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INVESTIGATING THE RELATIONSHIP BETWEEN INFLAMMATORY BOWEL DISEASE AND DIABETES

A Thesis in

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by

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ABSTRACT

Inflammatory bowel disease (IBD) is a growing problem in the United States and the issue is even more concerning with recent studies showing a link to developing diabetes. Diabetes carries a high morbidity and a significant decrease in quality of life. The aim of this study was to find possible links between IBD symptom experience, quality of life and treatments and diabetes. A cohort of 525 IBD patients was selected from those who saw an IBD specialist within the last five years at the Hershey Medical Center and filled out a survey relating to their IBD experience. A statistical analysis was performed including bivariate andmultivariable logistic regression models to assess if any treatment or symptom variables showed a significant correlation to diabetes. There was a significant increase in the incidence of diabetes for IBD patients who received mesalamine (OR = 2.06, P = .0018). Also fatigue and anti-TNF both showed increased incidence of diabetes when looking at CD patients alone (OR: 6.86, p value: 0.026 and OR: 2.21, p value: 0.034 respectively). These findings suggest possible links between IBD and diabetes. However, future prospective studies must be performed to assess causality.

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Chapter 1–Introduction

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) carries severe morbidity and has a large impact of patients' quality of life. The disease overall is characterized by chronic, relapsing inflammation throughout the gut and requires an endoscopy for diagnosis. There is not one single cause of IBD and its origin can be attributed to a combination of different phenomena. In general, it is thought to be caused by an irregular immune reaction to environmental factors, genetics, or a change in gut microbiota. The complicated nature of how the disease starts and its recent increase in prevalence makes it a prime candidate for research. [1, 2]

IBD is typically grouped into two subtypes: Crohn's Disease (CD) and Ulcerative Colitis(UC). UC is focused in the mucosal layer of the colon while CD is transmural and can be found most commonly in the ileum although it can also spread to the colon as well.[2] CD and UC are associated with different types of damage to the tissue but are both consistent with chronic relapsing inflammation. However, given that cause of the inflammation in IBD is caused by multiple factors in tandem, it is thought that UC and CD share similar mechanisms of disease.[3] Typical symptoms include but are not limited to fatigue, diarrhea, fecal urgency, abdominal pain, and extraintestinal manifestations.

Recent research into new treatments have shown positive results by targeting specific mechanisms in the immune system. Some common treatments include immunomodulators (biologics and mesalamine), anti-inflammatory drugs (such as steroids and anti-tumor necrosis factor(TNF)), and antibiotics. Anti-TNF is usually used in patients that have more sever disease. There is a need for further treatments as the

current options carry problems with tolerance and harsh side effects.[4]

Diabetes

Diabetes is a widespread disease effecting 451 million people worldwide, with that numberexpected to increase to 693 million by 2045.[5] Diabetes is subgrouped into many different diseases but the two most common are types I and II. The common thread throughout these groups is a deficiency of insulin which is required by the body in order to uptake glucose into its cells.[6] Type I diabetes is a genetic disease and is consistent with the body losing its ability to produce enough insulin due to permanent damage to the insulin producing B cells in the pancreas.[7] Type II diabetes is caused by chronic over nutrition or obesity and results in the body's cells not properly producing or responding to insulin.

Diabetes carries with it very high morbidity and mortality. Over $850 billion dollars were spent and over 5 million deaths were caused due to the disease worldwide in 2017 alone.[5] Those numbers will only increase with 10.5% of the U.S. population being diagnosed with diabetes in 2018.[6] It has also been shown to be a risk factor for many other life threatening diseases such as coronary artery disease, heart disease, and pancreatic cancer. It is imperative that the risk of developing diabetes is lowered to increase quality of life of the general population before the problem continues to grow.

Diabetes and IBD Relationship

There is not a current established link that shows IBD is a risk factor for diabetes. However, some researchers believe there is a connection. The exact mechanism for this link is still unknown. Corticosteroids have been shown to lead to insulin resistance which could lead to a potential link to diabetes, as corticosteroids are used to treat IBD flare ups.[7] The autoimmune nature of both diseases could also link

them through similar genetic predispositions. There have been a few studies looking into the relationship between IBD and diabetes.

One study with 662 type 1 diabetes patients and 602 controls found that diabetes patients were more likely to have IBD than controls (OR 5.5; 95% CI 1.2–24.9).[9] This shows the relationship between diabetes and IBD. This study did not look at specific predictors for what could be causing this relationship, but the authors did note that quality of life scores are generally lower in patients that carry both diseases as opposed to just one.

Another study in Korea used national health insurance data to compare 8,070 IBD patients with 40,350 non-IBD patients.[4] The authors found that the mean incidence of diabetes was higher in IBD patients than patients without (HR: 1.135, 95% CI [1.048 – 1.228]). Even afteradjusting for various demographic variables, such as age and sex, this increase was significant. However, this study was limited in the data the authors were able to obtain. The authors could not look at the severity of the disease to see if there was any impact on risk for diabetes which is something that will be looked at in the current study.

A third study in Denmark looked at a cohort of 6,028,844 people. This researched showed that there was a significant increase in diabetes developed in IBD patients compared to expected during follow up in the standardized incidence ratio (SIR, 1.54).[10] This furthers the idea that there could be a relationship between diabetes and IBD. However, this study did not look into IBD treatments as a possible mechanism for the relationship.

Goal of This Study

The link between IBD and diabetes has already been suggested and other studies

have shown that the two diseases are related, but specific patient outcomes were not assessed. The aim of this study is to look at the potential role of IBD in diabetes with respect to IBD disease activity, quality of life (QOL) and symptom experience.

Chapter 2 – Materials and Methods

Data Collection

The data for this study was collected using IRB study protocol #00013788. The population consisted of patients that saw an IBD specialist at the Hershey Medical Center between October 2015 and June 2020 and completed the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) which is related to their IBD symptoms and treatments. The data was then generated using electronic medical records (EMR) web intelligence queries, manually abstracted from chart reviews or taken from the survey directly. All patients selected must have been greater than 17 years of age and had an established diagnosis of CD, UC, or colitis of an indeterminate nature based on standard clinical criteria routinely used to identify IBD. Patients also must have completed an ileocolonoscopy and subsequent contemporaneous surveys for the Harvey-Bradshaw Index (HBI), Simple Colitis Activity Index (SCCAI), and Hospital Anxiety and Depression Scale (HADS). The cohort was further manually reviewed for IBD related symptoms such as absence of gross gastrointestinal (GI) tract alterations. Patients were also only included if they had an endoscopy in the electronic medical records (EMR) within 60 days of filling out the survey. Patients were excluded if they showed evidence of an active infection, pregnancy, or current malignancy. This data forms the dataset of IBD patients to be used in this study.

Variables

Patients were first divided by disease status as Crohn's disease (CD, ulcerative colitis (UC) and indeterminate colitis (IC). Subsequent analyses were performed for all patients (including IC), CD only and UC only. Patients with indeterminate colitis were not assessed separately due to the fact that there were not enough patients to successfully

run an analysis. Diabetes and prediabetes patients were identified by their A1C test in the EMR and together they formed the "diabetes" group for this study. Prediabetes patients were excluded from previous studies in the setting of IBD so it was included here to assess its value. All patients who did not have one of those diagnoses were included in the "No Diabetes" group. There were a number of different variables that were examined in this statistical analysis to assess symptoms (fatigue, diarrhea, fecal urgency, anxiety/depression, abdominal pain), disease activity (endoscopic severity (Endo), any extraintestinal manifestation (EIM), bleeding, disease complications) , and treatments (anti-TNF, steroids, immunomodulators (IMM), opiate use). Likert scale variables were recorded as binary variables for the purpose of creating contingency tables. Abdominal Pain and Fatigue were only of interest if they were more severe so they were coded as a "Yes" for any patient that gave a score of 5 or higher on their survey and a "No" for any score lower than a 5. Bleeding was coded as a "Yes" if they received a score of 2 or higher and a "No" for any score of 0 or 1. The rest of the variables included in the analysis were either a "Yes" if they showed that symptom or took that medication, otherwise they were classified as "No."

Statistical Analysis

The cohort was first divided by subgroup depending on disease type (CD or UC) and by diabetes status (diabetes/prediabetes vs. no diabetes). A univariate analysis was performed for all the variables in the database for IBD patients overall and by diabetes status. This included basic summary statistics as well as summary counts and percentages for the patients in each category. Two-way tables were created and a Fisher's exact test or a chi square test was performed to assess significance and compute odds ratios for the categorical variables. For quantitative variables, a two-sample t-test

or Wilcoxon rank sum test was used to see if there are any significant differences in the means between patients with and without diabetes.

A multivariable logistic regression model was then fit to assess the impact that any of the variables (Age, EIM, Pain, Mesalamine, Gender, Fatigue, Diarrhea, erythrocyte sedimentation rate (ESR), Disease Complications) had as a predictor for diabetes amongst IBD patients. These variables were included because they were a demographic variable that should be controlled for (Age and Gender) or they showed some significance in the bivariate analysis and it was important to assess its significance level when controlling for other variables (EIM, Pain, Mesalamine, Fatigue, Diarrhea, ESR, Disease Comp). Separate analyses were performed for each disease subtype (CD or UC), in addition to analyses based on all patients, to see if there were any differences amongst them. For each model, parameter estimates, p-values, odds ratios and the corresponding 95% confidence intervals were extracted.

All statistical analysis was performed using R and its integrative development environment RStudio.[14,15] Statistical significance was assessed at the 0.05 level and no adjustment for multiple testing was applied due to the exploratory nature of the study.

Chapter 3 – Results

There was a total of 561 patients included in the study. Of the patients with diabetes, all of them had type 2. Table 1 summarizes demographic data by disease status.

Table 1: Demographic Data

Demographic Data				
All Disease				
		No Diabetes	Diabetes	p-Value
Total Patients		498	63	
Age, Years		42.26 ± 0.49	58.14 ± 0.50	<.001
Gender	Female	275	29	.18
	Male	223	34	
CD Only				
Total Patients		337	32	
Age, Years		41.49 ± 0.50	51.44 ± 0.49	<.001
Gender	Female	195	15	0.26
	Male	142	17	
UC Only				
Total Patients		140	26	
Age, Years		44.47 ± 0.50	63.21 ± 0.51	<.001
Gender	Female	67	13	1
	Male	73	13	

The diabetes patients showed a significantly higher age overall and also within each disease subgroup. There was no significant different in prevalence of diabetes when comparing males to females in all disease, CD only or UC only.

Table 2: Bivariate Analysis – All Disease

All Disease					
Variable		No Diabetes	Diabetes	Odds Ratio 95% CI	p-Value
Fatigue	No Yes	91 405	7 54	1.73 (0.75, 4.66)	0.22
Diarrhea	No Yes	364 114	49 11	0.72 (0.33, 1.46)	0.42
Fecal Urgency	No Yes	137 15	21 2	.76 (0.42, 1.40)	0.37
Anxiety/Depression	No Yes	318 180	44 19	0.76 (0.41, 1.38)	0.4
Abdominal Pain	No Yes	173 322	25 36	0.77 (0.44, 1.39)	0.4
Bleeding	No Yes	307 176	43 18	0.73 (0.38, 1.34)	0.32
Endo	No Yes	342 156	45 18	0.88 (0.46, 1.6)	0.77
Any EIM	No Yes	284 214	40 23	0.76 (0.42, 1.35)	0.35
Disease Complications	No Yes	320 178	48 15	0.56 (0.28, 1.06)	0.07
Anti-TNF	No Yes	351 147	40 23	1.37 (0.76, 2.44)	0.31
Mesalamine	No Yes	417 81	45 18	2.06 (1.06, 3.84)	0.022*
Immunomodulators	No Yes	389 109	49 14	1.02 (0.5, 1.96)	1
Steroids	No Yes	440 58	54 9	1.26 (0.52, 2.76)	0.54
Opiate Use	No Yes	453 45	55 8	1.46 (0.57, 3.35)	0.36

Table 2 shows the bivariate analysis for all patients with IBD. Mesalamine was the only variable that showed a statistically significant result. Showing patients who were given mesalamine as an IBD treatment, had a significantly higher incidence of diabetes (OR: 2.06).

Table 3: Bivariate Analysis – UC Only

All UC Only					
Variable		No Diabetes	Diabetes	Odds Ratio 95% CI	p-Value
Fatigue	No Yes	25 114	6 18	0.66 (0.22, 2.24)	0.408
Diarrhea	No Yes	105 30	18 6	1.17 (0.35, 3.42)	0.79
Fecal Urgency	No Yes	40 97	11 13	0.49 (0.18, 1.32)	0.15
Anxiety/Depression	No Yes	98 42	19 7	0.86 (0.28, 2.34)	0.82
Abdominal Pain	No Yes	41 98	13 11	0.36 (0.13, 0.94)	0.032*
Bleeding	No Yes	69 68	18 6	0.34 (0.1, 0.96)	0.028*
Endo	No Yes	82 42	19 7	0.52 (0.17, 1.4)	0.19
Any EIM	No Yes	92 48	16 10	0.66 (0.45, 3.06)	0.66
Disease Complications	No Yes	139 1	26 0	0	1
Anti-TNF	No Yes	111 29	21 5	0.91 (0.25, 2.78)	1
Mesalamine	No Yes	91 49	13 13	1.85 (0.73, 4.72)	0.18
Immunomodulators	No Yes	110 30	22 4	0.67 (0.16, 2.19)	0.6
Steroids	No Yes	123 17	24 2	0.61 (0.06, 2.83)	0.74
Opiate Use	No Yes	128 12	25 1	0.43 (0.001, 3.15)	0.69

Table 3 shows the bivariate analysis for UC patients alone. Among these patients with bleeding and abdominal pain, a significantly lower incidence of diabetes was shown (OR: 0.34,

0.36). None of the other variables showed a significant impact in incidence, although, the OR for Mesalamine followed the same trend as the all disease patients. The other treatments (anti-TNF, IMM, steroids, and opiate use) saw odds ratios less than 1 indicating a trend that there is a decrease in diabetes incidence amongst patients that took them.

Table 4: Bivariate Analysis – CD Only

CD Only					
Variable		No Diabetes	Diabetes	Odds Ratio 95% CI	p-Value
Fatigue	No Yes	61 275	1 31	6.86 (1.1, 284.46)	0.026*
Diarrhea	No Yes	246 76	26 5	0.62 (0.18, 1.73)	0.5
Fecal Urgency	No Yes	94 231	9 23	1.04 (0.44, 2.65)	1
Anxiety/Depression	No Yes	203 134	21 11	0.79 (0.33, 1.79)	0.71
Abdominal Pain	No Yes	125 210	10 22	1.31 (0.57, 3.20)	0.57
Bleeding	No Yes	229 96	22 10	1.08 (0.44, 2.49)	0.84
Endo	No Yes	243 163	22 10	1.17 (0.478, 2.7)	0.684
Any EIM	No Yes	179 165	17 8	0.51 (0.186, 1.29)	0.15
Disease Complications	No Yes	167 177	12 13	1.02 (0.42, 2.53)	1
Anti-TNF	No Yes	223 114	15 17	2.21 (0.99, 4.95)	0.034*
Mesalamine	No Yes	306 31	29 3	2.2 (0.75, 5.69)	0.09
Immunomodulators	No Yes	267 77	17 8	1.63 (0.59, 4.17)	0.32
Steroids	No Yes	305 39	19 6	2.46 (0.76, 6.92)	0.10
Opiate Use	No Yes	310 34	20 5	2.27 (0.63, 6.79)	.17

Table 4 shows the bivariate analysis for CD patients alone. Patients with fatigue showed

a large significant increase in the incidence of diabetes, (OR: 6.86) with only one of the diabetes patients showing no fatigue. Anti-TNF use as an IBD treatment also showed a significant increase in the incidence of diabetes (OR: 2.21). The other variables did not show any significant effect, but mesalamine continues to follow the same trend which is evident in the OR of 2.2.

Table 5: Multivariable Logistic Regression – All Disease

Multivariable Logistic Regression All Disease			
	Estimate and 95% CI	P Value	Odds Ratio and 95% CI
Age	0.05 (0.028, 0.081)	<0.001*	1.06 (1.03, 1.08)
EIM	0.14 (-0.68, 0.98)	0.74	1.15 (0.5, 2.62)
Pain	-0.072 (-0.3, 0.15)	0.52	0.93 (0.75, 1.16)
Mesalamine	0.46 (-0.51, 1.37)	0.34	1.57 (0.622, 4.00)
Male	0.20 (-.62, 1.03)	0.49	1.23 (0.54, 2.78)
Fatigue	0.69 (-0.56, 2.24)	0.62	1.99 (0.51, 7.74)
Diarrhea	-0.60 (-1.88, 0.45)	0.3	0.55 (0.18, 1.71)
ESR	0.01 (-0.011, 0.031)	0.33	1.011 (0.99, 1.03)
Disease Comp	-0.7 (-1.62, 0.16)	0.12	0.49 (0.21, 1.21)

Table 5 shows the multivariable logistic regression model results for all IBD patients. The only variable that showed significance when controlling for all other variables was age which showed a parameter estimate of 0.05 ($p < .001$) and an OR of 1.06 indicating that as age increases the likelihood of diabetes also increases.

Table 6: Multivariable Logistic Regression – CD Only

Multivariable Logistic Regression CD Only			
	Estimate 95% CI	P Value	Odds Ratio and 95% CI
Age	0.04 (0.004, 0.071)	0.032*	1.04 (1.00, 1.07)
EIM	-0.86 (-2.04, 0.28)	0.14	0.43 (0.14, 1.34)
Pain	-0.10 (-0.39, 0.18)	0.47	0.9 (0.68, 1.2)
Mesalamine	0.31 (-1.71, 1.89)	0.72	1.36 (0.24, 7.61)
Male	0.47 (-0.69, 1.68)	0.43	1.61 (0.5, 5.17)
Fatigue	0.98 (-0.93, 3.98)	0.39	2.66 (2.84, 24.85)
Diarrhea	-1.78 (-4.73, -0.042)	0.1	0.17 (0.02, 1.41)
ESR	0.016 (-0.012, 0.042)	0.24	1.02 (0.99, 1.04)
Anti - TNF	1.18 (0.08, 2.40)	0.042*	3.26 (1.04, 10.19)

Table 6 shows the multivariable logistic regression model results for patients with CD alone. Age remained statistically significant. Anti-TNF was also a significant predictor. As anti-TNF increases amongst CD patients, the likelihood of being diabetic also increases (p: 0.042, OR: 3.26). None of the other variables showed a significant effect in this model.

Table 6: Multivariable Logistic Regression – UC Only

Multivariable Logistic Regression UC Only			
	Estimate 95% CI	P Value	Odds Ratio and 95% CI
Age	0.10 (0.044, 0.18)	0.002*	1.11 (1.03, 1.19)
EIM	1.57 (-0.16, 3.69)	0.10	4.82 (0.74, 31.53)
Pain	-0.29 (-0.81, 0.17)	0.23	0.75 (0.46, 1.21)
Mesalamine	1.07 (-0.51, 2.81)	0.19	2.91 (0.58, 14.62)
Male	-0.64 (-2.38, 0.98)	0.44	0.53 (0.1, 2.69)
Fatigue	1.16 (-1.01, 3.78)	0.33	3.21 (0.31, 32.95)
Diarrhea	0.91 (-1.11, 2.93)	0.36	2.48 (.35, 17.57)
ESR	0.02 (-0.029, 0.067)	0.4	1.02 (0.97, 1.07)
Bleed	-0.7 (-2.40, 0.88)	0.39	0.5 (.10, 2.46)

Table 6 showed the multivariable logistic regression model for UC patients alone. Age again showed significance like the other models. As age increases amongst UC patients, the likelihood of a patient also being diabetic increases (p-value: 0.002, OR: 1.11). None of the other variables showed a significant effect in this model.

Chapter 4 – Discussion

This study showed that there does appear to be a link between IBD and diabetes. In all IBD patients (Table 3), mesalamine showed a significant increase while anti-TNF and fatigue showed trends in the same direction. This suggests that there is a correlation between diabetes and increased IBD activity because those three variables are associated with more severe disease and overall lower quality of life. Abdominal pain and bleeding showed trends in the opposite direction but they were not significant. This could be due more to the fact that there were more CD patients than UC in this dataset. A more balanced dataset might show different results since the two diseases appear to show opposite results for these two variables.

CD showed a positive trend with all 5 variables in Table 5 with fatigue and anti-TNF showing a significant correlation (OR: 6.86 and 2.21 respectively). Fatigue appears to have a very strong correlation as very few diabetes patients showed no fatigue. Although none of the trends were significant in the logistic regression for CD, fatigue, diarrhea, mesalamine, and ESR showed that diabetes patients are more likely to have higher scores for these variables. The data shows that CD patients with lower quality of life tend to be at more of a risk of also having diabetes. Diabetes only exacerbates quality of life as well. This trend is interesting and is something that further research could be helpful to find ways to reverse it.

Ulcerative colitis appears to show less conclusive results than those of CD. In the bivariate analysis bleeding and abdominal pain actually showed a statistically significant odds ratio in the opposite direction (OR: 0.34, 0.36 respectively) while fatigue and anti-TNF were also trending in the same direction. This is showing that people with more severe UC symptoms are less likely to also have diabetes. The difference between CD and UC patients with more severe disease and lower quality of life also having diabetes is something that should be looked

at further to see what exactly could be causing this.

This study was not without its limitations and there are a few things that could have been done differently to yield more comprehensive results. Several of the variables showed trends in certain directions but they were not significant which is something that could have possibly been corrected with a larger sample size. There were also some analyses that would have been looked at if there were more patients. There was not enough indeterminant colitis patients to subgroup them on their own and could only have been included in all disease. Additionally, the population did not have enough diabetes patients on its own which is why prediabetes was included with diabetes for all analyses. However, with a larger sample size, both prediabetes and diabetes could have had their own subgroup analysis.

Additionally, there were a few variables that the dataset did not include that could have been valuable. Metformin, a drug commonly used to treat diabetes, has been shown to have anti-inflammatory effects on mice colon.[12] However, this data on whether patients were on this drug or not was not available but could have been interesting to see what the results showed. Obesity is also something that has been shown to be a risk factor IBD.[13] It is difficult to quantify obesity as BMI is not always the most accurate, but another way of indexing overweight and obesity could have been useful in a logistic regression model since it is also a risk factor for diabetes. We did not have access to BMI data for all patients in this study so it was not included in this analysis.

For future studies there are a few avenues that could be taken. This data appears to show a trend in CD patients when it comes to quality of life and disease activity. However, there were many odds ratios that were close to being significant which could have been with a larger sample size. As more patients see IBD specialists at the Hershey Medical Center and fill out the

SIBDQ, this study can be updated with a larger sample size over time to see if any of the variables show different outcomes. Additionally, causality could not have been assessed due to the nature of a retrospective study. A prospective observational study could further explain whether IBD is a risk factor for developing diabetes, or if diabetes just contributes to more severe IBD symptoms and thus lower quality of life.

Chapter 5 – Conclusion

The aim of this study was to assess the role that symptoms and treatments for IBD have one the development of diabetes. In all IBD patients, it appeared that mesalamine use correlates with an increased incidence of diabetes. Patients with CD showed evidence that lower quality of life could lead to increased diabetes levels as shown by the trends in anti-TNF and fatigue. It could be important to screen CD patients exhibiting higher fatigue and taking anti-TNF for prediabetes/diabetes.

This study showed that there could be a link between the symptoms and treatments IBD patients are taking to the incidence of diabetes. This could be a potential problem because IBD alone carries with it significant morbidity/mortality and diabetes will only add to that. If clinicians are able to identify patients that are at greater risk for developing diabetes that could greatly increase quality of life. This study does not show who is at greater risk for developing diabetes directly, but it does identify possible variables that could be looked at in future studies to assess who is at greater risk.

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