Review Article

Crohn's disease

Increasing trend in Saudi Arabia

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ABSTRACT

في هذا الاستعراض حاولنا استكشاف العوامل الوبائية والعوامل المؤثرة على داء كرون مع إيداء اهتمام خاص بالمملكة. جمعنا البيانات المنشورة من المملكة العربية السعودية وأجرينا بحثا في Medline حول وبائيات وعوامل الخطورة والأسباب المحتملة لتزايد هذا الداء. هناك ازدياد في انتشار هذا الداء في جميع أنحاء العالم مع وجود أدلة واضحة تشير إلى ازدياد انتشاره في المناطق التي شهدت معدلات منخفضة من ذي قبل مثل آسيا بما في ذلك المملكة حيث ارتفع معدل انتشاره إلى 5 أضعاف على مدى العقود الثلاثة الماضية. وكانت النتائج مماثلة لما ذكر في المراجع العالمية. ويفترض أن العوامل البيئية بما في ذلك التدخين والنظام الغذائي ونمط الحياة له دور في حدوث انتشار داء كرون. نرى أن هناك حاجة ماسة لدراسات وبائية ميدانية واسعة النطاق للتعرف على دور العوامل الوراثية والبيئية وتنشيط دور مركز تسجيل حالات داء كرون. ونتوقع أن تغيير النظام الغذائي ونمط الحياة، فضلاً عن انتشار التدخين بين الأجيال الشابة لها دور هام في ارتفاع معدل انتشار هذا الداء في المملكة وسائر بلاد العالم.

We attempted, through systematic review to explore the epidemiology and risk factors of Crohn's disease (CD) with special attention to the Kingdom of Saudi Arabia (KSA). We selected articles that contained population-based, epidemiological, and clinical character studies of CD. We collected data concerned with the prevalence, demographic features, and the possible etiology of CD that might explain its emergence in KSA. The prevalence of CD in Western countries ranged between 11-43/100,000 with flawless evidence of CD prevalence emerging in previously low incidence areas like Asia. Prevalence in KSA has markedly increased over the last 3 decades. Combined ileal and colonic involvement was the most frequently affected site. Diet, smoking, drugs, and westernization of life are assumed to contribute to the pathogenesis. There is convincing evidence of CD emerging in Asia, including KSA. Westernization of lifestyle and smoking is probably the major contributing factors. Genetic studies are warranted.

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Inflammatory bowel disease (IBD) has previously been regarded as a disease of Western communities. A number of studies have shown a high IBD incidence and prevalence in the United States of America (USA), United Kingdom (UK), and Northern Europe.[1,2] On the contrary, IBD has been considered uncommon in Asian populations.[3,4] However, a rising incidence and prevalence have recently been observed with a strong epidemiological evidence suggesting westernization of lifestyle, changing eating habits, and smoking as possible explanation for the emergence of IBD in such communities. For instance, young Asians born in UK are at a significantly higher risk of developing IBD than indigenous Europeans. Also, first-generation Indian immigrants to the UK have had a higher chance of developing IBD than those living in India.[5,6] Several recent studies from various parts of the world have exposed an increasing incidence of Crohn's disease (CD). Crohn's disease is a chronic, transmural, granulomatous, patchy inflammatory bowel disease with a relapsing course associated with local and systemic complications. It may affect any part of the gastrointestinal tract; however, ileocecal region, terminal ileum, and the colon are the most frequently affected sites. Cohn's disease occurs in 3 various clinical types in form of inflammatory, stricturing, and penetrating type. Although genetic, environmental, and immunological mechanisms have been postulated, the etiology and exact pathogenesis remain unknown.

In the Middle Eastern Arab countries, the disease is yet not well-documented. Limited studies have

described single-center rates of disease that tends to be imprecise in providing true population rates. Hence, population-based studies that capture all health system contacts are more likely to reflect the true disease burden as opposed to studies conducted from hospitals. This review is partially aimed to explore the epidemiology of CD in the Kingdom of Saudi Arabia (KSA), and tried to elaborate on possible causes of CD's increasing trend in KSA. The drastic change in the diet and life style, as well as the increasing smoking among younger Saudi generation may partially be responsible for the increasing trend of CD in KSA.

Epidemiology. It is estimated that CD's lifetime prevalence in Caucasian population is 0.5-1%.[7] It is highest in America, North Europe, and UK, where it ranges from 100-200 per 100,000.[8,9] Individuals living at the Northern Hemisphere are more at risk to develop the disease. A north-south gradient of 11.5-8.0/100,000 has been reported by Shivanada et al.[10] Recently, various studies have shown an increasing incidence of CD in several European countries including Iceland,[11] France,[12] Croatia,[13] Denmark,[14] and Greece.[15] Studies from France and across Europe have shown also a north-south gradient.[10,16] In contrast, in Italy and Spain, there has been a rather homogenous incidence through the investigated localities.[17,18] Also, in the USA there has been an approximately 30% increase in the prevalence of CD in Minnesota since 1991.[19] Furthermore, the prevalence of CD in 9 million Americans from 33 states has been 43/100,000 in individuals below the age of 20 years, and 201/100,000 in adults with a north-south gradient.[20] However, despite of the significantly increasing rate for hospitalization of patients with CD, bowel resection has remained constant.[21] Recently, CD has also been reported from New Zealand,[22] Ethiopia,[23] and various Asian countries including Kuwait,[24,25] Lebanon,[26] Iran,[27,28] India,[29,30] Japan,[31] Singapore,[32] and China.[4] The most reliable data among the Asian countries comes from Japan and Korea. In Korea, the mean annual incidence rates of CD have increased significantly from 0.05 per 100,000 in 1986 to 1990, and to 1.34/100,000 in 2001 to 2005. The adjusted prevalence rates in 2005 was 11.24/100,000.[33] In Japan, the cumulative number of CD has risen 3 times since early 1990.[34]

Crohn's disease in KSA. Three decades ago, apparently KSA is free from IBD. Kirsner and Shorter[35] in 1982 have claimed that IBD is either rare or even not existing in KSA. However, in the same year, Mokhtar and Khan[36] have reported from Jeddah the first 2 cases of CD in KSA. Three years later, another 3 cases seen between 1979 and 1985 have been reported from Riyadh.[37] A further 7 cases have also been seen in Riyadh over a period of 6 years.[38] Subsequently, more reports with a larger number of patients have started to appear more in the literature.[39-47] Most cases have been encountered in the last 15 years.[42,46,47] These reports are summarized in **Table 1**. Ninety-five percent of the patients were Saudi nationals with a median age of 25.5 years. Males and females were almost equally affected with a ratio of 1:1.3.

Incidence. Various studies have shown a worldwide increasing incidence of CD in the US and several European, as well as African and Asian communities .[10,16,19,20,23,33,34] In KSA, publications started to appear in 1982 and onwards showing also an increasing incidence. In the 1980's the incidence has been 0.32/100,000, and has increased 5-folds in the 1990's to 1.66/100,000.[42] Currently the incidence calculated from the available studies in KSA was 1.91/100,000, which is probably underestimated due to under-reporting. This thought was supported by the higher prevalence in Riyadh (6.72/100,000), where most publications have originated. A more recent study has shown a drastic increase in CD with steady ulcerative colitis.[47] To obtain an exact incidence and prevalence rates, a database registry is essential.

Clinical presentation. From the available data from KSA studies, abdominal pain (86%), diarrhea (69%), and weight loss (58%) were the most frequent presenting symptoms (**Table 2**). Weight loss in the pediatric and adolescent age, as well as in adults was similar to what has been reported by Cuffari and Darbari[48] in the pediatric age group. Perianal disease (5%), arthralgia (5%), pallor (5%) and finger clubbing (2%) were also encountered, where other extraintestinal manifestation, such as erythema nodosum, jaundice, and sclerosing cholangitis were less frequent (1% each). Oral ulceration has been the primary presentation in 2 children from South India.[30] A high extra-intestinal manifestation rate of approximately 40% of the patients has been reported from Iran,[27,28] compared to a median value of 23% obtained from KSA reports. In the pediatric and adolescence age, extraintestinal manifestation in the range of 25-30% has been reported.[49] From the 2 studies we have previously reported from King Khaled University Hospital (KKUH) in Riyadh,[42,46] 10% of the patients had a family history, which was similar to those reported from Iran and Copenhagen,[14,27] and higher than that reported from Greece.[15] The patient's median age of 25.5 years reported from KSA was lower than that reported from Iran and Denmark.[14,27] Both genders were almost equally affected with a male to female ratio of 1:1.3, which concurred with the Italian

and Iranian findings.[17,28] Variable results with a female preponderance (1:1.69) have been reported from Greece.[15] The duration of symptoms was 36 in Saudis compared with 8.3 months in Danish patients. This could be due to diminished awareness and patient's education on CD in KSA, as it was until recently not documented compared to Denmark, where the disease is known for several decades with high incidence. Probably, for the same reason, the symptoms duration in Iranian series has been rather closer to our findings.[27]

Locations and phenotype. In comparison with Western results, there has been a variation in the site distribution according to Montreal Classification.[50] The ileum (L1) was affected in 22.8%, colon (L2) in 17.8%, ileum (L3) and colon in 55%, and upper gastrointestinal tract (GIT [L4]) in 3.8% (**Table 3**). While in this analysis, combined ileal and colonic involvement was the most frequent site (**Figure 1**), the colon has been more frequently affected in Western studies.[11,14,15] In contrast, Hyams data are rather closer to our results.[51] The behavior of the disease in KSA has been reported from 2 studies. We have previously found non stricturing-non penetrating type as the most frequently encountered type in 62%, while stricturing and penetrating types have been equally represented.[46] Similar findings have been reported from Greece and Hong Kong.[15,52]

What are the risk factors for developing CD? In a genetically susceptible host it is assumed that CD develops as a result of an interaction between environmental, microbial, and immunological factors. The gut is attacked by the immune system as a cross reaction against intestinal microbe antigens.[53] Susceptibility to develop CD constitutes a combination of environmental and genetic factors.[54] Among the genetic factors, nucleotide-binding oligomerization domain 2 (NOD2) encoded by caspase-recruitment domain 15 (CARD15) is considered as an important factor in the pathogenesis of CD. The NOD2 is involved in the innate immune response. It is a cytoplasmic protein, which acts as a sensor of muramyl dipeptide (MDP), derived from peptidoglycan (PGN), a constitute of bacterial wall.[55,56]

Table 1 - The frequency of Crohn's disease in the Kingdom of Saudi Arabia.

Author	Date reported	Institution	n	Median age	Male to female ratio
Mokhtar and Khan[36]	1982	KAUH, Jeddah	2	--	--
Mohamed et al[37]	1987	AFH, Riyadh	3	--	--
Hossain et al[38]	1990	KKUH, Riyadh	7*	32.4	1.3:1
Toonisi[39]	1993	KAUH, Jeddah	17†	10	1:1.4
Al-Gindan et al[40]	1996	KFUH, Al Khobar	12	23	1.4:1
Isbister and Hubler[41]	1998	KFSHRC, Riyadh	28	--	--
Al-Ghamdi et al[42]	2004	KKUH, Riyadh	77	25.3	1:1.33
Al Salamah[43]	2005	KSMC, Riyadh	28	34	1:2.1
Contractor et al[44]	2005	KFSH, Al Qassim	15	--	1:2
El Mouzan[45]	2006	KKUH, Riyadh	16†	--	--
Azzam et al[46]	2007	KKUH, Riyadh	42	26.5	1:1.38
Al Mofarreh and Al Mofleh[47]	2013	Dr. Al Mofarreh Polyclinic, Riyadh	455	27	2:1
Total			**695**	**25.5**	**1:1.3**

*no. of patients also included in reference #7, †pediatric, KAUH - King Abdulaziz University Hospital, AFH - Armed Forces Hospital, KKUH - King Khalid University Hospital, KFUH - King Fahad University Hospital, KFSHRC - King Faisal Specialist Hospital & Research Centre, KSMC - King Saud Medical City, KFSH - King Fahad Specialist Hospital

Table 2 - Clinical features of Crohn's disease in Saudi Arabia.

Reference	Toonisi[39]	Al-Gindan et al[40] 1996	Al-Ghamdi et al[42] 2004	Al Salamah[43] 2006	Contractor et al[44] 2006	Azzam et al[46] 2007	Al-Mofarreh et al[47] 2013	Average (%)
Abdominal pain	88	100	87	46	93	97	91	(86)
Diarrhea	70	58	78	43	73	93	66	(69)
Weight loss	50	83	53	--	60	50	51	(58)
Hematochezia	35	8	25	7	60	50	45	(38)
Fever	40	42	26	--	--	--	6	(29)
Perianal disease	23	25	--	7	33	9	25	(19)
Extraintestinal manifestations	28	25	--	--	--	10	29	(23)
Surgery	59	17	12	36	47	--	--	(34)

Table 3 - Anatomical distribution of Crohn's disease in Saudi Arabia according to Montreal Classification.

Site	Al-Gindan et al[40]	Al-Ghamdi et al[42]	Contractor et al[44]	Azzam et al[46]	Al-Mofarreh et al[47]	Total
Ileal (L1)	25	16	20	24	29	**22.8**
Colonic (L2)	8	6	27	31	17	**17.8**
Ileo-cecal (L3)	67	78	53	40	40	**55.6**
Upper GIT (L4)	0	0	0	5	14	**3.8**
Total	**100**	**100**	**100**	**100**	**100**	**100**

GIT - gastrointestinal tract

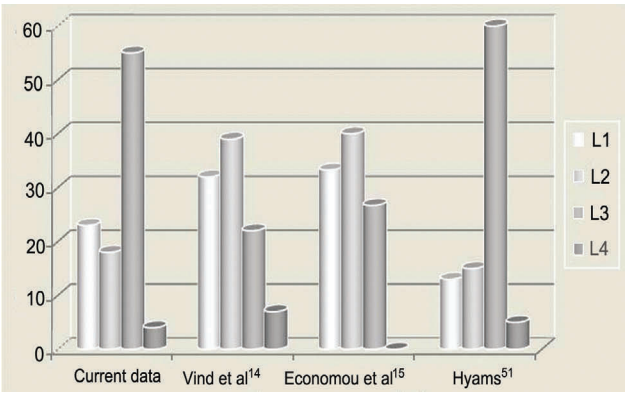

Figure 1 - Anatomical distribution of Crohn's disease according to Montreal classification. A comparison of the current data with the Western data. L1 - ileum, L2 - colon, L3 - Ileocecal, L4 - upper gastrointestinal tract

It is secreted via recognition of MDP and it protects the mucosa against bacterial invasion.[57] The role of NOD2/CARD15 genetic mutation is recognized as an important risk factor. Recently it has been reported that NOD2/CARD15 is rather a component of a complex risk factor constituting other genetic and environmental factors essential for the development and progress of the disease. The NOD2/CARD15 gene mutation is associated with younger age at the diagnosis in addition to an increased risk of ileal involvement, ileocecal resection, and reoperation. Therefore, its role as a predictor of relapse and its application in the preventive strategies has been suggested.[58] As a susceptibility gene, CARD15 acts also a disease-modifier gene in patients with CD.[59] Beside NOD2/CARD15, smoking, family history, and Jewish ethnicity is an independent risk factors for the development of the disease.[60] The same findings have also been observed by another group of investigators.[61] A univariate analysis has shown that some variables, significantly associated with CD include Jewish ethnicity, first degree relative with IBD, having ever smoked, or lived long with a smoker. The analysis may also support the hygiene hypothesis, where CD patients are less likely to have lived in a farm, drunk unpasteurized milk, and used well water.[62] Also, investigators from King's College, London School of Medicine in UK has reported smoking, family history, and CARD15 mutation as risk factors for CD.[63] Similar association was found in a recent study from KSA showing that the 3 major CARD15/NOD2 variant alleles, and the CD14 -159C/T polymorphism are associated with CD susceptibility in the Saudi population.[64] In contrast, a lacking association between NOD2/CARD15 and CD have been observed in different communities. For instance, Economou et al[15] has not found any change in the prevalence of CARD15 during their study period, which indicates an absence of genetic background, and therefore, they have suggested that the increasing incidence of CD is neither related to genetic nor to environmental factors. Similar findings with negative association between CD and genetic polymorphism of NOD2/CARD15, NOD 1/CARD4 and intercellular adhesion molecule 1 (ICAM-1) have also been reported from Tunisia, Turkey, and Japan.[65-67] Recent reports have suggested genetic variation in the gene encoding tumor necrosis factor superfamily, member 15 (TNFSF 15) genes in Japanese with IBD.[68] This indicates different genetic variations in different ethnic groups.

Crohn's disease develops as a result of an abnormal immune response of the bowel mucosa, triggered by environmental factors in individuals with gene variations.[69] Patients with CD may suffer of several neutrophils function defects with impairment of migration, recruitment, phagocytic function, and superoxide generation.[70-73] In addition to the immune system dysfunction, the development, and progression of CD are also affected by oxidative stress.[74] Oxidative stress is believed to play an essential role in the pathogenesis of CD as an etiological and/or a triggering factor. The increased activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) during disease activity, becomes normal during remission.[75] We have also found a significantly decreased SOD

plasma antioxidant activity in CD patients compared to the control group, which supports the hypothesis of enhanced oxidative stress and diminished antioxidant defense in CD.[76]

Furthermore, several blood cells have also been incriminated in the pathogenesis of CD. For instance, infiltration of neutrophils that occurs in response to chemokines, plays an important role in the pathogenesis.[77] Infiltration of polymorphonuclear cells (PMN) and mononuclear cells have been considered as the major pathological feature of IBD.[78,79] Persistent neutrophils infiltration is partially responsible for tissue damage.[79] In addition, noxious substances produced by neutrophils, including reactive oxygen species (ROS), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and proteases, also actively contribute to tissue injury.[80] Serum levels of growth-related oncogene (GRO-alpha) have been significantly higher in IBD (CD and UC) patients than in the healthy individuals, and could be important in enhancing the inflammatory process.[81] Besides neutrophils, other blood cells, such as platelets activating factor (PAF) and phorbol myristate acetate (PMA)-stimulated eosinophils are potentially primed and activated in CD.[82] Furthermore, the presence of activated mast cells found in the mucosa and muscularis propria in patients with CD suggests their role in the transmural inflammatory response, possibly in tissue remodeling.[83]

What are the possible explanations for the recently increasing incidence? Smoking, diet, drugs, and other environmental factors are assumed to contribute to the pathogenesis of CD in genetically susceptible individuals. Smoking and appendectomy has been non-debatable risk factors among unselected Danish population.[84] The association between smoking and CD is well established, while patients who continue to smoke, are at more risk to run a severe course and to have more complications, ex-smokers usually run a similar course to non-smokers.[85] Smoking, antibiotics, nonsteroidal anti-inflammatory drugs (NSAID) and enteric infections affect the composition of the gut microbiome, which is a key factor in IBD pathogenesis, or disrupts the intestinal barrier.[86] The role of dietary risk factors has been investigated by several authors. In a case-control study from Sweden, consumption of fast food and sucrose has been associated with CD.[87] Another case-control study from Netherlands has found a correlation between nutritional factors with special emphasis on cola drinks, chewing gum, and chocolate consumption, and CD.[88] Similarly in a multicenter case-control study from Japan, sugars, sweeteners, sweets, fats, and oils have been considered as dietary risk factors.[89] Furthermore, CD has been correlated with dietary fat, animal fat, n-6 polyunsaturated fatty acids, animal protein, milk protein, and ratio of 6 to n-3 fatty acids, less correlated with intake of total protein, not correlated with fish protein, and inversely correlated with intake of vegetable protein. The multivariate analysis has shown that increased intake of animal protein was the strongest independent factor.[31] Alzoghaibi et al[90] have reported a significantly increased IL-8 secretion from smooth muscle cells isolated from CD stricture in patients exposed to linoleic acid. The increased secretion of IL-8 has been blocked by antioxidants. These data suggest that the increased IL-8 secretion could play an important role in the inflammatory process by recruiting neutrophils to the stricture. Olive oil, low fat diet, and medium-chain triglycerides have been useful in CD.[91]

In a nationwide case-control study from Italy, the highest proportion of CD in females has been associated with lack of breastfeeding. In the same study in women, oral contraceptives have accounted for 11% of CD.[92] Additionally a co-twin control study from Sweden-Denmark has correlated CD with smoking, recurrent gastrointestinal infections, and hospitalization for gastrointestinal infections.[93] In familial CD in Belgium, appendicitis during adolescence, lack of oats, rye, and bran, unpasteurized cheese, and drinking well water has been considered as environmental risk factors.[94] Refrigeration has also been considered by a group of French investigators as a potential risk factor for CD. The cold chain hypothesis has suggested the importance of some bacteria species, identified in CD lesions, such as Yersinia and Listeria in addition to a defective host recognition of pathogenic bacteria components and excessive host response in the pathogenesis of CD.[69]

Vitamin D deficiency has been reported to be common especially in patients with longstanding CD and therefore, screening and appropriate supplement has to be considered in patient's management.[95] The risk of CD development, hospitalization and surgery, which increases with low vitamin D level, decreases with normalization.[96] In the Arabian countries data reporting the effect of different genetics or environmental factors contributing to the pathogenesis of IBD are scanty. A national data registry is initiated and is expected to help in understanding the epidemiology and genetics of this disease entity.

Recent advances. Recent studies have provided more information regarding the immunopathogenesis of CD. The CD is a predominantly T helper cells 1 and 17 (Th1 and Th17) process. Several factors

including luminal antigens, cells of the innate and adaptive immune system and their secreted mediators, as well as the intestinal epithelial cells are implicated in the pathogenesis of CD. The intestinal mucosal permeability is also altered in CD by IBD5 gene organic cation transporter (OCTN) and guanylate kinase discs large homolog 5 (Dlg5). This may induce an increased bacterial adherence and inadequate exposure of the mucosal immune system to bacterial products leading to the inflammatory process.[97]

Mucosal innate immune response has a pivotal role in early development of CD. The CD is associated with a general impairment of the innate immune response and a decreased production of IL-8 and IL-1β cytokines.[98] Intestinal macrophages are also involved via IL-23/INF-gamma axis.[99] Mucosal immune system aberrant response represents a critical initiating step of the inflammatory process in CD.[100] Recently, a number of susceptibility regions on several chromosomes have been identified and renamed as 9 IBD locus. Studying single-nucleotide polymorphisms (SNPs) in molecules involved in bacterial recognition seems to be essential to define genetic backgrounds at risk of IBD. The NOD1/CARD4, Chemokine ligand 20 (CCL20), IL-11, and IL-18 are novel genes that potentially may lead to the identification of therapeutic agents for the patients with IBD.[101] A recent growing interest has been demonstrated concerning the role of autophagy in innate immunity and pathogenesis of CD. Interaction of the potent autophagic inducer NOD2 and the autophagic regulator ATG16L1 seems to be essential for intracellular bacterial recognition initiation of the autophagic process and clearance of intracellular pathogens. In contrast, mutant NOD2 and ATG 16 L1 is associated with a defective induction of autophagy and clearance, which employs autophagy as an important factor in the pathogenesis of CD.[102-105]

Recently, INF-gamma has been detected in a proportion of patients with fistulizing CD. This suggests an influential role of INF-gamma polymorphism in CD.[106] Other factors involved in the protection from CD include the recently discovered susceptibility IL23R allele.[107]

In conclusion, there is a worldwide increase of CD incidence. Recent studies from KSA have also documented the presence and the increasing incidence of the disease. The role of genetic and environmental risk factors is obvious. Smoking and dietary factors among others documented in Western communities is most likely the responsible factors for the rapidly increasing rate in KSA. National data registry is mandatory to study the incidence, prevalence, risk factors management, and the natural course of CD in KSA. This was recently started in our institution at the King Khalid University Hospital, Riyadh, KSA.

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