, anxiety, and depression all are well-correlated to IBS prevalence. Many new studies proved the link between IBS incidence and eating habits, vitamin D deficiency, lower life quality, and no practicing of physical exercises. Despite the negative consequences of smoking and alcohol consumption, they don't have an impact on IBS prevalence. An alteration in genes expression is recorded in families with IBS history. A corresponding increased and/or decreased percentage in the microbiota in the GIT tract together with the host immunity strongly affected IBS symptoms. Due to continuous studying and alterations in the diagnostic criteria nowadays, the Rome III standard is the most predominant used standard in IBS diagnosis. Both pharmacological and non-pharmacological treatments were used in IBS management. Further studies are still required to cover the multifactorial factors behind IBS development. In addition, more emphasis on the complementary medicine as an alternative and less side effect treatment is required.

Conflict of Interest

None

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