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The Association of Diabetes Mellitus and Inflammatory Bowel Disease

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ABSTRACT

Background and aim: Inflammatory Bowel Disease (IBD) and Diabetes mellitus (DM) etiology are still unclear, but both have genetic basis and share several complications. So we aimed to search for whether the two diseases are associated with each other and whether there are risk factors that increase the incidence of diabetes mellitus in inflammatory bowel disease patients.

Methods: This study was conducted on 130 inflammatory bowel disease patients who were diagnosed by colonoscopy and biopsy from EL-Raghy Assiut University Hospital and were not known to have DM before the study in the period from October 2019 to June 2021.

These patients underwent a full history, a thorough clinical examination, and routine lab investigation, especially fasting blood sugar (FBS) and glycosylated hemoglobin (HbA1c).

Results: Out of 130 patients; 26 (20%) were found to be diabetics and the other 104 (80%) were non-diabetics. The mean age of the studied patients was 32.45 ± 9.05 years, majority (78.5%) of them were males. And we found that patients with DM were significantly younger than those without DM. The family history of DM was higher among those patients with DM. The susceptibility of DM is increasing with the lengthening of IBD duration. No significant difference was present between both groups of patients as regards the type of treatment for IBD.

Conclusion: Diabetes mellitus risk increases in patients with IBD who are younger than 30 years old, have a positive family history of diabetes mellitus, and have had IBD for more than 3 years.

Key words: Association, Diabetes mellitus, Inflammatory Bowel Disease.

INTRODUCTION

Inflammatory bowel disease (IBD) is relapsing destructive inflammation of the gastrointestinal tract due to an abnormal immune reaction to gut microflora. This is subdivided into two main groups: Ulcerative colitis and Crohn's disease [(1)]. IBD happens in genetically susceptible patients [(2)].

Diabetes mellitus is chronic hyperglycemia due to insulin secretion defects, lack of insulin action, or both. with abnormalities in proteins, carbohydrates, and lipids due to the anabolic function of insulin [(3)]. There are two types: type one and type two: Type one is caused by pancreatic beta cell destruction, mostly due to autoimmune destruction. Type two is caused by insulin resistance and causes a functional insulin defect [(4)].

Though both diseases' etiology is still unclear, it's mostly that in individuals who are genetically susceptible, both environmental and host factors lead to uncontrolled immune reactions[(5)]**.** Both diseases share multiple complications as; hepatobiliary, neurological, post-operative, vascular and osteoarticular [(6)].

Corticosteroids are used as a line of treatment for IBD [(7)]. The information about the incidence of hyperglycemia or diabetes due to corticosteroid in IBD is limited [(8)]. IBD may show both metabolic or endocrinal associations as; insulin resistance and lipid abnormality [(9)].

In this study; our target was to evaluate the association and the risk factors that increase the incidence of diabetes mellitus in inflammatory bowel disease patients.

MATERIALS AND METHODS

Ethical approval:

The study protocol was approved by the Medical Ethics Committee of the Institutional Review Board of the Faculty of Medicine, Assiut University, Egypt (IRB No. 17101049). Informed and written consent were obtained from all participants according to The Code of Ethics of the World Medical Association (declaration of Helsinki) for studies involving humans. The study protocol is registered at clinicaltrials.gov ID: NCT04105348.

Study Participants:

A cross-sectional hospital-based study at EL-Raghy Assiut University Hospital on all IBD patients who needed medical advice in the period from the first of October 2019 to the end of June 2021. 130 patients were enrolled with IBD in the form of 100 patients with ulcerative colitis (UC) and 30 patients with Crohn's disease (CD), as diagnosed by colonoscopy and histopathological examination and who were not known to have DM. 102 of them were males and 28 of them were females, with a mean age of 32.45 ± 9.05 years old, with a body mass index (BMI) of 24.12 ± 2.37 Kg/m^2 and 100 patients (76.9%) had UC and 30 patients (23.1%) had CD. Patients were excluded from the study if they were under the age of 18 or had DM before IBD diagnosis.

All patients in this study were subjected to a full history including the patient's age, residence in a rural or urban area, smoking, marital status, family history of DM, family history of IBD, time of IBD onset, and type

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and duration of their treatment. Also; thorough clinical examination besides patients' sex and body mass index. And Full laboratory tests including; complete blood count (CBC) (by ADVIA 2120i (Germany)); Hemoglobin (mg/dl), Leucocytic count (10^3/ul), Platelet count (10^3/ul), liver function tests (LFTs) (by ADVIA 1800 (Japan)); serum albumin level (mg/dl), aspartate aminotransferase (AST) (u/l), alanine aminotransferase (ALT) (u/l), Bilirubin (mmol/l), kidney function tests (KFTs) (by ADVIA 1800 (Japan)); serum creatinine (mg/dl), serum urea (mmol/l), erythrocyte sedimentation rate (ESR) (by ALI FAX (Italy)); 1st hour (ml/h), 2nd hour (ml/h), C-reactive protein (CRP) (by ADVIA 1800 (Japan)) (mg/dl), FBS (by ADVIA 1800 (Japan)) (mg/dl) and Glycosylated HB (by ADVIA 1800 (Japan)) (%).

Statistical Analysis

Data were collected and analyzed by using SPSS (Statistical Package for the Social Sciences, version 20, IBM, and Armonk, New York). Continuous data were expressed in form of mean ± SD and compared by student t test while nominal data were expressed in form of frequency (percentage) and compared by *Chi²*-test. Predictors of diabetes mellitus among enrolled patients with IBD were determined by regression analysis. Significance was defined by $P < 0.05$.

RESULTS

Baseline characteristics:

There was a significant difference between the 2 studied groups as regard age and family history of DM or IBD (Table 1).

Table (1): Baseline data of studied patients based on the presence of DM

	Total (n= 130)	**IBD without DM (n= 104)**	**IBD with DM (n= 26)**	***P* value**
Age (years)	32.45 ± 9.05	33.24 ± 9.76	29.31 ± 4.07	**0.04**
Sex				
Male	102 (78.5%)	85 (81.7%)	17 (65.4%)	0.07
Female	28 (21.5%)	19 (18.3%)	9 (34.6%)	
BMI (kg/m^2)	24.12 ± 2.37	23.39 ± 3.06	24.30 ± 2.15	0.16
Residence				
Rural	94 (72.3%)	76 (73.1%)	18 (69.9%)	0.70
Urban	36 (27.7%)	28 (26.9%)	8 (30.8%)	
Smoking	23 (17.7%)	21 (20.2%)	2 (7.7%)	0.14
Family history of DM	31 (23.8%)	16 (15.4%)	15 (57.7%)	**< 0.001**
Family history of IBD	18 (13.8%)	18 (17.3%)	0	**0.02**
Marital status				
Single	36 (27.7%)	28 (26.9%)	8 (30.8%)	0.70
Married	94 (72.3%)	76 (73.1%)	18 (69.2%)	

Data expressed as frequency (percentage) or mean±(SD); **BMI**: body mass index; **DM:** diabetes mellitus; **IBD**: inflammatory bowel disease

The susceptibility of DM is increasing with the increase of disease duration. No significant difference was present between both groups of patients as regards the type of treatment of IBD or the type of IBD (UC or CD) (Table 2).

Table (2): Characteristics of IBD based on the presence of DM

	Total (n= 130)	**IBD without DM (n= 104)**	**IBD with DM (n= 26)**	***P* value**
Disease duration (year)	4.04 ± 2.46	3.76 ± 2.27	5.13 ± 2.92	**< 0.001**
Type of IBD				
UC	100 (76.9%)	78 (75%)	22 (84.6%)	0.30
CD	30 (23.1%)	26 (25%)	4 (15.4%)	
Steroid therapy	78 (60%)	63 (60.6%)	15 (57.7%)	0.79
5-ASA therapy	65 (50%)	52 (50%)	13 (50%)	1.00
Thiopurin therapy	43 (33.1%)	32 (30.8%)	11 (42.3%)	0.26
Biological therapy	11 (8.5%)	9 (8.7%)	2 (7.7%)	0.87

Data expressed as frequency (percentage) or mean±(SD); **UC**: ulcerative colitis; **CD**: crohn's disease; **ASA**: amino salicylate acid; **DM:** diabetes mellitus; **IBD**: inflammatory bowel disease

Baseline Lab investigations:

As regard basal laboratory data the levels of fasting blood sugar and glycosylated hemoglobin were higher in DM group (Table 3).

Table (3): Baseline laboratory data among studied patients based on presence of DM

	Total (n= 130)	**IBD without DM (n= 104)**	**IBD with DM (n= 26)**	***P* value**
Hemoglobin (mg/dl)	11.08 ± 1.93	11.14 ± 2.01	10.85 ± 1.62	0.48
Leucocyte (10^3/ul)	7.15 ± 1.78	7.26 ± 1.67	6.71 ± 1.34	0.12
Platelets (10^3/ul)	296.2±7.04	296.51 ± 7.73	294.05±7.89	0.92
Albumin (mg/dl)	35.67 ± 6.21	35.47 ± 5.99	36.52 ± 7.20	0.46
AST (u/l)	21.29 ± 5.3	21.21 ± 5.22	21.65 ± 4.94	0.91
ALT (u/l)	22.04 ± 3.90	22.29 ± 3.46	21.05 ± 5.27	0.148
Bilirubin (mmol/l)	6.35 ± 1.38	6.27 ± 1.41	6.65 ± 1.25	0.213
Creatinine (mg/dl)	1.01 ± 0.23	1.02 ± 0.23	0.94 ± 0.22	0.107
Urea (mmol/l)	5.04 ± 0.64	5.01 ± 0.51	5.17 ± 1.02	0.258
1st hour ESR (ml/h)	44.73 ± 6.69	45.08 ± 6.74	43.34 ± 6.42	0.239
2nd hour ESR (ml/h)	64.68 ± 11.40	65.46 ± 11.42	61.57 ± 10.98	0.121
CRP (mg/dl)	12.74 ± 2.76	12.90 ± 2.87	12.11 ± 2.18	0.195
FBS (mg/dl)	117.57±29.81	107.52 ± 12.15	204.19 ± 40.72	< **0.001**
Glycosylated HB (%)	5.46 ± 1.57	4.84 ± 0.61	8.46 ± 1.22	< **0.001**

Data expressed as frequency (percentage) or mean±(SD); **DM:** diabetes mellitus; **IBD**: inflammatory bowel disease; **FBS**: fasting blood sugar; **HB**: hemoglobin

Regression analysis of the results:

Regression analysis for the prediction of DM among patients with IBD:

Based on the current study; it was found that predictors of diabetes mellitus among patients with IBD were young age < 30 years, family history of diabetes mellitus and disease duration more than 3 years (Table 4).

Table (4): Regression analysis for the prediction of DM among patients with IBD

	Odd's ratio	**95% confidence interval**	***P* value**
Age (< 30 year)	1.96	1.34-2.71	**0.01**
Family history of DM	8.71	2.85 – 16.51	< **0.001**
Family history of IBD	0.34	0.11-1.67	0.99
Disease duration (> 3 year)	1.22	1.12-3.94	**0.03**

DM: diabetes mellitus.

DISCUSSION

The current study was conducted on 130 patients who were known to have IBD to assess the frequency of diabetes mellitus among those patients. Out of those patients, 26 (20%) were found to be diabetics and the other 104 (80%) were non-diabetics.

In line with a cross-sectional study with 12,601 IBD patients, the third most common comorbidity was type-1 diabetes in IBD patients (prevalence, 1.0%); however, the odds were not significantly elevated for type-1 diabetes in both UC and CD patients [10].

In contrast, they reported that the frequency of DM among patients with IBD was 3.5% [11]. Also, they stated that out of 2810 IBD patients, 141 (5%) had DM [12].This discrepancy may be attributed to a different population, sample size, and/or selection bias during study design.

In the current study, only four (13.3%) patients with CD developed DM, while 22 (22%) patients with UC developed DM. It was found that there were no significant differences between the two types of IBD and the frequency of DM (p= 0.22). This was in line with two studies that reported no significant difference between UC and CD regarding the frequency of DM [10, 11].

In this study, patients with DM had a significantly younger age and a higher frequency of family history of DM. Also, we found that patients with DM had no family history of IBD. In contrast, 18 (17.3%) patients without DM had a family history of IBD. Other data such as sex, body mass index, residence, and marital status showed no differences between both groups.

In line with the current study, another study reported that IBD patients with DM had a younger age and a higher frequency of family history of DM. The authors also found that, both groups of patients, either with DM or without had insignificant differences in sex and body mass index [12].

In our study, no significant difference was found between the diabetics and nondiabetics regarding

sex. This is in contrast to other studies that found that male sex was higher among those patients with DM. This discrepancy as regards sex may be attributed to different study designs, large sample sizes among their studies, and different populations [13].

In the current study, we found a significantly longer duration of the disease among those patients with DM (5.13 ± 2.92 vs. 3.76 ± 2.27 years) in comparison to those without therapy. In line with these findings, a previous study found that diabetic patients had a longer duration of IBD, where they found that the increased risk of Type-2 DM was in IBD patients significantly with a longer duration of the disease [13].

In terms of baseline laboratory data, both groups of patients had insignificant differences with the exception of significantly higher fasting blood sugar (204.19 ± 40.72 vs. 107.52 ± 12.15 (mg/dl)) and glycosylated hemoglobin (8.46 ± 1.22 vs. 4.84 ± 0.61 (%)) among patients with IBD and DM. This is consistent with other studies that found similar findings in addition to increased cholesterol levels among those patients with IBD and DM [12].

Our results found that therapy of IBD was in the form of steroids, 5-ASA, thiopurin, and biological therapy was used in 78 (60%), 65 (50%), 43 (33.1%), and 11 (8.5%) patients, respectively, and we found no significant difference was present between both groups of patients as regards type of therapy. Also, we didn't find any significant association between the risk of DM and the types of therapy used by the patients in the current study.

Eleven (21.2%) patients who didn't receive steroid therapy developed DM, while 15 (19.2%) patients who received steroid therapy developed DM. It was found that there was no difference between the steroid therapy and the frequency of DM.

In agreement with the current study, another study found that regarding IBD treatment agents, the use of systemic steroids didn't make difference between IBD patients with and without DM [14]. Also, another study found that both groups of IBD based on DM had no difference as regards steroid therapy [12].

In the current study, 13 (20%) patients who received 5'-ASA therapy developed DM, and also, another 13 (20%) patients who didn't receive 5'-ASA therapy developed DM. It was found that there was no significant difference between 5'-ASA therapy and the frequency of DM (p= 0.18).

The effects of sulfasalazine on hemoglobin A1c (HbA1c) levels remain debatable with limited evidence. Sulfasalazine may cause hemolysis, which falsely may show low HbA1c readings. A case report of a patient receiving sulfasalazine with type 1 diabetes showed low HbA1c readings [15].

The current study found that 11 (25.6%) patients who received thiopurine therapy developed DM, while 15 (17.2%) patients with no thiopurine therapy developed DM. It was found that there was no difference between thiopurine therapy and the frequency of DM.

A double-blind randomized control trial comparing placebo to azathioprine demonstrated no effect on the level of HbA1c at one year of follow-up. These data revealed that azathioprine therapy did not enhance the risk of diabetes in patients with IBD as compared to the general population [16].

Also, we found that two (18.2%) patients who received biological therapy developed DM, while 24 (20.2%) patients with no biological therapy developed DM. It was found that there was no difference between biological therapy and the frequency of DM.

In agreement with the current study, it was found that regarding IBD treatment agents as biologic agents, immunomodulators, or systemic steroids, there was no difference between IBD patients with and without DM, but IBD DM patients had an increased use of 5-aminosalicylic acid agents (64.5% vs. 54.5%; P = 0.04) [14].

Based on the current study; it was found that predictors of diabetes mellitus among patients with IBD were young age < 30 years (odd's ratio= 1.96, 95% confidence interval= 1.34-2.71), family history of diabetes mellitus (odd's ratio= 8.71, 95% confidence interval= 2.85-16.51) and disease duration more than 3 years (odd's ratio= 1.22, 95% confidence interval= 1.12-3.94).

In line with another study that said that a potential risk of type-1 and type-2 DM in IBD patients may be present after adjustment of diabetes risk factors as; BMI, drinking, sex, exercise, smoking, age and steroid usage [12]. According to the findings of large-scale population-based cohort studies, there is a potential risk of both type-1 and type-2 DM in patients with IBD, although the causal relationship between diabetes and IBD is questionable because of the population and the study design heterogeneity [12].

Also, the authors reported that the overall risk of diabetes increases with age; however, the risk of diabetes development at younger age in IBD patients is significant in comparison to the general population specially when below 40 years old.[12]

Risk of diabetes increases by 2.4 fold in younger CD patients below 40 years old when compared with the non-IBD. Also; a higher risk of diabetes is found in patients with UC below 40 years old when compared with the general population [12].

In line with current study data suggest that IBD plays a key role in the development of diabetes among people who are younger and have a low risk of metabolic disorders. It has been reported that chronic inflammation and metabolic disorders can be caused by microbial disturbances, as an environmental factor in early life, [17].

The risk of IBD increases with early exposure to environmental factors as antibiotics which affect the microbiota. In young individuals with IBD, several

environmental and genetic variables may influence glucose metabolism, leading to diabetes. However, the pathophysiology of diabetes in younger patients is unknown, and more research is needed. Because chronic inflammation is also associated with insulin resistance, Inflammatory and metabolic signaling in younger patients can increase the risk of diabetes in IBD [(18)].

CONCLUSION

Diabetes mellitus risk increases in patients under 30 years old who have a positive family history of diabetes mellitus and have had IBD for more than 3 years.

Also, types of medications used in Inflammatory Bowel disease treatment don't affect Diabetes mellitus incidence.

Limitations:

The current study's main limitations were: 1) a small sample size; 2) the incapableness of differentiation between type 1 and type 2 diabetes as study end points in this study population; 3) the severity of inflammatory bowel disease and diabetes was not evaluated; 4) lack of diabetes mellitus registration prior to inflammatory bowel disease diagnosis; and 5) being a single-center study.

But to our knowledge, this is the first study that discussed such an issue in our locality.

List of abbreviations:

DM, Diabetes Mellitus; IBD, Inflammatory Bowel Disease; 5ASA, 5 Amino Salicylic Acid; BMI, Body Mass Index; UC, Ulcerative Colitis; CD, Crohn's Disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, Erythrocyte sedimentation Rate; CRP, C Reactive Protein; FBS, Fasting Blood Sugar; HbA1c, Glycosylated Hemoglobin; CBC, Complete Blood Count; LFTs, Liver Function Tests; KFTs, Kidney Function Tests; T2D, Type 2 Diabetes; T1D, Type 1 Diabetes; TNF-α, Tumor Necrotic Factor –α

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