

Inflammatory bowel disease and diabetes: Is there a link between them?

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Abstract

Patients with inflammatory bowel disease (IBD) are reported to have an increased risk of diabetes. IBD therapies may also modulate blood glucose substantially. These observations are indicative of mechanistic connection(s) between IBD and diabetes.

Key Words: Inflammatory bowel disease; Abnormal glucose metabolism

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Core Tip: Inflammatory bowel disease is associated with an increased risk of diabetes. Mechanistic insights into their common pathogenesis may render novel therapeutic targets for these major chronic disorders.

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TO THE EDITOR

We read with interest the recent review, entitled "Effect of inflammatory bowel disease treatments on patients with diabetes mellitus", by Bower *et al*[1], which

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provided an excellent summary on the effects of different agents recommended for the treatment of inflammatory bowel disease (IBD) on glucose metabolism. These findings highlight the need for clinicians to consider the impact of IBD-related drugs on blood glucose control among IBD patients with diabetes, and also provide strong impetus to understand the potential mechanistic connection(s) between IBD and the onset of diabetes mellitus.

IBD refers to nonspecific chronic intestinal inflammatory conditions, including Crohn's disease (CD) and ulcerative colitis (UC). In the pursuit of the pathogenesis underlying IBD, 99 susceptibility loci/genes have been found to be related to IBD *via* genome-wide association studies. Interestingly, among those loci/genes, many are also associated with the risk of metabolic diseases, including type 1 and 2 diabetes[2]. A recent nationwide Danish cohort study has reported an increased risk of type 2 diabetes in patients with CD and UC, independent of glucocorticoid use[3]. Similarly, an elevated risk of type 1 diabetes was reported in pediatric patients with UC[4]. More recently, Jasser-Nitsche *et al*[5]. observed that in the German and Austrian population, children and adolescents with type 1 diabetes are at increased risk of IBD. These observations are, therefore, indicative of shared pathway(s) of pathogenesis between IBD and diabetes.

It is now widely appreciated that the gastrointestinal tract plays an important role in glucose homeostasis[6]. In recent years, there is mounting evidence that the gut microbial metabolites and their ensuing effects on the intestinal and systemic inflammation are associated with the occurrence and progression of diabetes; approximately 90% of type 2 diabetes is related to the disrupted gut microbiota, *i.e.* dysbiosis[7], a phenomenon also seen in IBD[8]. In the Danish cohort of IBD, specific abnormal microbial features are linked to the risk of type 2 diabetes[3]. Accordingly, dysbiosis may represent a common pathogenic factor of both IBD and dysglycemia.

Intestinal and metabolic homeostasis is also regulated by a number of gut-derived hormones, as a result of complex interactions between the ingesta and enteroendocrine cells. The incretin hormone glucagon-like peptide (GLP-1) is secreted from L-cells, which predominate in the distal small and large intestine[9]. GLP-1 regulates blood glucose metabolism *via* pleotropic actions, including stimulation of insulin secretion, suppression of glucagon secretion and energy intake, and slowing of gastric emptying [10]. In rodents, GLP-1 was reported to attenuate intestinal mucositis induced by chemotherapy[11]. In both patients with UC and CD and mice with colitis, the expression of GLP-1 receptor of intestinal biopsies was found to be reduced[12]; treatment with the GLP-1 receptor agonist, liraglutide, reduced levels of colonic inflammation in mice with colitis[12]. Accordingly, the reduction in the expression of dipeptidyl peptidase-4 - the enzyme that inactivates endogenously released GLP-1 - in the inflammatory bowel of patients with CD may have reflected a compensatory response of the gut to the development of inflammation[13].

Despite the reported association between the onset of IBD and diabetes, and the potential influence of IBD therapies on glucose metabolism, the common pathogenesis of IBD and diabetes remains elusive. Understanding the latter may provide novel therapeutic opportunities for these major chronic disorders.

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