

A LINKAGE BETWEEN INFLAMMATORY BOWEL DISEASES AND TYPE 2 DIABETES

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Abstract

Inflammatory Bowel Diseases (IBDs) are a class of gastrointestinal chronic inflammations, comprehending Ulcerative Colitis (UC) and/or Crohn Disease (CD) and affecting genetically predisposed subjects. IBDs represent a high cost for the health system, and they are characterized by a very specific co-morbidity. For such reasons, and since a positive correlation between IBDs and Diabetes Mellitus (DM) has been observed in the past, the aim of this work is to provide such result with a more solid basis through a cohort study, considering 49 consecutive patients comorbid with IBDs and Type 2 Diabetes (T2D). A high correlation between IBDs and T2D was observed. Interestingly, UC was showed the higher correlation, with a particularly high peak within the 65 to 74 years old range. Being T2D a both environmentally and genetically driven pathology (like IBDs), these diseases association could be due to environmental factors. Furthermore, 70.8% of case-control patients (48 cases versus 96 controls, consecutively selected) were suffering from UC, while CD held the remaining 25.0% (4.2% stood for undetermined colitis). This evidences that, among IBDs, the most related to DM is UC, although CD remains a related pathology. Interestingly, CD was found to be absent in the 55-64 years old range. Conversely, cohort study highlighted 73.81% of cohort was suffering from UC, while CD held the remaining 21.43% (4.76% was for non-determined colitis). This confirms that, among IBDs, the most linked to T2D is UC.

Keywords: Diabetes; Endocrinology; Epidemiology; Gastroenterology; IBD

Introduction

Ulcerative Colitis (UC) and Crohn Disease (CD) are known to be the most important among Inflammatory Bowel Diseases (IBDs), which are characterized by a gastrointestinal tract chronic inflammation. Such diseases affect genetically predisposed individuals, that were shown to be victim of a commensal microbiota tolerance disruption (Matricon *et al.*, 2010). IBDs are high

cost-related diseases, characterized by both specific morbidity and co-morbidity. Moreover, they were showed to lower life quality, especially because of surgery and complications. UC and CD represent a global health issue, being featured by an incidence, in Europe, of 12.7 and 24.3 /100,000 people per year, respectively, and a prevalence of 0.5 and 1.0%, respectively. Their incidence is constantly

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increasing worldwide, among both adults and children (Ventham *et al.*, 2013). Co-morbidities are usually specific immune-mediate diseases, as well as geriatric degenerative diseases, such as asthma, psoriasis, Type 1 Diabetes (T1D), rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, vitiligo, autoimmune thyroid disease and chronic glomerulonephritis (Weng *et al.*, 2007). T1D is probably the most frequent condition, and T1D-IBD association can have both important clinical and therapeutic implications. Moreover, T1D has been directly associated with dysfunctional bowel homeostasis, while no study ascertained type 2 diabetes (T2D) prevalence in IBD by now (Lamb *et al.*, 2019; Stojanović *et al.*, 2021). It was observed that UC-positive children (CD-negative) show a higher T1D prevalence with the respect to those affected by other IBDs (Kappelman *et al.*, 2011). Moreover, it was reported that, within such conditions, risk of infections and surgical complications increases dramatically among patients administered with immunosuppressive drugs (Manilich *et al.*, 2012; Ananthakrishnan *et al.*, 2015). IBDs were demonstrated to be multifactorial genetic disorders, occurring after exposure to one or more environmental triggers in susceptible individuals, happening to be positive for one or more risk alleles. Because of an augmented risk of CD in UC-positive families and vice versa, it was proposed a genetic model in which these are related pathologies, with some susceptibility loci in common but differing in others, which comes out in diverging disease evolutions (Satsangi *et al.*, 1997; Ahmad *et al.*, 2001). Environmental factors represent a crucial component within the pathogenetic process of IBDs. Many pharmacological molecules have been considered as a possible disease trigger (*i.e.*, antibiotics, isotretinoin, etanercept, rituximab, ipilimumab, oral contraceptives and nonsteroidal anti-inflammatory drug-NSAID) (Dubeau *et al.*, 2013). It was in fact reported that NSAIDs induced acute colon ulcers with CD histological evidence, sideropenic anaemia, diarrhoea and abdominal pain (Katsanos *et al.*, 2011). Corticosteroids are a key strategy in IBDs treatment. They are administered orally, topically or intravenously, so that they quickly ameliorate both moderate and severe UC and CD, although they are ineffective in remission maintenance in both diseases. Corticosteroids are characterized by many adverse effects and a better comprehension of their action mechanism led to the discovery of novel corticosteroids with minimal toxicity (Katz, 2004).

CD-related mortality is reported to be higher than that of the general world population, not to mention that young ages at diagnosis and need for

multiple surgeries were demonstrated to be additional risk factors. Strategy, management and research did not significantly change in the last three decades, and recent improvements in clinical treatment are far from being translatable into significant improved survival. CD is also related with mortality with both malignant and non-malignant gastrointestinal disorders, excluding colorectal cancer. About 30% of deaths could be directly associated with CD. Regarding UC, most of research did not show high death rates, but surgeries were associated with augmented mortality percentages. Parameters such as disease extent and age at diagnosis do not relate with survival, unlike to CD. However, an increased mortality risk within one year after diagnosis was observed, probably ascribable to acute severe colitis (Selinger and Leong, 2012).

The aim of this work is to determine prevalence of T2D in CD and UC patients, as well as to evaluate whether the coexistence of such diseases is associated with an increased abdominal complications risk and with an intestinal disease negative prognosis. Such investigation's relevance is due to a possible causality correlation between T2D and IBDs (still to be assessed), potentially conducting to novel primary prevention strategies, aimed to lower such disease incidence.

Patients and Methods

Case-control study

A preliminary case-control study was carried out. A total of 144 patients suffering from inflammatory bowel diseases (IBDs) (48 cases versus 96 controls) were consecutively selected, only in case of diabetes mellitus (both type 1 and 2) comorbidity. To be eligible, patients had to be suffering from both IBDs (UC and/or CD) and diabetes mellitus. IBDs patient not suffering from diabetes mellitus were excluded. Analysis was performed through a database analysis. Every case was compared with 2 controls suffering from IBDs, but without a diabetes diagnosis, as well as hyperglycaemia. Controls were comparable with every case in terms of age, gender, type and duration of the disease. In both cases and controls, immunosuppressive or biological therapy, as well as surgery, were used as prognostic indicators.

Cohort study

To achieve a more specific detail degree about IBD/diabetes correlation, a cohort study was performed, considering 49 consecutive patients comorbid with IBDs and Type 2 Diabetes (T2D). Eligibility and exclusion criteria were same as case-

control study. Those suffering by both steroidal and other causes diabetes (pancreas resection, haemochromatosis, etc.) were excluded to rule out confounding factors.

Statistical Analysis

Quantitative data are presented as mean values $\pm$ standard deviation. Frequency differences were analysed with a χ^2 test and, in case of small samples, with a Fisher Test. A $p < 0.05$ was considered as a statistically significance index. Evaluated population's diabetes mellitus (DM) prevalence within the case-control data were compared with ISTAT 2010-2011 report. Genetic variability was a potential confounder, yet unavoidable. Data were provided by Milan University Hospital, Italy, in 2017. This was an epidemiological and biostatistical study and calculation were carried out by using Microsoft Excel software. Potential biases were avoided by consecutive patients selection, so that prejudice and errors were not a possibility. Control-case minimum sample size was calculated through an online software (<https://www.surveysystem.com/sscalc.htm>) to be at last 142 (our sample was 144), while cohort study minimum value was 49 (our value stood exactly at 49). We did not have to remove any case, because no data were missing.

Results and discussion

Case-control study

A sample of 48 cases was compared to 96 controls. A subdivision by age classes shows that inflammatory bowel disease (IBDs) cases are associated with a higher diabetes mellitus (DM, both type 1 and 2) prevalence with the respect to the ISTAT 2011 Italian data ones (Figure 1), in the 0-54 years old range ($p=0.017$). This result could be due to the fact that, although IBDs onset span from childhood to the sixth decade (Ruel *et al.*, 2014) and T2D arise in late adult age (50.3 ± 11.2 , according to Noh *et al.* (Noh *et al.*, 2018)), T1D onset is generally observed before 20 years of age (Maahs *et al.*, 2010), lowering the range. Under a disease distribution perspective, ulcerative colitis (UC) seems to be more associated with diabetes with the respect to the Crohn disease (CD), particularly in the 0-65 years old range. (Figure 2.)

Sexual distribution mostly showed male patients (62.5%), suggesting a male sex-related DM-IBDs potential association. Patients were found to be co-morbid with Type 1 Diabetes (T1D, 18.7%) and Type 2 Diabetes (T2D, 81.3%), potentially

demonstrating a positive correlation between IBDs and DM, especially involving T2D. Interestingly, 70.8% of patients were suffering from UC, while CD held the remaining 25.0% (4.2% stood for undetermined colitis). This evidences that, among IBDs, the most related to DM is UC, although CD remains a related pathology. Interestingly, while UC is present for all age classes, CD was found to be absent in the 55 - 64 years old range. Such result could be explained by the just cited potential higher UC - DM correlation and, in general, by the consecutive selection of patients. In fact, such method does not allow to select subjects characterized by specific features, such as diseases like CD.

Patients' details show significant percentages of both overweight and obese individuals (39.6 and 16.7%, respectively), suggesting a negative correlation between Body Mass Index (BMI) and IBDs. Noteworthy, percentages suggest that, within the high BMI category, overweight individuals not suffering from obesity are the most linkable to IBDs/DM coexistence (Table 1). A familiar predisposition for DM was observed in 31.3% of the considered individuals, so that a genetic correlation between IBDs and diabetes could be possible, but it remains to be determined which is the dominant pathology or what kinds of link and balance are standing. Importantly, both cases and controls were related to a comparable use of biological and

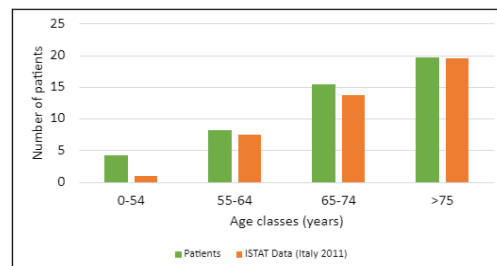


Figure 1. Prevalence of diabetes mellitus (both type 1 and 2) in IBD patients and ISTAT 2011 Italian data

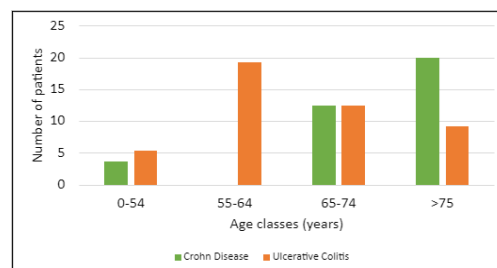


Figure 2. Diabetes mellitus (both type 1 and 2) distribution in IBD patients (Case/Control study)

immunosuppressive therapy (Table 2). Coming to details, 27.1% of cases recurred to immunosuppressive treatment, and so did the 20.8% of controls, while smaller percentages made use of biological therapy, 4.2% and 13.5% respectively. Interestingly, a quite high portion of cases went on surgery (20.8%) but a small percentage within controls did as much (7.2%), so that it can be inferred that the co-morbidity with DM subjects could represent a risk factor that possibly led to surgery (Table 2). Nonetheless, it was observed that surgery need badly arose after IBDs appearance; this finding clearly suggests that, while diabetes can be held under control and immunotherapy is under development (Bluestone *et al.*, 2021) (although it cannot be cured, at least for now), IBDs are capable to shift the patient balance in the surgery chamber (Table 3).

Case-control study limitations were mainly due to consecutive selection of patients, which did not permit to recruit the most appropriate subjects. So, we could not select patients considering genetic variability as an inclusion/exclusion criterion.

Cohort study

A subdivision in age classes shows that inflammatory bowel diseases (IBDs) are associated with Type 2 Diabetes (T2D) in a bell-shaped manner (Figure 3), with a peak in 65-74 years old range (32.64%), followed by 55-64 years old (26.52%). Under a disease distribution point of view, UC seems to be more associated with diabetes with the respect to CD, particularly in the 65-74 age span, followed again by 55-64 years old. (Figure 4.)

Table 1. Case-control patients demographics, IBD type, comorbidities and BMI. SD: standard deviation. BMI: Body Mass Index

Parameters	Mean±SD	Number (%)
Sex	-	
- Males		30 (62.5%)
- Females		18 (37.5%)
Age (years)	65.1±11.8	
Disease type		
- Ulcerative colitis		34 (70.8%)
- Crohn disease		12 (25.0%)
- Undetermined colitis		2 (4.2%)
Disease duration (years)	28.3±9.4	
BMI (kg/m ²) - mean value	27.4±4.2	
BMI		
- Overweight (25-30)		19 (39.6%)
- Obesity (>30)		8 (16.7%)
Diabetes mellitus familiarity		15 (31.3%)
Diabetes type		
- Type 1		9 (18.7%)
- Type 2		39 (81.3%)

Table 2. Case-control patients therapeutic regimens

Therapy	Cases (n=48)	Controls (n=96)	p values
Immunosuppressive treatment	13 (27.1%)	20 (20.8%)	n.s.
Biological treatment	2 (4.2%)	13 (13.5%)	n.s.
Surgery	10 (20.8%)	7 (7.2%)	0.036
Ileal Pouch	4 (11.7%)	3 (4.4%)	0.10

Table 3. Case-control patients surgery necessity rates, subdivided according to BMI, diabetes type, therapy and diabetes onset. BMI: Body Mass Index. IBD: Inflammatory Bowel Disease

Parameters	Surgery necessity		p values
	Yes (n=10)	No (n=38)	
BMI			
- Normal weight < 25	4	17	1.000
- Overweight > 25	6	21	
Diabetes type			
- Type 1	3	6	1.000
- Type 2	7	32	
Therapy			
- Insulin	1	6	0.238
- Oral Hypoglycemic drugs	9	32	
Diabetes onset			
- Before IBD	1	9	0.663
- After IBD	9	29	

Sexual distribution mostly showed male patients (59.52%), in nice agreement with the case/control study data. This finding strengthens the above stated hypothesis, suggesting the association between T2D and IBDs to possibly be sex related, especially with males. The considered cohort was characterized by long-standing IBDs (26.41 ± 11.25 years). Interestingly, 73.81% of cohort was suffering from UC, while CD held the remaining 21.43% (4.76% was for non-determined colitis). This finding enforces the evidence that, among IBDs, the most linked to T2D is UC, although CD remains a strongly related pathology.

Patients' details show significant percentages of both overweight and obese individuals (35.71 and 16.67%, respectively), suggesting a positive correlation between Body Mass Index (BMI) and IBDs. Noteworthy, percentages suggest that, within the high BMI category, overweight individuals not suffering from obesity are the most linkable to IBDs/DM coexistence (Table 4). A family predisposition for T2D was observed in 21.43% of the considered individuals, so that a genetic correlation between IBDs and diabetes could be possible, but, again, it remains to be determined which is the dominant pathology or what kinds of link and balance are standing. Such an association is possibly due to human microbiome variations in species composition, particularly at the phylum level, as reported by Manos (Manos, 2022), although a direct causality has yet to be investigated.

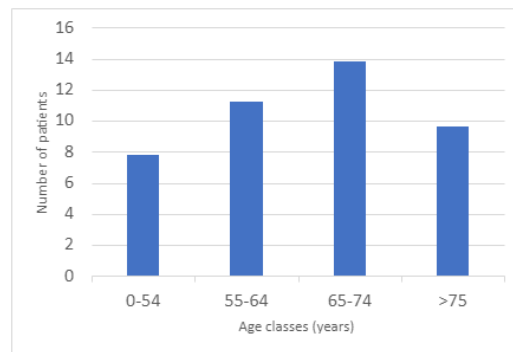


Figure 3. Prevalence of Type 2 Diabetes (T2D) in inflammatory bowel diseases (IBDs) patients

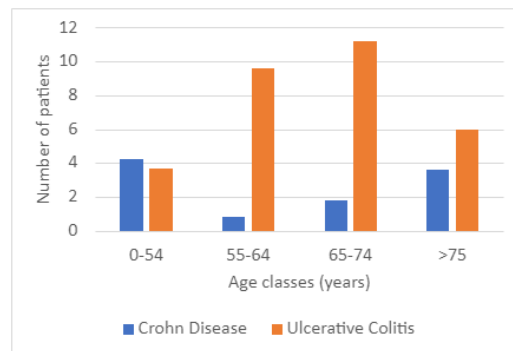


Figure 4. Inflammatory bowel diseases (IBDs) distribution in Type 2 Diabetes (T2D) patients

Table 4. Cohort study's patients demographics, IBD type, comorbidities and BMI. SD: standard deviation. BMI: Body Mass Index

Parameters	Mean±SD	Number (%)
Sex	-	
- Males		25 (59.52%)
- Females		17 (40.43%)
Age (years)	63.55±11.56	
Disease type		
- Ulcerative colitis		31 (73.81%)
- Crohn disease		9 (21.43%)
- Undetermined colitis		2 (4.76%)
Disease duration (years)	26.41±11.25	-
BMI (kg/m ²) - mean value	22.71±4.44	-
BMI		
- Overweight (25-30)		15 (35.71%)
- Obesity (>30)		7 (16.67%)
Diabetes familiarity	-	
- Type 1		4 (9.52%)
- Type 2		9 (21.43%)

Table 5. Cohort study's patients IBDs location in gut. UC: Ulcerative colitis, CD: Crohn disease, NDC: Non-determined colitis

IBD type	Transverse colon	Sigmoid colon	Ileus	Large intestine	Proximal rectum	Whole colon	Total
UC	35.71	21.43	0	0	11.90	4.76	73.81
CD	2.38	0	7.14	9.52	0	2.38	21.43
NDC	0	4.76	0	0	0	0	4.76
Total	38.09	26.19	7.14	9.52	11.90	7.14	100

A peculiar evaluation was carried out observing what intestinal zones were affected by IBDs (Table 5) and it turned out that the most affected gut location, among our cohort, were transverse (38.09%) and sigmoid colon (26.19%). Noteworthy, after a more accurate observation it was clear that, in both intestinal sites, the dominant IBD was UC. Other sites, such as ileus, large intestine, proximal rectum and whole colon, showed comparable general percentages of affection, characterized by a balance between UC and CD.

Since patients were consecutively selected also in cohort study too, limitations of such study section can be identified in lack of recruiting selectivity.

Conclusions

IBDs, particularly UC, seems to be associated to Type 2 Diabetes (T2D). This study made clear that IBD and T2D are related diseases and that IBDs are positively associated with BMI. Plus, it could be inferred that the IBDs/T2D comorbidity might be characterized by a UC prevalence, especially localized in both transverse and sigmoid colon. It could be reasonable to infer that, since T2D is a both environmentally and genetically driven pathology, just like IBDs, association between them could be partially rooted in environmental factors.

Abbreviations

T1D: Type 1 Diabetes
 T2D: Type 2 Diabetes
 IBD: Inflammatory Bowel Disease
 UC: Ulcerative Colitis
 CD: Crohn Disease
 DM: Diabetes Mellitus
 BMI: Body Mass Index
 NDC: Non-determined colitis
 n.s.: non-significant

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