

Ethnic Variations in Inflammatory Bowel Diseases Among Israel's Populations

Mahmud Mahamid MD^{2,4,5*}, Ariella Bar-Gil Shitrit MD^{1*}, Hana Amara MD³, Benjamin Koslowsky MD¹, Rami Ghantous RN^{4,6} and Rifaat Safadi MD⁷

¹Department of Gastroenterology, Shaare Zedek Medical Center, Jerusalem, Israel

²Department of Internal Medicine and ³Gastroenterology Institute, Nazareth Hospital EMMS, Nazareth, Israel

⁴Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

⁵Department of Internal Medicine and ⁶Liver Unit, Holy Family Hospital, Nazareth, Israel

⁷Department of Gastroenterology and Liver Diseases, Hadassah–Hebrew University Medical Center, Ein Kerem Campus, Jerusalem, Israel

ABSTRACT: **Background:** Crohn's disease and ulcerative colitis are the two major classic presentations of inflammatory bowel diseases (IBD). Studies have shown a wide variation in the incidence and prevalence attributed to different geographic and ethnic populations.

Objectives: To assess the clinical characteristics of IBD among Arabs in Israel and to compare them to characteristics of IBD among Ashkenazi Jews.

Methods: This retrospective, comparative study compared the clinical characteristics of IBD among 150 Arabs from the Holy Family Hospital and the Nazareth Hospital EMMS, both located in Nazareth, Israel, to those of 97 age- and sex-matched Ashkenazi Jewish patients from Shaare Zedek Medical Center, Jerusalem, Israel.

Results: The Arab cohort, which included 106 patients (70%) with Crohn's disease and 44 (29%) with ulcerative colitis, was compared to 97 Ashkenazi patients (81% with Crohn's disease and 17% with ulcerative colitis) ($P < 0.05$). Alcohol consumption was found in both groups, but Arabs smoked more (46% vs. 12%, respectively, $P < 0.05$). Obstructive phenotype was lower in Arabs (10% vs. 32%, $P < 0.05$). 5-aminosalicylic acid and anti-tumor necrosis factor alpha were prescribed for the Arab and Ashkenazi groups (89% and 21%, respectively). The need for surgical intervention due to disease severity and/or complications was not significant (22% vs. 24%).

Conclusions: Despite similar reports of NOD2/CARD15 mutations, Crohn's disease is more common than ulcerative colitis within the Arab-Israeli population. Increased smoking rates may explain milder disease severities in Arabs, as reflected by lower obstructive pattern and frequent use of milder therapeutic modalities.

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KEY WORDS: Crohn's disease, ethnic differences, inflammatory bowel diseases (IBD), ulcerative colitis

Crohn's disease and ulcerative colitis are the two major classic presentations of inflammatory bowel diseases (IBD). Many studies have shown a wide variation in the incidence and prevalence attributed to different geographic and ethnic populations [1,2]. This finding is also true among the rate of IBD in various ethnic groups in Asia. It appears that certain racial groups are more susceptible to IBD. While there is a genetic predisposition, environmental factors may be responsible for these differences. Moreover, the clinical phenotypes, response to therapies, and rates of complications may differ among distinct ethnic groups [3-7].

Arab countries have been marked as an area with low incidence of IBD, although biases may arise from low diagnostic awareness, and a high incidence of infectious diarrhea [3]. Nonetheless, it is clear that the incidence and prevalence rates of IBD among Arabs in Israel are low compared with that of the Ashkenazi Jewish population [4,5]. Approximately 20% of the population in Israel is Arab [4,5]. Available studies suggest an increased incidence of IBD among Arabs living in Israel compared with Arabs in other countries. Published data suggest that the disease course of ulcerative colitis is milder in Arabs from Middle Eastern Arab countries compared to that reported in Western countries, whereas Crohn's disease has a similar clinical course to that described in Western countries [8-11].

The Jewish population in Israel is heterogeneous and is historically divided into two major groups: Ashkenazi Jews from Central and Eastern Europe and non-Ashkenazi Jews from the Mediterranean, North Africa, and Asia. The incidence and prevalence of inflammatory bowel diseases has been reported to be twofold to fourfold higher in Ashkenazi Jews than in non-Jewish Caucasians [12].

Previously published data showed that the carrier rate of the NOD2 polymorphisms (R702W, G908R, and 1007fsInsC) is higher in Ashkenazi Jewish Crohn's disease patients than in non-Ashkenazi Jews [13]. In addition, Ashkenazi Jews display a 1.9-fold higher frequency of variant MTHFR 677T than do non-Ashkenazi Jews [14,15].

*The first and second authors contributed equally to this study

The aims of this study were to assess the clinical characteristics of IBD among Arabs in Israel, and to compare the disease characterization to that of Ashkenazi Jews with IBD.

PATIENTS AND METHODS

This retrospective, comparative study compared the clinical characteristics of IBD among 150 Arabs from the Holy Family Hospital and the Nazareth Hospital EMMS, both located in Nazareth, Israel, to those of 97 age- and sex-matched Ashkenazi Jewish patients from Shaare Zedek Medical Center in Jerusalem, Israel. Informed consent was waived due to the non-interventional study design.

Following the approval of the local ethics review board at EMMS Nazareth Hospital, this study included all IBD patients seen at that medical center from January 2005 to December 2014. The data collected from medical records included age, gender, anthropometric parameters, disease type, disease extension, endoscopic and radiological findings, pathology and laboratory test results, disease management, complications, need for surgical intervention, hospitalizations, and risk factors for IBD.

The diagnosis of IBD and the ulcerative colitis or Crohn’s disease subtype were confirmed through clinical, endoscopic, pathological, and radiological investigations. Crohn’s disease was defined as the presence of discontinuous lesions, aphthous ulcers, and cobblestone pattern on endoscopy. Histological evidence of Crohn’s disease included focal ulcerations with acute and chronic inflammation. Radiological evidence included strictures, perforations, and fistulas. Endoscopic findings of ulcerative colitis included continuous superficial lesions, proximal extension from rectum, loss of vascular pattern, and areas of spontaneous bleeding. Histological evidence of ulcerative colitis included crypt abscesses and gland atrophy. Disease extension was defined using the terms proctitis, left side colitis, and pancolitis for ulcerative colitis. Crohn’s disease extension, however, was described by small bowel involvement only, ileocolitis, and colitis.

Complications of IBD and the presence of extra-intestinal manifestations were recorded. Disease management was categorized as medical, surgical, or both. Medication history was obtained through a careful review of clinical records. Anthropometric measurements collected included height, weight, and body mass index.

Patients were considered active smokers when current cigarette use was confirmed at the most recent documentation of smoking history. Patients were considered prior smokers if they reported previous cigarette use but denied current smoking at the most recent documentation of smoking history. Nonsmokers were those who denied any history of cigarette use. A similar classification was used for alcohol consumption.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 19 (SPSS, IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation. Chi-square was used to test differences in categorical variables between the two groups, and analysis of variance (ANOVA) or *t*-test was used for comparisons of continuous variables. A multiple logistic regression analysis was used to determine the association between the examined factors and cardiovascular risk. A *P* value of < 0.05 was considered significant.

RESULTS

The study included 248 ethnically diverse subjects: 150 (61%) were Arab IBD patients and 97 (39%) Ashkenazi Jewish IBD patients. The Arab cohort included 28% (42/150) Muslims and the rest identified as Christian Arabs. Other baseline characteristics of the two groups are presented in Table 1. The percentage of males in the Arab group was higher. Among the Arab patients, 106 (70%) were diagnosed with Crohn’s disease and 44 (29%) with ulcerative colitis, compared to 81% and 17%, respectively in the Ashkenazi Jewish cohort (*P* < 0.05). Mean age at diagnosis was 19 ± 12 years among the Arab group and 20 ± 10 years for the Ashkenazi Jewish group. Mean age at the end of follow-up was 23 ± 11 vs. 32 ± 10 years, respectively (*P* < 0.05). This difference was due to shorter follow-up periods for the Arab patients of 3 ± 7.1 vs. 6 ± 11 years, respectively (*P* < 0.05). Family history of the disease was found significantly less often in Arab IBD cases (7% vs. 16%, respectively, *P* < 0.05). Smoking was significantly more common among Arab IBD patients (70/150, 46%) compared with 7% (7/97) of Ashkenazi Jews (*P* < 0.05). Reported alcohol consumption was lower (5%, 8/150) among Arab patients compared to 9% (9/97) among the Ashkenazi Jewish cohort (*P* < 0.05).

The disease manifestations and natural history showed different outcomes in both groups [Table 2]. Obstructive phenotype

Table 1. Patient characteristics of both study groups

Characteristic	Arab group N=150	Ashkenazi Jewish group N=97	<i>P</i> value
Male gender (%)	80 (53%)	56 (58%)	NS
Age at end of follow-up, median ± SD, years	23 ± 11	32 ± 10	< 0.05
Age at diagnosis, median ± SD, years	19 ± 12	20 ± 10	NS
Disease duration, mean ± SD, years	3 ± 7.1	6 ± 11	< 0.05
Crohn’s disease (%)	106 (70%)	79 (81%)	< 0.05
Family history of inflammatory bowel disease (%)	11 (7%)	15 (16%)	< 0.05
Current smoker (%)	70 (46%)	7 (7%)	< 0.05
Alcohol consumption	8 (5%)	9 (9%)	< 0.05

NS = not significant, SD = standard deviation

Table 2. Disease characteristics of both study groups

Characteristic	Arab group N=150	Ashkenazi Jewish group N=97	P value
Obstructive phenotype (%)	15 (10%)	31 (32%)	< 0.05
Ileocolitis or Crohn's colitis (%)	58 (38%)	48 (50%)	< 0.05
Extra-intestinal manifestation (%)	28 (19%)	8 (8%)	< 0.05
Surgical intervention (%)	33 (22%)	23 (24%)	NS
5-amino salicylic acid (%)	134 (89%)	20 (21%)	< 0.05
Immunomodulatory drug (%)	34 (23%)	15 (16%)	< 0.05
Biological treatment (%)	6 (4%)	41 (42%)	< 0.05

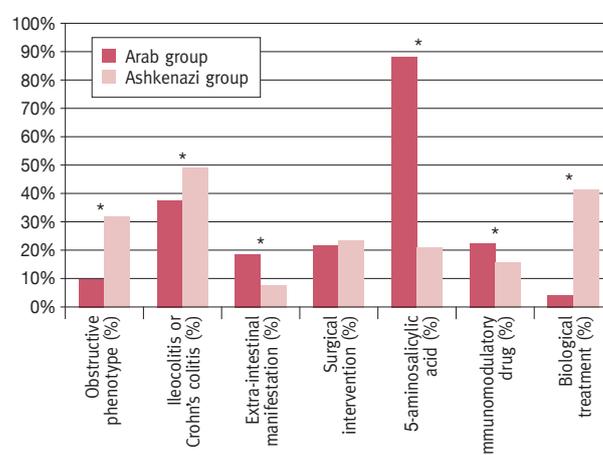
NS= not significant

was noted in 10% of the Arab cohort (15/150), compared with 32% (31/97) of the Ashkenazi Jewish cohort ($P < 0.05$). Disease extension also differed. Most Arab Crohn's disease patients (38%, 58/150) had ileocolitis or colitis, while 50% (48/97) of the Ashkenazi Jewish had small bowel disease and ileocolitis. Proctitis and/or left side colitis was present in 84% of Arab ulcerative colitis patients compared with 55% in Ashkenazi Jews, who had pancolitis. Extra-intestinal manifestations recorded within 19% (28/150) of the Arab group and 8% (8/97) of the Ashkenazi Jewish cohort. Interestingly, group skin manifestation and axial arthropathy were high (84%) in the Arab group with regard to extra-intestinal manifestation in the Arab group than Ashkenazi Jewish group. The rate of hospitalization due to disease exacerbation was less frequent among Arabs, but without clinical significance (54% vs. 70%, respectively). The need for surgical intervention due to disease severity and/or complications was not significant between the two groups (22% vs. 24%).

Medical therapy showed significantly higher use of 5-amino salicylic acid (5-ASA) among the Arab group 89% (134/15) compared with only 21% (20/97) of the Ashkenazi Jewish group ($P < 0.05$). Immunomodulators were used more often among Arabs (23%), compared to 16% among Ashkenazi Jews ($P < 0.05$). The use and need for steroids was similar between the Arab group and Ashkenazi Jewish (41% vs. 42%, respectively). However, the use of biological drugs was significantly lower among the Arab group than the Ashkenazi Jewish group (4% vs. 42%, respectively; $P < 0.05$). The main results are presented in Figure 1.

DISCUSSION

Despite similar reported reports of NOD2/CARD15 mutations, our study showed that Crohn's disease and ulcerative colitis are more common within the Arab-Israeli population than the Ashkenazi Jewish-Israeli population. The fact that ulcerative colitis is less common among Arabs may be due to detection bias, as symptoms of ulcerative colitis can be milder and fewer patients may seek medical advice; however, among Crohn's dis-

Figure 1. The main differences among the both study groups* $P < 0.05$

ease, Arabs subjects the higher rates of smoking controversially is associated with milder disease severities in Arabs, as reflected by lower obstructive pattern and frequent use of milder therapeutic modalities.

The incidence of IBD is increasing among ethnic populations in whom this disease was previously considered rare [10]. Israeli population-based studies found a high incidence and prevalence of IBD. In the past, both ulcerative colitis and Crohn's disease were more common in Ashkenazi than in Sephardi Jews. However, later studies demonstrated that the IBD rate has increased among all ethnic groups in Israel, including Arabs and Ethiopian Jews [11-13].

To the best of our knowledge, the present study is the first to detail the clinical characteristics of Arab IBD patients in Israel in comparison with the disease manifestations and natural history of Ashkenazi Jewish IBD patients. We found significant differences among the characteristics of IBD in the two groups. The prevalence and incidence of IBD among Israeli Arabs are still high, but we also believe that the disease presentation, location, severity, and management differ in this ethnic group [13].

According to our findings, as well as previously published data, the prevalence and incidence of IBD are low among the Ashkenazi Jewish population compared with the Arab population in Israel. Although Crohn's disease predominates in both ethnic groups, it appears to be less frequent among Israeli Arabs. Alternatively, ulcerative colitis is more prevalent in the Arab population. The increased incidence of Crohn's disease among Arabs may be related to environmental factors. Interestingly, despite smoking as a risk factor for Crohn's disease exacerbation and severity, the number of smokers was significantly higher among Arabs. Paradoxically, disease phenotype appears to be milder among Arabs. This finding might indicate that smoking has a protective effect.

The location and extension of the IBD was distinct in the groups. While proctitis (involvement of rectum) and left side colitis were predominate among Arabs with ulcerative colitis, pancolitis was also less predominate among Ashkenazi Jewish patients. Similarly, Crohn's disease was located more proximally in Ashkenazi Jews with isolated small bowel involvement and/or ileocecal involvement, compared with colonic and/or ileocolonic involvement among Arabs.

The prevalence of extra-intestinal manifestations was not similar between the two groups, but skin manifestations and axial arthropathy were more common among Arabs compared to peripheral arthropathy among Ashkenazi Jews.

The natural history of the disease appears to be distinct in both ethnic groups. The obstructive pattern is the predominant characteristic of Crohn's disease among Ashkenazi Jewish patients. This form of disease presentation was rare among Arabs, which may explain the higher disease severity among Ashkenazi Jews and the therapeutic variations.

Medical management was clearly different between the groups. The 5-ASA was the most common drug prescribed in the Arab group, while only a minority of Ashkenazi Jewish received this drug. However, compared with Ashkenazi Jews, more Arabs received immunomodulatory drugs. Yet, immunomodulatory drug treatments between the two groups was not significant; however, Ashkenazi Jews received more biological treatments. This difference may reflect milder disease and colonic location of Crohn's disease among Arabs compared with Ashkenazi Jews. Therefore, intensive therapy for more severe Ashkenazi phenotypes is compensated for the need of hospitalization and surgical intervention in both ethnic groups.

LIMITATIONS

Our study is limited by its retrospective character. Other limitations were the small population size. There might have been a selection bias, as subjects were recruited from patients who visited the hospital for health examinations; thus, they were more concerned about their health status. Moreover, the comparison between the treatment modalities in both ethnic groups is problematic as data were collected from different therapy centers with varying therapy protocols.

CONCLUSIONS

We found different characteristics and natural history of IBD between the Arab and Ashkenazi Jewish populations in Israel. Crohn's disease is more prevalent than ulcerative colitis in Arabs.

Disease manifestations appear to be less severe, with more use for and need of 5-ASA, and a low rate of biological drug use. Smoking might be suggested as a protective factor among this ethnic group, although most were Crohn's disease patients.

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Correspondence

Dr. M. Mahamid

Dept. of Internal Medicine, Nazareth Hospital EMMS, Nazareth 16100, Israel

Phone: (972-4) 602-8851

Fax: (972-4) 755-9051

email: mahmudmahamid@yahoo.com

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“There is a fountain of youth: it is your mind, your talents, the creativity you bring to your life and the lives of the people you love. When you learn to tap this source, you will have truly defeated age”

Sophia Loren (born 1934), actor and singer