ORIGINAL RESEARCH

Association of Antidiabetic Drug Target Genes with Inflammatory Bowel Disease: A Mendelian Randomization Study

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Background: An unmet medical need for the treatment of inflammatory bowel disease (IBD) exists. A part of antidiabetic drugs had potential effects on IBD in various observational research.

Objective: To investigate the potential of antidiabetic drugs on IBD.

Methods: We undertook a summary-data-based Mendelian randomization (SMR) using the expression quantitative trait loci (eQTL) expressed in the blood or colon and a two sample Mendelian randomization (TSMR) utilizing single nucleotide polymorphism (SNP) of antidiabetic drug target genes mediated by blood glucose traits. Participants encompassed patients with IBD (25,042 cases/34,915 controls), UC (12,366 cases/33,609 controls), and CD (12,194 cases/28,072 controls). Data on eQTL in the blood or the colon were from the eQTLGen consortium (31,684 individuals) or GTEx Consortium V8, respectively. SMR was performed by SMR software (20,220,322); the primary method for TSMR was inverse-variance weighted (IVW) or Wald ratio through R studio (2023.06.0+421). Sensitivity analyses were carried out.

Results: A 1-SD upper expression of the *KCNJ11* gene (target gene of sulfonylureas) in the blood reduced the risk of CD (OR per 1-SD = 0.728, 95% CI = 0.586–0.903, P = 0.004) according to the result of SMR. *ABCC8* (target gene of sulfonylureas) expressed in the colon did not affect CD, UC, or IBD. T2D-mediated *KCNJ11* has a protective effect on CD (OR = 0.475, 95% CI = 0.297–0.761, P = 0.002). Gene predicted no relationship between T2D and CD.

Conclusion: Sulfonylureas (SUs) may have side effects on CD. This work provides some suggestions for the selection of antidiabetic drugs in patients with CD.

Keywords: antidiabetic drugs, inflammatory bowel disease, Mendelian randomization

Introduction

Inflammatory bowel disease (IBD), mainly incorporating ulcerative colitis (UC) and Crohn's disease (CD), is a progressive gastrointestinal disease that alternated between relapse and remission. The clinical manifestations include hematochezia, abdominal pain, and diarrhea,[1,2] possibly accompanied by extra-intestinal impairments, for instance, liver, joint and skin. IBD prevailed in 0.3% of Europeans,[3] and a growing number of incidence of IBD in individuals over 60 years old, posing a challenge for the management of the disease.[4]

Type 2 diabetes (T2D) is a common metabolic disorder, and mainly occurs in middle-aged and elderly people.[5] Chronic inflammation has been demonstrated in the pathogenesis of T2D.[5] Observational studies have shown an increasing prevalence of T2D in chronic inflammatory diseases such as rheumatoid arthritis and psoriasis,[6] so was IBD.[7,8] Accordingly, how to manage hypoglycemic drugs for patients with IBD is worth exploring and meaningful. Traditional pharmaceutical interventions, including

biguanides (such as metformin), sulfonylureas (SUs), thiazolidinediones (TZDs), insulin, alongside innovative antidiabetic agents like dipeptidyl peptidase-4 inhibitors (DPP-IVi), sodium-glucose cotransporter 2 inhibitors (SGLT-2i), and glucagon-like peptide-1 receptor agonists (GLP-1RA), have proven efficacy in managing T2D.[9] Observational studies have shown the effect of different classes of antidiabetic drugs on IBD, yet the results have been inconsistent. In terms of the possible association between IBD and T2D, clarifying the effect of antidiabetic drugs on IBD is necessary, challenging, and charming.

Randomized controlled trials (RCTs) are the criterion for determining the efficacy of drugs. Nevertheless, undertaking an RCT requires temporal demands, substantial financial requisites, and the augmented necessity for human involvement. Mendelian randomization, a statistical method, employs genetic variants as instrumental variables (IVs) to deduce causal links between exposures and outcomes. This method's principle is the random assignment of parental genetic variants to offspring, influencing the offspring's phenotype. In parallel, genetic variation preceding the disease can help prevent reverse causality. Thus, to some extent, it is similar to RCTs. This method is additionally employed to infer the effects of drug target genes on outcomes. The expression quantitative trait loci (eQTLs) encoding drugs can be applied as IVs to perform an MR analysis.[10] Several studies have investigated the relationship between statins and COVID-19 and antihypertensive drugs and psychiatric disorders utilizing this method.[10,11]

In this study, we performed an MR analysis to explore the effects of antidiabetic drugs on IBD.

Method
Study Review

Two methods, SMR and TSMR, were utilized to elucidate the effects of antidiabetic drugs on IBD. These methodologies necessarily rely on three core assumptions: i) strong association between genetic variation with exposure (relevance); ii) the absence of connection between genetic variation and confounding factors (independence); iii) the impact of genetic variations on outcomes is exclusively mediated by the exposure (exclusion restriction). The flow chart of the present study was shown in Figure 1.
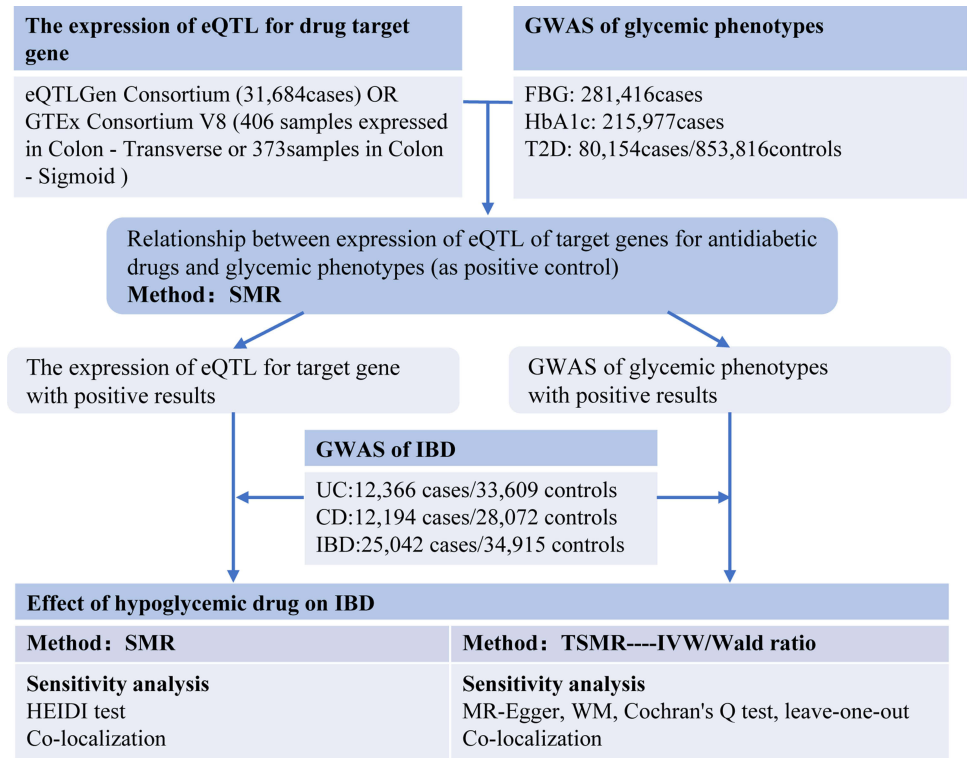
The expression of eQTL for drug target gene	GWAS of glycemic phenotypes
eQTLGen Consortium (31,684cases) OR GTEx Consortium V8 (406 samples expressed in Colon - Transverse or 373samples in Colon - Sigmoid)	FBG: 281,416cases HbA1c: 215,977cases T2D: 80,154cases/853,816controls

Relationship between expression of eQTL of target genes for antidiabetic drugs and glycemic phenotypes (as positive control)
Method：SMR

The expression of eQTL for target gene with positive results	GWAS of glycemic phenotypes with positive results

GWAS of IBD

UC:12,366 cases/33,609 controls
CD:12,194 cases/28,072 controls
IBD:25,042 cases/34,915 controls

Effect of hypoglycemic drug on IBD

Method：SMR	Method：TSMR----IVW/Wald ratio
Sensitivity analysis HEIDI test Co-localization	**Sensitivity analysis** MR-Egger, WM, Cochran's Q test, leave-one-out Co-localization

Figure 1 Flow chart of Study.
Abbreviations: eQTLs, expression quantitative trait loci; GWAS, genome-wide association study; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; T2D, type 2 diabetes; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; SMR, summary-data-based Mendelian randomization, TSMR, two sample Mendelian randomization; HEIDI, heterogeneity in dependent instruments; IVW, inverse-variance weighted; WM, weighted median.

Effect of Antidiabetic Agents on IBD

Data Sources and Instrumental Variables Selection

SMR

We searched target genes of antidiabetic drugs DrugBank (https://go.drugbank.com/) and ChEMBL (https://www.ebi.ac.uk/chembl/); consistent genes in both databases were included in the analysis (Supplementary Table 1).

Given that the mechanisms of metformin were complicated and inconsistent in the two databases, it was not included. The expression quantitative trait loci (eQTLs) of the above drug target genes were obtained from the eQTLGen consortium (https://www.eqtlgen.org/), inclusive of blood samples from 31,684 subjects, of which the cis-eQTLs were selected to act as a proxy for these drugs. In addition, we sought the relevant genes from GTEx Consortium V8 (http://www.gtexportal.org/) if those were not available in the eQTLGen consortium. The cis-eQTLs with $p < 5*10-08$, minor allele frequency (MAF) > 0.01, and F value [calculate as $(beta/SE)^2$] > 10 were selected as IVs for analysis as previous study.[11]

The antidiabetic agents were mainly applied to treat T2D for lowering blood glucose and glycated hemoglobin, so we utilized GWAS summary data from the European population for FBG (281,416 cases), HbA1c (215,977 cases), and T2D (80,154/853,816 cases) as the positive control.[12,13] We included the genes with statistical significance in SMR or TSMR. The data for IBD derived from a meta-analysis encompassed patients with IBD (25,042 cases/34,915 controls), UC (12,366 cases/33,609 controls) and CD (12,194 cases/28,072 controls).[14] Data sources were detailed in Table 1. The GWAS data were adjusted for sex and/or age and/or body mass index (BMI). Furthermore, these data underwent rigorous quality control to ensure data reliability.

TSMR

GWAS summary data of T2D, FBG, or HbA1c, whose SMR result was statistically significant with cis-eQTLs of target genes, were used as the proxy. SNPs with $P < 5*10-08$ and weakly linkage disequilibrium ($r^2 < 0.1$) with the target gene (located within ± 100kb region and MAF > 0.01) were selected as IVs.[15] The GWAS data for IBD are the same as above.

Statistical Analysis

For SMR, IVs were cis-eQTLs; SMR software (20,220,322) was used to coordinate and analyze them. For TSMR, the primary method was IVW; when there was only an IV, the Wald ratio method was used. These analyses were conducted using RStudio (2023.06.0+421).

Sensitivity Analysis

For SMR, pleiotropy is due to an SNP associated with multiple genes, which was checked for the HEIDI test. The P-value of HEIDI < 0.01 indicated pleiotropy.[10] Genes with pleiotropy were excluded in the further analysis as in previous studies.[10]

For TSMR, MR-Egger and weighted median (WM) were employed for sensitivity analysis if there were sufficient IVs. Heterogeneity was detected by Cochran's Q test; the leave-one-out method tested whether the result was responsible for a single SNP.

Table 1 Data Sources for Phenotypes

Phenotypes	Data Sources
FBG	https://magicinvestigators.org/downloads/
HbA1c	https://magicinvestigators.org/downloads/
T2D	https://www.diagram-consortium.org/
UC	https://www.ebi.ac.uk/gwas/studies/GCST004133
CD	https://www.ebi.ac.uk/gwas/studies/GCST004132
IBD	https://www.ebi.ac.uk/gwas/studies/GCST004131

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; T2D, type 2 diabetes; UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease.

We conducted co-localization analyses taking advantage of the cis-eQTL of the gene and GWAS (located within ± 1MB window) or glucose GWAS and IBD GWAS within the target gene region (located within ± 500kb window), which provided the possibility of two phenotypes sharing genetic variation.

Multiple testing was performed with Bonferroni corrections to adjust the threshold of significance. For SMR, P value <0.0028 (6 genes and 3 phenotypes) was of significance, while 0.0028 < P value < 0.05 meant evidence for the suggestion. For TSMR, P value < 0.008 (2 drugs and 3 phenotypes) stood for significance, while 0.008 < P value < 0.05 was on behalf of suggestion.

Effect of Blood Glucose on IBD
IVs Selection
Three criteria met as follows: ① $P < 5*10E-8$; ②$r^2 < 0.001$ and kb = 10,000 for removing linkage disequilibrium; ③ the value of F >10.

Statistical Analysis
The primary analysis method was IVW, the most efficient one, whose assumption was that all the IVs played a role. Additional methods were MR-Egger and WM. If the results of these three methods were not in the same direction, the p-value was tightened as previous study.[16]

Sensitivity Analysis
Cochran's Q test was used for the heterogeneity; the MR-Egger intercept test determined whether there was horizontal pleiotropy; the MR-PRESSO test detected the outliers. Leave-one-out was conducted to evaluate the robustness of this research and detect outliers. After removing the outlier, we conducted a reanalysis.

Result
Gene Selection of Antidiabetic Drugs
Seven common hypoglycemic target genes were searched in 2 databases (Supplementary Table 1), of which *ABCC8* cannot be queried in the eQTLGen consortium since we searched this gene expressed in the colon for data analysis in the GTEx Portal. Six genes were associated with type 2 diabetes, fasting blood glucose, or glycosylated hemoglobin, except *GL*P1R (Supplementary Table 2).

Relationship Between Cis-eQTL of Antidiabetic Drug Targets and IBD
The suggestive evidence showed that increasing *SLC5A2* in the blood may increase the risk of UC (OR per 1-SD = 1.968 95% CI = 1.007–3.848, P = 0.048). It was suggestive evidence that increasing the expression of *PPARG* in the blood alleviated CD (OR per 1-SD = 0.861, 95% CI = 0.758–0.978, P = 0.021), not UC or IBD. It was the evidence for a recommendation that increasing *KCNJ11* in the blood may reduce the risk of CD (OR per 1-SD = 0.728, 95% CI = 0.586–0.903, P = 0.004) or IBD (OR per 1-SD = 0.833, 95% CI = 0.706–0.983, P = 0.031) (Figure 2). *DPP4* or *INSR* in the blood or *ABCC8* in the colon did not affect IBD, UC, or CD (Supplementary Table 3).

Association Between T2D, HbA1c, or FBG -Mediated Antidiabetic Drug and IBD
We analyzed the cis-eQTL of different hypoglycemic target genes with T2D, HbA1c, or FBG as positive controls, and the positive results were used as proxy hypoglycemic agents (Supplementary Table 2). Only two target genes (*KCNJ11* and *PPARG*) were found agents in the GWAS of T2D. *ABCC8*, another gene that codes for sulfonylureas, and *KCNJ11* could not be discovered as a proxy in HbA1c GWAS. One SNP proxied for *KCNJ11* by T2D was shown as Supplementary Table 4.

The results were consistent with SMR, and increasing expression of *KCNJ11* reduced the risk of CD (OR = 0.475, 95% CI = 0.297–0.761, P = 0.002). The suggestive evidence suggested that increasing *KCNJ11* expression mediated by T2D lowered the risk of increased IBD (OR = 0.663, 95% CI = 0.460–0.956, P = 0.028) (Figure 3).
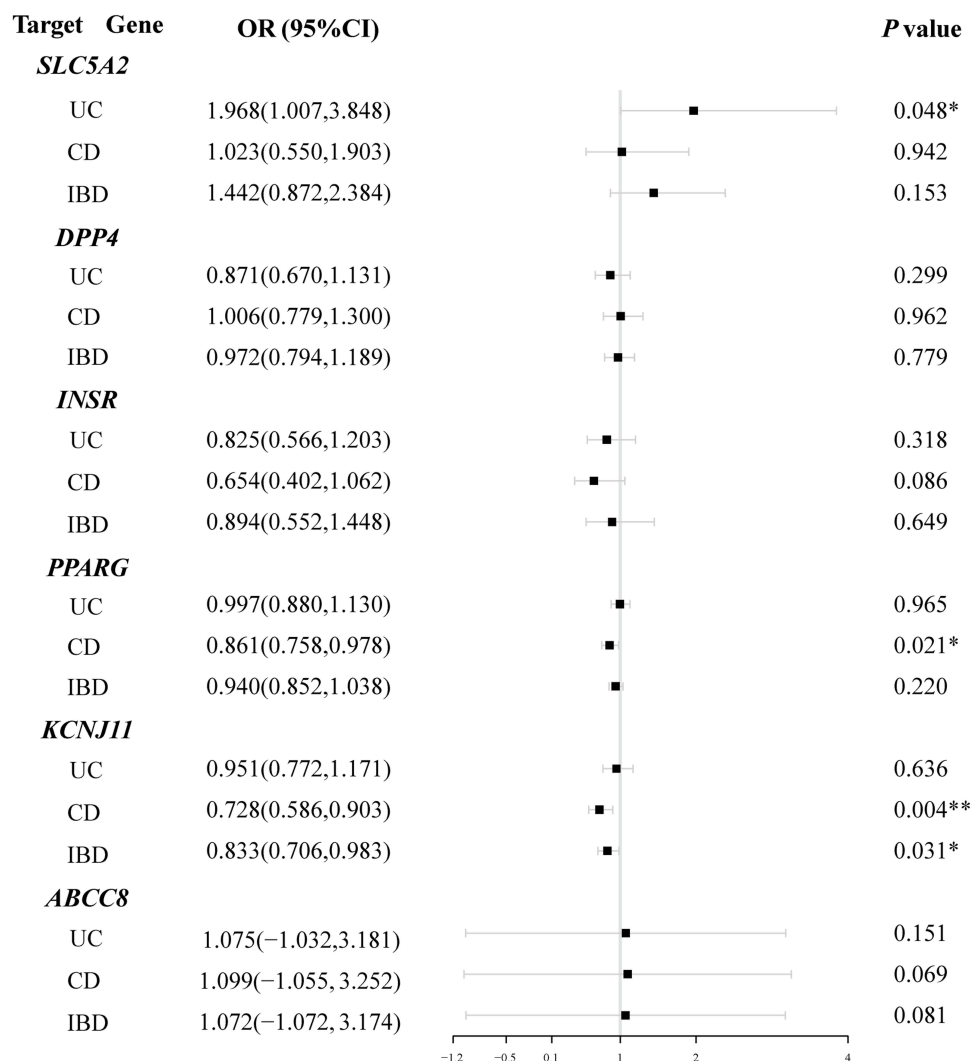
Target Gene	OR (95%CI)		*P* value
SLC5A2			
UC	1.968(1.007,3.848)		0.048*
CD	1.023(0.550,1.903)		0.942
IBD	1.442(0.872,2.384)		0.153
DPP4			
UC	0.871(0.670,1.131)		0.299
CD	1.006(0.779,1.300)		0.962
IBD	0.972(0.794,1.189)		0.779
INSR			
UC	0.825(0.566,1.203)		0.318
CD	0.654(0.402,1.062)		0.086
IBD	0.894(0.552,1.448)		0.649
PPARG			
UC	0.997(0.880,1.130)		0.965
CD	0.861(0.758,0.978)		0.021*
IBD	0.940(0.852,1.038)		0.220
KCNJ11			
UC	0.951(0.772,1.171)		0.636
CD	0.728(0.586,0.903)		0.004**
IBD	0.833(0.706,0.983)		0.031*
ABCC8			
UC	1.075(−1.032,3.181)		0.151
CD	1.099(−1.055, 3.252)		0.069
IBD	1.072(−1.072,3.174)		0.081

−1.2 −0.5 0.1 1 2 4

Figure 2 Relationship between cis-eQTL of antidiabetic drug targets and IBD (Results based on SMR).
Notes: *P < 0.05, **P < 0.01.
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; OR, odds ratio; CI, confidence interval; eQTL, expression quantitative trait loci; SMR, summary-data-based Mendelian randomization.

Two SNPs were as IVs for T2D-mediated *PPARG* (Supplementary Table 5). T2D-mediated *PPARG* had no effect on inflammatory bowel disease (Figure 3). So was HbA1c-mediated *PPARG* (Supplementary Tables 6 and 7).

Sensitivity Analysis

In the SMR analysis, no pleiotropy between *KCNJ11* and CD was detected in the light of results of HEIDI test (Supplementary Table 3). No substantial evidence existed to support the association between the cis-eQTL of *KCNJ11* and CD within the gene region (posterior probability = 52.5%) (Supplementary Table 8).

For TSMR, there was only one SNP agent for *KCNJ11*, which was insufficient to conduct a heterogeneity test. For *PPARG*, no heterogeneity was detected on the basis of Cochran's Q test (Supplementary Tables 9 and 10). Insufficient SNP was included to perform other sensitivity analyses. The results of colocalization analysis indicated that there was no substantial evidence of the correlation between the T2D and CD in the *KCNJ11* region (posterior probability = 0.229%) (Supplementary Table 11).

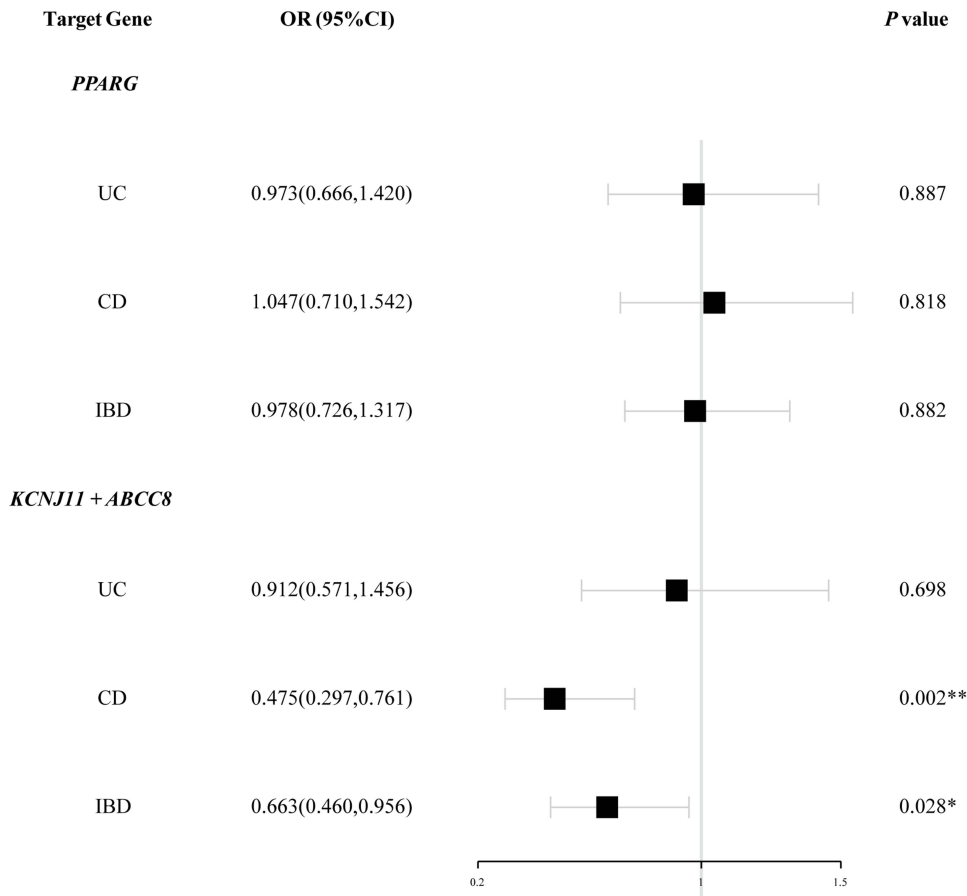| Target Gene	OR (95%CI)		P value
PPARG			
UC	0.973(0.666,1.420)		0.887
CD	1.047(0.710,1.542)		0.818
IBD	0.978(0.726,1.317)		0.882
KCNJ11 + ABCC8			
UC	0.912(0.571,1.456)		0.698
CD	0.475(0.297,0.761)		0.002**
IBD	0.663(0.460,0.956)		0.028*

Figure 3 Association between T2D, HbA1c, or FBG mediated hypoglycemic agents and IBD (Results based on TSMR).
Notes: *P < 0.05, **P < 0.01.
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD, inflammatory bowel disease; HbA1c, glycated hemoglobin A1c; FBG, fasting blood glucose; TSMR, two sample Mendelian randomization; OR, odds ratio; CI, confidence interval.

Relationship Between T2D and CD

We conducted a Mendelian randomization study to elucidate the relationship between T2D and CD. One hundred and thirty-seven SNPs were proxies for T2D, and the result showed no causality between T2D and CD (Supplementary Tables 12 and 13, Supplementary Figure 1, and 2).

Discussion

Mendelian randomization is a common tool used to deduce causality only under certain assumptions (relevance, independence, and exclusion restriction). This study employed two methods to demonstrate the impact of antidiabetic drugs on individuals with IBD. This study found that reduction of the expression of *KCNJ11* in the blood increased the risk of CD according to the results of SMR and TSMR. At the same time, no evidence showed that an association existed between *ABCC8* in the colon and IBD, CD, or UC in terms of SMR, suggesting employing SUs (inhibitors of *KCNJ11* and *ABCC8*) may increase the risk of CD. In parallel, the evidence pointed to no causality between T2D and CD, implying any association of *KCNJ11* with CD is independent of its association with T2D. Suggestive evidence showed that TZDs (*PPARG* agonists) could reduce the risk of CD, while *SGLT2* lowered the risk of UC according to the result of SMR. Whereas, TSMR did not support the former result, and we did not perform TSMR resulting from lacking a proxy for the latter. In addition, the association between *PPARG* or *SLC5A2* and glycemic traits was contradictory with clinical practice; these results should be explained with prudence accordingly. Moreover, we found that DPP4 inhibitors (DPP4i) or INSR agonists did not affect IBD.

Previous studies have explored the potential relationship between antidiabetic drugs and IBD, but conflicting results existed. Wang et al and Radel et al found that DPP4i did not increase the risk of IBD,[17,18] and this result was consistent with our study. Devin et al reported that DPP4i increased the overall risk of IBD by 75% compared with other hypoglycemic agents, and this risk was significant at 1–2 years and 3–4 years after treatment with the drug.[19] The activation of PPARγ, which is encoded by PPARG, inhibits NF-κB and MAPK signaling pathways to decrease the production of inflammatory factors and inflammatory cell infiltration.[20] TZDs, PPARγ (encoded by *PPARG*) agonists, have shown benefits for the intervention of UC in clinical studies. A double-blind RCT study illustrated that oral rosiglitazone (one of the TZDs) improved the rate of clinical response and clinical remission in patients with mild-to-moderate active UC. However, it did not improve the rate of endoscopic remission and was associated with edema and myalgia.[21] Another two clinical studies have also shown the potential benefits of oral or enema rosiglitazone in treating active UC.[22,23] These small samples of RCTs confirmed the benefits of rosiglitazone on UC, but the benefit on CD remained unclear. Our study shows that TZDs may benefit CD according to the results of SMR, but not for UC. Of note, the effect of *PPARG* on glycemic traits was not accordant with clinical practice; therefore, the results should be interpreted cautiously.

Strengths and Limitations

Mendelian randomization can effectively avoid reverse causality and confounding factors. In the present study, we utilized two genetic tools for proxy antidiabetic drugs to estimate the effects of those drugs on IBD; the two classes of results could confirm each other. The IVs we selected were strongly associated with antidiabetic drugs in each method. Sensitivity analyses were also performed to account for the robustness of the results.

This work has several limitations. Firstly, colocalization analysis showed weak evidence of shared genetic variation in the *KCNJ11* with CD. This was because colocalization generally provides more conservative results.[24] Secondly, the effects predicted by genetic variation are cumulative over a lifetime, and the impact of short-term administration using these drugs on IBD is not clear. Thirdly, our study used data from European subjects and cannot be generalized to other ancestry. Fourthly, no SNP was proxied to *ABCC8* in HbA1c GWAS; hence, we did not conduct TSMR. However, the *ABCC8* and *KCNJ11* are closely located on the same chromosome; T2D-mediated SNPs are the same in the two gene regions.

Conclusion

In conclusion, it was found that genetically proxied sulfonylureas has side effects on CD, whereas other hypoglycemic drugs showed no impact on IBD consistent with the results of SMR and TSMR. This study could offer insights into the clinical medical management of hypoglycemic agents in IBD patients with T2D. However, the impact on public policy remains unclear, because clinical guidelines are unlikely to be changed on the basis of MR evidence alone. Further clinical studies are needed to confirm this work and explore the possible mechanisms.

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Disclosure

The authors report no conflicts of interest in this work.

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