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Original Article

Risk Factors, Frequency and Outcome of New-Onset Diabetes Mellitus in Inflammatory Bowel Disease: Three-Year Follow-up Study

Ainan Arshad[1], Muhammad Ehteram ul Haq,[2] Ahmed Ayaz1,[3] Zainab Abdul Rahman,[4] Sarosh Abid Farooqui,[5] Muhammad Saleem[6]

[1]Department of Internal Medicine, Aga Khan University, Karachi, Pakistan.
[2]Department of Emergency Medicine, Usman Memorial Hospital, Karachi, Hospital
[3]Medical College, Aga Khan University, Karachi, Pakistan
[4]Medical College, Dow University of Health Sciences, Karachi, Pakistan
[5]Medical College, Sindh Medical College, Karachi, Pakistan
[6]Department of Endocrinology, diabetes and metabolism, Aga Khan University, Karachi, Pakistan.

Abstract

Background: Research was conducted to analyze the Risk factors, frequency and outcome of new-onset of diabetes mellitus in inflammatory bowel disease patients.

Methods: This review was conducted at a Tertiary care setup of Pakistan, it is a retrospective study of evaluation of IBD patients presented during the period of 2012-2017. Medical records were then analyzed to determine if they developed new-onset of diabetes mellitus within three years. If so, outcome measures were compared in the diabetic and non-diabetic group.

Results: 364 patients were enrolled in the study. 206 (57%) were males and 158 (43.4%) were females; average mean age for diagnosis of IBD patients was 28.5 ± 8.0 years. 19 (5.2%) patients went on to develop new-onset DM. Majority of patients were of the ulcerative colitis. Risk factors for developing new onset of DM in IBD patients were female gender (p= 0.026), previous history of hypertension (p= <0.001) and previous history of ischemic heart disease (p= 0.004). Patients who developed DM had a significantly higher number of flares within the next three years (p= 0.001).

Conclusion: We concluded that patients of Inflammatory Bowel Disease (IBD) are at a significant risk of developing new-onset DM irrespective of steroid treatment. Furthermore, these patients are prone to an increased number of flares in the long run. Hence, we believe that these results warrant early screening and watch for glycemic control in IBD to improve long-term outcomes.

Keywords: Diabetes Mellitus, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis

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Corresponding Author: Ainan Arshad, **Email:** ainan_arshad@hotmail.com

Introduction

Inflammatory bowel disease (IBD) is an autoimmune condition related to inflammation of the GI tract.[1] The exact cause of inflammatory bowel disease remains unclear. However, it has been associated with complex interactions between gut microbiome, genetics and environmental factors.[2] Extraintestinal manifestations have also been reported with involvement of multiple organs including joints, eyes, skin, liver, lungs and pancreas.[3] It has also been related to other metabolic and endocrine manifestations including metabolic bone disease, hypogonadism and insulin resistance.[4] Kang and his colleagues, in their nationwide population-based study reported an increased

risk of diabetes mellitus (DM) in IBD patients irrespective of the steroid usage.[5] It has been hypothesized that development of DM could lead to increased complications, poor outcomes and ultimately, a poor quality of life. There are limited number of studies that have studied this relationship. Hence, we conducted this study to analyze the risk factors, frequency and outcome of DM in IBD patients.

Methods

This review was conducted at a tertiary care setup of Pakistan, it is a retrospective study in which we evaluated the electronic health records to identify all adult patients presenting with the diagnosis of IBD during the period of 2012-2017 were enrolled in the study. We excluded all patients already diagnose with diabetes mellitus in order to evaluate the effect of newly developed diabetes. Furthermore, patients were also excluded if baseline HbA1C, fasting plasma glucose and random plasma glucose values were unavavailable.

Patients data was collected from medical records on a pre-designed proforma which recorded the age, demographics, patient and hospitalization characteristics and number of flares. The trend in HbA1C, fasting plasma glucose and random plasma glucose values were then monitored till three years after diagnosis. We used American Diabetes Association guidelines in setting parameters for diagnosis of diabetes mellitus which is characterized by fasting serum glucose of greater than or equal to 126 mg/dL, HbA1C of greater than or equal to 6.5% or a random serum glucose of greater than or equal to 200 mg/dL with classic symptoms of hyperglycemia.[6] Inpatient and outpatient records were also hand searched to determine diagnosis of diabetes. This review was approve by the Ethical Review Committee (Study number: 2019-1408-3533)

IBM SPSS 22.0 was used for data analysis. Clinical characteristics were compared between the diabetic and non-diabetic groups, we used chi-square test for categorical and student T test for continuous variables. Multivariable logistic regression was use to determine association between patient hospitalization characteristics and diabetes development.

P-values$\geq$0.05 were consider significant.

Results

512 patient were diagnosed with IBD during the period 2012-2017. 364 patients match the inclusion criteria and were included in the study. 206 (57%) were males and 158 (43.4%) were females; average mean age for diagnosis of IBD patients was 28.5 ± 8.0 years. UC accounted for 91% of all the IBD patients. Table I presents the demographics and clinical characteristics of the patients.

Of the 364 patients, 19 (5.2%) develop new-onset of Diabetes mellitus (Figure 1). All of these patients were of the UC subtype. Female gender [OR: 2.989 (1.110-8.048); p= <0.026], previous history of hypertension [OR: 6.891 (2.223-21.364); p= <0.001] and history of Ischemic heart disease [OR: 19.111 (1.148-318.078); p= <0.004] were significantly associated with a risk of developing new-onset of Diabetes Mellius. Patients with newly onset diabetes were at risk of having higher number of flares in three years (2.8 ± 2.7vs 1.4 ± 1.8; p= 0.001). Smoking, steroid or alcohol association was not found in development of Diabetes Mellitus. Table II compares the clinical characteristics and hospitalization factors of patients with diabetic and non diabetic groups.

Table 1: *Frequency of Allergies in a Sample of 300 Medical Students in Lahore, Pakistan, in 2014*

Characteristics	Overall (N = 365)	Crohn's (N = 33)	UC (N = 331)
Demographics			
Age on onset (years)	28.5 ± 8.0	29.03±10.8	28.45± 7.5
Male	206 (56%)	23 (70%)	183 (55%)
Female	158 (44%)	10 (10%)	148 (45%)
Hypertension	22 (6%)	0(0%)	22(7%)
IHD	2 (0.5%)	0(0%)	2(0.6%)
Chronic Kidney Disease	1 (0.3%)	0(0%)	1(3.2%)
Malignancy	6 (2%)	0(0%)	6(2%)
Stroke	4 (1%)	0(23%)	4 (1%)
Smoking	20 (6%)	3(9%)	17(5%)
Alcohol	5 (1%)	2(6%)	3(1%)
Clinical Characteristics			
Mean number of flares	1.4±1.9	0.9 ± 2.1	1.5 ± 1.9
Surgical Resection	22 (6%)	2(6%)	20(6%)
Steroids	141 (39%)	14(42%)	127(38%)
Mesalazine	295 (81%)	22(67%)	273(82%)
Azithioprine	138 (38%)	8(24%)	130(39%)
Inflixamab	9 (3%)	4(12%)	5(2%)
New onset Diabetes	19 (5%)	0 (0%)	19 (6%)

Discussion

In our study, we evaluated the risk factors, frequency and outcomes of new-onset of diabetes mellitus in IBD patients. Of the 364 patients that were included, 5% (n = 19) developed diabetes. The diagnosis of DM in IBD was 5% which is comparatively higher to previous large scale studies conducted. A Korean

Table 2: *Risk factors for Developing Diabetes in IBD Patients (n = 364)*

Characteristics	Developed DM (N = 19)	Did not develop DM (N = 345)	P-value	Odds Ratio (95% CI)
Gender			0.024	2.989 (1.110-8.048)
Male	6 (32%)	200 (58%)		
Female	13 (68%)	145 (42%)		
Hypertension	5 (26%)	17 (5%)	<0.001	6.891 (2.223-21.364)
IHD	1 (5%)	1 (0.3%)	0.004	19.111 (1.148-318.078)
Stroke	1 (5%)	3 (0.8%)	0.074	6.333 (0627-63.950)
Chronic Kidney Disease	0 (0%)	1 (0.3%)	0.814	0.948 (0.925-0.971)
Malignancy	0 (0%)	6 (17%)	0.562	0.947 (0.924-0.970)
Smoking	0 (0%)	20 (6%)	0.280	0.945 (0.921-0.969)
Alcohol	0 (0%)	5 (2%)	0.597	0.947 (0.924-0.971)
IBD Subtype				
CD	0 (0%)	33 (9.6%)		
UC	19 (100%)	312 (90.4%)		
On steroids	10 (52.6%)	131 (37.9%)	0.202	1.815 (0.719-4.584)
Surgical Resection	1 (5.3%)	21 (6.1%)	0.883	0.857 (0.109-6.735)
Number of Flares	2.8 ± 2.7	1.4 ± 1.8	0.001	
Mean Hb	11.6 ± 1.9	12.3 ± 7.9	0.681	
Mean CRP	3.1 ± 3.6	2.5 ± 4.0	0.539	
Mean Total Cholesterol	158.9 ± 30.5	162.8 ± 35.8	0.781	
Mean LDL	116.12 ± 41.0	103 ± 41.3	0.435	
Mean Triglycerides	126.4 ± 51.5	125.9 ± 52.6	0.982	
Mean HDL	44.3 ± 9.8	43.9± 9.0	0.923	
Mean CR	0.8 ± 0.3	0.7 ± 0.2	0.675	

nationwide population-based study by Kang et al, was the first ever to evaluate the risk and incidence of DM in patients of IBD. They studied 8070IBD patients across Korea and reported a 0.2% incidence of DM66.

The relationship between IBD and Diabetes mellitus in the past has been ambiguous and studies have shown conflicting results. Halling and colleagues conducted a cross-sectional study in Denmark, evaluating 47,325 IBD patients and concluded that DM was significantly associated with both types of IBD.[7] In another study evaluating 1200 pediatric IBD patients, the prevalence of DM was higher than in controls (OR= 2.7; CI= 1.1–6.6).[8] On the other hand, Weng et al. assessed 12,601 IBD patients and concluded that the odds for Diabetes was not significantly increased in IBD.[9] Additionally, a cross-sectional study conducted in the United States did not find any association between IBD and new-onset of DM.[10]

IBD has shown an increase in the risk of DM, but exact mechanism is still unclear. Possible explanation behind the development of diabetes mellitus in inflammatory bowel disease patients can be a common origin as both are autoimmiune disorder. Some studies have suggested that chronic inflammation and dysbiosis in IBD and is the driving force behind development of DM.[11] Another theory hypothesizes that due to increase in permeability of the intestinal mucosa in IBD, gut microbes trigger systemic inflammation with the help of T helper 17 lymphocytes, ultimately resulting in autoimmune diseases such as DM.[12] Lastly, it has also been proposed that several genetic factors such as phosphatase non-receptor type (PTPN)2 and PTPN22 mutations, have a pivotal role development of IBD and DM. PTPN2 mutation in Dm is involved in apoptosis of pancreatic beta cells, while in IBD, it regulates the innate immune response and intestinal epithelial barrier function.[13]

Limitation of this study was its retrospective cohort design. Secondly, we could not distinguish between type 2 and type 1 diabetes mellitus in the study popu-

lation. Lastly, association of diabetes and severity of IBD could not be evaluated as our dataset lacked sufficiant granularity.

Conclusion

We have concluded that a significantly large portion (5.2%) of IBD patients are at risk of developing new-onset DM irrespective of steroid treatment. Furthermore, these patients are prone to an increased number of flares in the long run. Hence, we believe that these results warrant early screening and monitoring of glycemic control in IBD patients which could prove to be extremely valuable in managing this grave outcome.

Conflict of Interest: None

Funding Source: None

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