IBD REVIEWS

Scientific and technological research article

Enviromental factors (exposome) associated to inflammatory bowel disease development

Valeria C L Salgado[1], Paula AE Santo[2], Cyrla Zaltman[3]

Gastroenterology Division, Department of Internal Medicine, Federal University of Rio de Janeiro. Rio de Janeiro, Brazil, Brasil [1], Gastroenterology Division, Department of Internal Medicine, Federal University of Rio de Janeiro. Rio de Janeiro, Brazil, Brasil [2], Gastroenterology Division, Department of Internal Medicine, Federal University of Rio de Janeiro. Rio de Janeiro, Brazil, Brasil [3]

Corresponding Author: Cyrla Zaltman; c.zaltman@gmail.com

Abstract

Inflammatory bowel disease (IBD) is multifactorial, with interactions between genetic susceptibility (genome), individual immunological factors (immunome), gut microbiota (microbiome), and environmental exposure (exposome). The exposome start their action at intrauterine life going through childhood to adulthood and act as likely triggers for the disease. Changes in the exposome favor the emergence of autoimmune diseases reinforced by non-modifiable genetic factors over the years, therefore the epidemiology of IBD might vary between countries, probably linked by the interaction between different gene pools and distinct environmental factor exposure. This article aims to review the main environmental factors related to the development of inflammatory bowel disease.

Keywords: Inflammatory bowel disease, exposome, environmental factors.

Resumen

La enfermedad inflamatoria intestinal (EII) es multifactorial, con interacciones entre la susceptibilidad genética (genoma), los factores inmunológicos individuales (inmunoma), la microbiota intestinal (microbioma) y la exposición ambiental (exposoma). El exposoma comienza su acción en la vida intrauterina pasando de la niñez a la edad adulta y actúa como probable desencadenante de la enfermedad. Los cambios en el exposoma favorecen la aparición de enfermedades autoinmunes reforzadas por factores genéticos no modificables a lo largo de los años, por lo que la epidemiología de la EII puede variar entre países, probablemente vinculada por la interacción entre diferentes grupos de genes y la exposición a distintos factores ambientales. Este artículo tiene como objetivo revisar los principales factores ambientales relacionados con el desarrollo de la enfermedad inflamatoria intestinal.

Palabras clave: Enfermedad inflamatoria intestinal, exposoma factores medioambientales.

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses ulcerative colitis (UC) and Crohn's disease (CD), which are recurrent immune-mediated diseases characterized by a chronic inflammatory process that involves the gastrointestinal tract. [1,2] The etiology is multifactorial, with interactions between genetic susceptibility (genome), individual immunological factors (immunome), gut microbiota (microbiome), and environmental exposure (exposome). [3,4]

The epidemiology of IBD might vary among countries, probably linked by the interaction between different gene pools and distinct environmental factor exposure. [2] In the last two decades, the necessity of developing therapies that can alter the natural history of the disease favored the development of research on the pathogenesis of IBD, resulting in a better understanding of the favorable interaction of genome, exposome, microbiome and immunome. [5,6]

ENVIRONMENTAL FACTORS (EXPOSOME)

The term exposome refers to all environmental factors that the individual is exposed throughout life. [7] Within this broad definition, the microbiome is considered an endogenous component of the exposome, while the other factors represent the exogenous exposome. Changes in the exposome favor the emergence of neoplasms and autoimmune diseases reinforced by non-modifiable genetic factors over the years. [6] The importance of this factor could be verified from migratory population studies, in which it was detected that adults' immigrants from countries with low incidence of IBD to countries with high incidence did not develop the disease. However, children or young people who migrated or belonging to the first generation of immigrants, had the same incidence of the disease as the local population. Therefore, it is concluded that despite sharing the same genetics, the life phase of the individual and the place of immigration are important factors for the IBD development. [6,8] Other environmental risk factors have been also associated with IBD, such as local geography, social and educational situation, infections, smoking, diet, stress, appendectomy, increased permeability of the mucous barrier and Intestinal dysbiosis. [5,6]

I. PERINATAL FACTORS

Type of delivery

The type of delivery affects the composition of the child's intestinal microbiome. The newborn acquires its intestinal microbiota primarily through maternal contact and during the first year of life. The intestinal microbiota of infants born vaginally is similar to that of the vagina and maternal intestine. Those born by cesarean delivery have intestinal microbiota similar to that of maternal skin. These differences are reflected in the mechanism of tolerance and development of the infant's immune system in this period and is perpetuated until 7 years of age. [9,10] It is postulated that cesarean delivery increases the risk of developing IBD when compared to those born by vaginal delivery. [11] However, a recent control case study did not confirm this hypothesis. [9]

Breastfeeding

The composition of the infant's intestinal microbiota differs between those fed breast milk and those with adapted formula. [12,13] The breast milk contains lactoferrin which acts in preventing bacterial proliferation resulting from iron absorption and immunoglobulin A, in neutralizing toxins and preventing the binding of bacteria to intestinal epithelium. [1,14] This protection factor to the development of IBD may be related to breastfeeding time (required period of 3 to 12 months), or the amount of milk ingested, but there are still controversies. [1, 15,16,17]

Vaccination

Previously, vaccination was believed to be responsible for reducing early childhood infections favoring the predisposition of immunological diseases. Viral and bacterial components existing in vaccines were also considered risk factors to a deregulated inflammatory response. [14,18] However, more recent studies do not confirm the association between childhood vaccination and the adult immunization against influenza H1N1 virus and IBD development. [18] Recent meta-analysis including 11 studies (2.400 IBD and 34.000 controls), did not show a significant increase of disease development risk after immunization with BCG, diphtheria, tetanus, chickenpox, pertussis, mumps, measles and rubella. [19] The reactivation or development of IBD related to vaccinations with inactivated viruses has not been established. [20]

II. HYGIENIC HYPOTHESIS

This hypothesis was originally proposed by Strachan in 1989, in which better hygienic conditions would lead to lack of exposure to enteric infections in childhood, favoring an inadequate response of the immune system in adulthood and the development of autoimmune diseases. [14,21]

The potential mechanisms have not yet been fully clarified, but it is known that failure in innate immunity and imbalances in the regulatory functions of T cells involved in acquired immunity are probably related. Moreover, changes in the microbiota from environmental stimuli can also mediate mechanisms of immunological tolerance. [14,17,22]

In developing countries, the emergence of IBD could be related to improvements of sanitary conditions, reduction in the prevalence of infectious and parasitic diseases, changes in dietary habits and quality of life, resembling what occurs in Westernized countries, where the prevalence of the disease is higher. [22] Thus, precarious hygiene conditions, low degree of industrial development and population clusters have been considered protective factors for the development of IBD. The prevalence of the disease has an inverse relationship in countries with a high infant mortality rate and high prevalence of infectious diseases. [8,16]

Individual living in urban area has a higher incidence of IBD in comparison to rural area, probably due to lower exposure to infectious agents and parasitosis. [23,24,25] Items related to the individual's housing conditions such as hot and piped water use has been used in the evaluation of hygienic hypothesis, with a strong association between the best socioeconomic condition and CD development, but not established for UC. [24]

Although the results of these studies are controversial, we can say that the hygienic hypothesis contemplates in a global way the different aspects directly or indirectly related to the environment, being an interface in the interaction with immunological and genetic factors involved in the genesis of IBD.

III. AIR POLLUTION

At the experimental level it was verified that air pollution can lead to a pro-inflammatory response, with effects on the intestinal epithelium and intestinal microbiota, favoring the onset of IBD. [26] The increase of carbon dioxide in atmospheric air may also be associated with a higher risk of early-onset CD. [27]

IV. MICROBIAL AGENTS

Helicobacter pylori

Helicobacter pylori gastric infection is suggested to be a protective factor for IBD. [23] This is probably due to the regulation of the expression of anti-inflammatory mediators promoted by this infection, which would benefit the host. This effect seems to be significant even among children who have not previously been exposed to antibiotics. [28] However, there are no data in the literature that prove the action of the bacterium in the degree of activity of the disease. [2]

Helminth infection

Similarly, helminth infection has been associated with a reduction in the prevalence of IBD, with an important role in immunoregulation of intestinal microbiota. [24] Helminths act on innate and acquired immunity, stimulating the immunological response of type Th2, with production of anti-inflammatory cytokines (IL-10 and IL-4), suppressing Th1 type response, predominant in CD and also lymphocyte response Th17. [1,29]

Mycobacterium Avium subspecies Paratuberculosis (MAP)

The MAP, agent of paratuberculosis, has been postulated as probable causal agent of CD due to the similarity between this and Johne's disease, manifested by granulomatous chronic ileitis in ruminants. Its transmission occurs through the consumption of contaminated raw meat and non-pasteurized cow's milk. Although this agent was isolated in intestinal tissue and blood samples from patients with CD, the exact relationship between MAP and CD remains inconclusive to date. [17]

Bacterial infections

Adherent invasive Escherichia Coli (AIEC) is able to survive and replicate in macrophages without inducing response from host cells, stimulating infected cells to release tumor necrosis factor (TNF-alpha), and can be found in patients with ileal CD. [1,5,20]

The previous acute gastroenteritis has been implicated as a trigger for the IBD development, as demonstrated in *Salmonella* and *Campylobacter* infections and may increase by up to three times the risk of disease's developing, mainly in the first year after infection. [2,13,30]

Another factor suggested in the increased risk of IBD appearance is the use of refrigerators because it allows an increase in contamination of food by psychotropic bacteria, which survive at low temperatures, such as *Listeria monocytogenes* and *Yersinia enterocolitica*. [24,31]

IBD patients have been shown to be more predisposed to enteric infections, particularly by *Clostridium difficile* (CDI). Infection by this agent has been gradually growing with significant morbidity and associated with relapses in disease activity. Patients hospitalized with IBD and CDI have a risk of mortality four times higher than patients without infection and, as a treatment, fecal microbiota transplantation has been considered, favoring the control of diarrhea and disease activity. [32]

Other infections

Paramyxovirus infection (measles virus) in the perinatal phase or childhood could cause infection of the mesenteric microvascular endothelium, and lead to a chronic granulomatous vasculitis, similar to CD. It was postulated that this could be only a co-factor capable of increasing the risk of CD, however this theme is still controversial. [17]

V. DIETARY FACTORS

The diet has been addressed as a possible influencing factor in the etiopathogenesis of IBD, because it may predispose individuals to a pro-inflammatory process, with alteration of the mucus layer and increased permeability of the intestinal barrier. [21,33]

Diet rich of fibers has a protective role in IBD, particularly with soluble fibers, but not with insoluble fibers. [21,26] A prospective cohort study describes that high-fat diet intake in soluble fibers can reduce the CD risk by up to 40%. [34] Fibers are metabolized by the intestinal microbiota into short chair fatty acids and capable of inhibiting the transcription of pro-inflammatory mediators, reducing the inflammatory process. [21] In turn, vegetables and fruits that are rich in antioxidants protecting the individual to develop the disease. [35]

Diet intake with high animal protein content may be associated with CD development due to higher lipid content, which is greater with a consumption of red meat in comparison to white or processed meats. [36] The diet rich in eggs and dairy products has already been described as risk factor to IBD, however the consumption of fish is considered as a protective factor for colonic and ileal CD. [37]

The excessive consumption of refined sugar and processed carbohydrates seems to have an implication of the higher risk for development of IBD. [26,37] The use of sweeteners such as saccharin and sucralose were also associated with a higher risk of IBD, and postulate so that they would act on the intestinal microbiota, inhibiting some strains and reducing the inactivation of digestive proteases, which would allow the reduction of the protective layer of mucus. [38] The final result would be the breakdown of the intestinal barrier and contrary hyperstimulation of the immune response of the mucosa.

Micronutrients, such as vitamins, are important allies in the nutritional support of patients with autoimmune diseases. Vitamin A acts in the migratory process of T and B lymphocytes to the intestine and vitamin D contributes to the increase of innate immunity in IBD by stimulating protein synthesis with antimicrobial management. They have immunoregulatory properties and are therefore described as a protective factor in IBD. [14,21,39]

Nowadays, vitamin D and the higher incidence of CD have been given great importance, especially in geographic regions with lower exposure to ultraviolet rays. [40] Deficiency of this vitamin was associated with higher morbidity and severity of IBD, justifying supplementation thereof. But there are still controversies whether this supplementation could act both in the prevention and treatment of IBD and the dose to be used. [39]

VI. HABITS OF LIFE

Obesity

The mesenteric adipose tissue of individuals with IBD presents morphological and functional changes where there is an increase in the infiltration of immune system cells, such as macrophages and T cells, which assist in maintaining the inflammatory bowel response and existing disease. [41] Obesity is also associated with intestinal dysbiosis, similar to that observed in IBD, with lower microbiome diversity and alterations in the predominant bacterial *phylums*. [42]

Physical activity

Recent studies propose that regular physical activity induces mechanisms of autophagy and immune system regulation, responsible for reducing the inflammatory process, through the production of anti-inflammatory cytokines. [43] Regular physical activity since childhood has been shown to reduce the risk of IBD development, with greater evidence for CD. [15] Some authors demonstrated a 44% of decrease in the risk of the disease, regardless of the effect of body mass index. [40]

Sleep quality

Recent studies have shown that sleep disorders and the interruption of the circadian cycle can trigger the activation of pro-inflammatory cytokines, and the emergence of several chronic inflammatory diseases. [44] Animal studies have shown that increased levels of interleukins 1(IL-1) and tumor necrosis factor (TNF-α) are associated with NREM sleep prolongation. Low levels of IL-1 induce NREM sleep, however at high levels there was a suppression of this phase of sleep, causing its fragmentation and interfering in their quality. Interleukins 6 (IL-6), in the acute phase of the disease, suppress the REM phase of sleep, promoting wakefulness in individuals with active IBD. [14]

Smoking

Smoking is considered an important environmental risk factor for IBD, capable of modifying the phenotype of diseases, with protective effect for UC and causal effect on CD. [21] It is active in the onset of IBD and its severity is an effect modulated by the sex and genetics of the individual, location and activity of the disease, daily consumption of cigarettes and concentration of absorbed nicotine. [23]

While in CD smoking interferes in the clinical course of the disease, in the UC its non-use (non-smokers and former smokers) favors the development and clinical worsening of the disease. [45]

VIII. SURGERIES

Appendicectomy

Although is not clear whether appendicitis increases this risk or if individuals at risk of CD tend to develop more appendicitis, it was described that 47% of individuals submitted to this surgery were more likely to develop CD than those who were not. [46] Some reports demonstrated this association mainly in the first postoperative year, when incipient CD could lead to undue appendectomies. [1,17,21] However, this risk appears to be reduced if appendectomy occurs before 10 years of age and CD patients submitted to appendectomy have a more frequently a proximal involvement, a worse prognosis, with higher risk of stenosis and surgeries. [47]

Regarding UC, appendectomy has been described as a protective factor mainly among children operated before the age of 10, when the risk of appendicitis is considerable. [1,17,21]

Tonsillectomy

Evidence of association of tonsillectomy with CD is weak, although a recent meta-analysis with 23 studies has shown a risk association for CD, and not an association with UC. [48]

IX. DRUGS

Antibiotics

The microbiome imbalance associated with antibiotic exposure is the main cause of the increase of the risk of developing IBD. A dose-response effect seems to be present, as well as an inverse relationship between the age at which exposure to antibiotics occurs and the increased risk of IBD. [49]

Evidence that antibiotics would interfere with IBD activity and recurrence is limited due to the diversity of substances with different spectrums of action. Which is why these are still widely used during infectious complications of IBD, especially in the presence of abscesses and perianal CD. [14]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

These drugs promote direct damage to the intestinal mucosa, increasing intestinal permeability by inhibition of cycloxigenase (COX), and reducing the production of prostaglandins. They may act as a trigger of the disease, favoring relapses in 20% of cases of quiescent IBD. [1,2,21,37]

Contraceptive

The association between the use of contraceptives and IBD development is not yet established. The thrombogenic property of the drug, related to gastrointestinal microinfarctions, may explain this hypothesis. [50] Estrogen stimulates an immunological response and proliferation of macrophages, while progesterone acts as immunosuppressive. [2,17] This action would not be reduced with dose reduction, but would be reversible with its discontinuity. [50]

Prolonged exposure to contraceptive use has already been shown to increase the risk of recurrence of CD by up to three times, and this effect is greater in smokers and reverted with the suspension of medication. [1,21] In relation to UC, this increase in risk appears to be lower than that of CD. [2]

Isotretinoin

It is a retinoid derived from vitamin A used in the treatment of severe acne and folliculitis and was implicated as a promoter of IBD. [1,51] Retinoids are verified to

be involved in regulating the immune response of the intestinal mucosa, but its mechanism is uncertain. [1] In 2010, CROCKETT et al. demonstrated a strong association between UC and previous exposure to high doses of isotretinoin, but not with CD. [52] However, this finding is not confirmed by further study. [23]

In conclusion, the detection of environmental risk factors and their interaction can provide an opportunity for preventive strategies against IBD development, mainly early in life. Other factors that can influence disease development later in life, such as tobacco use and diet, can be easily changeable. Future studies are necessary to detect and confirm the predictive risk factors to IBD expansion, mainly in developing countries where its incidence is increasing.

REFERENCES

1. Frolkis A, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, Fedorak RN et al. Alberta IBD Consortium. Environment and the inflammatory bowel diseases. Can J Gastroenterol. 2013; 27(3): e18-24.
2. Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol. 2013; 5: 237-247.
3. Kotze PG, Underwood FE, Damião AOMC, Ferraz JGP, Saad-Hossne R, Toro M, et al. The Progression of Inflammatory Bowel Disease Throughout Latin America: A Systematic Review. Clin Gastroenterol Hepatol 2020;18(2):304-312.
4. Martins AL, Volpato RA, Gomes MP. The prevalence and phenotype in Brazilian patients with inflammatory bowel disease. Gastroenterology. 2018;18(1):1-7.
5. Zhang Y-Z, LI Y-Y. Inflammatory bowel disease: pathogenesis. World J Gastroenterol 2014; 20(1):91–99.
6. Fiocchi C. Inflammatory Bowel Disease pathogenesis: where are we? J Gastroenterol Hepatol 2015; 30(Suppl 1):12–18.
7. Rogler G, Zeitz J, Biedermann L. The Search for Causative Environmental Factors in Inflammatory Bowel Disease. Dig Dis 2016; 34: 48-55.
8. Ko Y, Butcher R, Leong RW. Epidemiological studies of migration and environmental risk factors in the inflammatory bowel diseases. World J Gastroenterol 2014; 20 (5): 1238-1247.
9. Bernstein C, Banerjee A, Targownik L, Harminder Singh, J. Ghia, C. Burchill et al. Cesarean section delivery is not a risk factor for development of Inflammatory Bowel Disease: a population-based analysis. Clin Gastroenterol Hepatol 2016; 14(1):50–57.
10. Rautava S. Early microbial contact, the breast milk microbiome and child health. J Dev Orig Health Dis 2016; 7(01):5–14.
11. Roberts SE, Wotton CJ, Williams JG, Griffith M, Goldacre MJ. Perinatal and early life risk factors for Inflammatory Bowel Disease. World J Gastroenterol 2011; 17(6):743–749.
12. Mikhailov TA, Furner SE. Breastfeeding and genetic factors in the etiology of inflammatory bowel disease in children. World J. Gastroenterol 2009;15 (3): 270-279.
13. Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, Wilson DC. Systematic review: the role of breastfeeding in the development of pediatric Inflammatory Bowel Disease. J Pediatr 2009; 155:421–426.
14. Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environment risk factors for inflammatory bowel disease: Evidence based literature review. World J Gastroenterology, 2016; 22: 6296-6317.
15. Hlavaty T, Toth J, Koller T, Krajcovicova A, Oravcova S, Zelinkova Z et al. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of Inflammatory Bowel Disease: a slovak case-control study. United Eur Gastroenterol J 2013;1(2):109–119.
16. Guo AY, Stevens BW, Wilson RG , Russel CN, Cohen MA, Sturgeon HC et al. Early life environment and natural history of Inflammatory Bowel Diseases. BMC Gastroenterol, 2014;14(1):216.
17. Molodecky NA, Kaplan GG. Environmental risk factors for Inflammatory Bowel Disease. Gastroenterol Hepatol 2010;6(5):339–346.
18. Pineton de Chambrun G, Dauchet L, Gower-Rousseau C, Cortot A, Colombel JF, Peyrin-Biroulet L. Vaccination and risk for developing Inflammatory Bowel Disease: a meta-analysis of case-control and cohort studies. Clin Gastroenterol Hepatol 2015;13(8):1405–1415.
19. Hansen TS, Jess T, Vind I et al. Environmental factors in Inflammatory Bowel Disease: a case control study based on a danish inception cohort. J Crohns Colitis 2011; 5(6):577–584.
20. Berg AM, Dam AN, Farraye FA. A. Environmental Influences on the Onset and Clinical Course of Crohn's Disease - Part 2: Infections and Medication Use. Gastroenterol Hepatol 2013; 9 (12):803- 810.
21. Ye Y, Pang Z, Chen W, Ju S, Zhou C.The epidemiology and risk factors of inflammatory bowel disease. Int J Clin Exp Med 2015; 8(12): 22529- 22542.
22. Salgado VCL, Luiz RR, Boechat N, Schorr BC, Leão IS, Nunes T et al. Crohn´s disease environmental factors in the developing world: A case-control study in a statewide catchment area in Brazil. World J Gastroenterol, 2017; 23: 5549-5556.
23. Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for Inflammatory Bowel Disease. Am J Gastroenterol 2006; 101(5):993–1002.
24. Koloski, NA, Bret L, Radford-Smith G. Hygiene hypothesis in Inflammatory Bowel Disease: a critical review of the literature. World J Gastroenterol, 2008; 14(2):165–173.
25. Soon IS, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. BMC Gastroenterology 2012;12:51.
26. Dam AN, Berg AM, Farraye FA. Environmental Influences on the Onset and Clinical Course of Crohn's Disease – Part 1: An Overview of External Risk Factors. Gastroenterol Hepatol 2013; 9: 711-717.
27. Kaplan GG, Hubbard J, Korzenik J, Sands BE, Panaccione R, Ghosh S, et al. The Inflammatory Bowel Diseases and ambient air pollution: a novel association. Am J Gastroenterol. 2010; 105(11):2412–2419.
28. Rokkas T, Gisbert JP, Niv Y, O'Morain C. The association between Helicobacter pylori infection and Inflammatory Bowel Disease based on meta-analysis. United Eur Gastroenterol J, 2015: 3(6):539–550.

29. Helmby H. Human helminth therapy to treat inflammatory disorders- where do we stand? BMC Immunolog, 2015;16 (12):1-5.

30. Jess T, Simonsen J, Nielsen NM, Jørgensen KT, Bager P et al. Enteric Salmonella or Campylobacter infections and the risk of Inflammatory Bowel Disease. Gut 2011; 60(3):318–324.

31. Andersen V, Olsen A, Carbonnel F, Tjønneland A, Vogel U. Diet and risk of Inflammatory Bowel Disease. Dig Liver Dis 2012; 44:185–194.

32. Ananthakrishnan AN. Environmental risk factors for Inflammatory Bowel Disease Gastroenterol Hepatol 2013; 9(6):367–374.

33. Rapozo D, Bernadazzi C, Souza HSP. Diet and microbiota in inflammatory bowel disease: The gut in disharmony. World J Gastroenterol 2017; 23: 2124-2140.

34. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Korzenik JR, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's Disease and Ulcerative Colitis. Gastroenterology 2013;145(5):970–977.

35. Sobczak M, Fabisiak A, Murawska N, Wesołowska E, Wierzbicka P, Wlazłowski M et al. Current overview of extrinsic and intrinsic factors in etiology and progression of Inflammatory Bowel Diseases. Pharmacol Rep 2014; 66(5):766–775.

36. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing Inflammatory Bowel Disease: a systematic review of the literature. Am J Gastroenterol 2011; 106(4):563–573.

37. Legaki E, Gazouli M. Influence of environmental factors in the development of inflammatory bowel disease. World J Gastrointestinal Pharmacol Ther 2016;7: 112-125.

38. Qin X. Etiology of inflammatory bowel disease: A unified hypothesis. World J Gastroenterol 2012; 18 (15): 1708-1722.

39. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. Inflamm Bowel Dis 2015; 21 (11): 2708-2717.

40. Khalili H, Ananthakrishnan AN, Konijeti GG, Liao X, Higuchi LM et al. Physical activity and risk of Inflammatory Bowel Disease: prospective study from the Nurses' Health Study cohorts. BMJ 2013; 347: f6633.

41. Gonçalves P, Magro F, Martel F. Metabolic inflammation in Inflammatory Bowel Disease: crosstalk between adipose tissue and bowel. Inflamm Bowel Dis, 2015; 21(2):453–467.

42. Kim A. Dysbiosis: a review highlighting obesity and Inflammatory Bowel Disease. J Clin Gastroenterol 2015; 49(Suppl 1) :S 20–4.

43. Bilski J, Brzozowski B, Mazur-Bialy A, Sliwowski Z, Brzozowski T. The role of physical exercise in inflammatory bowel disease. The role of physical exercise in inflammatory bowel disease. Biomed Res Int. 2014; 2014 :429031.

44. Ali T, Orr WC. Sleep disturbances and Inflammatory Bowel Disease. Inflamm Bowel Dis 2014; 20(11):1986–1995.

45. Birrenbach T, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology and therapeutic implications. Inflamm Bowel Dis 2004; 10: 848-859.

46. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology, 2003; 124 (1): 40-46.

47. Cosnes J, Seksik P, Nion-Larmurier I, Beaugerie L, Gendre JP. Prior appendectomy and the phenotype and course of Crohn´s disease.World J Gastroenterol 2006;12 (8): 1235-1242.

48. Sun W, Han X, Wu S, Yang C. Tonsillectomy and the risk of Inflammatory Bowel Disease: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016; 31(6):1085-1094.

49. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE.Antibiotic exposure and Inflammatory Bowel Disease development among children: a population-based cohort study. Pediatrics 2012;130(4):e794–803.

50. Cornish JA, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of Inflammatory Bowel Disease: a meta-analysis. Am J Gastroenterol 2008;103 (9):2394–2400

51. Papageorgious NP, Altman A, Schoenfeld Y. Inflammatory Bowel Disease: Adverse Effect of Isotretinoin. IMAJ 2009;11: 505-506.

52. Crockett SD, Porter CQ, Martin CF, Sandler RS, Kappelman MD.Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-control Study. Am J Gastroenterol 2010; 105(9):1986-93.