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EDITORIAL

Antidiabetic drugs for IBD: a long but promising road ahead for drug repositioning to target intestinal inflammation

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Metformin is an oral antidiabetic drug classified as a biguanide that inhibits glucose release from the liver and enhances insulin sensitivity in peripheral tissues, particularly the muscles. Metformin has a variety of other pharmacologic effects as well, including anti-inflammatory, antifibrotic, and antitumor effects, as well as effects on the intestinal microbiota [1, 2], which has increased interest in its potential effects on intestinal inflammation.

A recently published historical cohort study based on administrative data from Taiwan demonstrated that the risk of inflammatory bowel disease (IBD) was reduced by half in patients with newly diagnosed type 2 diabetes treated with metformin compared to patients treated with other antidiabetic agents [3]. In a Danish study published in the October 2022 issue of the Journal of Gastroenterology, Allin et al. presented a nested case–control study using a database of approximately 300,000 people who had newly started on antidiabetic drugs [4]. Their results showed no association between the history or duration of metformin use and the risk of developing IBD; the results were similar when the patients were divided into groups with Crohn's disease (CD) or ulcerative colitis (UC), suggesting that metformin did not affect the risk of developing IBD in either CD, which is a relatively less common form of IBD in older patients, or UC, which is relatively more common in older patients [5].

These conflicting results cannot be explained simply by racial and geographic differences; several biases related to data acquisition and patient selection, largely due to the retrospective study design, are likely associated with the discrepancy. Neither study provides detailed information on the diabetes control status [6], background environmental factors [7], or detailed clinical, biomarker-based, and endoscopic studies of IBD disease activity or severity. Most importantly, because these studies focused on patients with type 2 diabetes, the mean age of the subjects was inevitably older than the general age at the onset of IBD, and thus these studies may only address the limited risk of IBD in older patients. These results must be cautiously interpreted as recent reports indicate that both the phenotype and treatment efficacy in patients with IBD differ between those who developed the disease at an older age and those who developed the disease at a young age [8, 9].

We believe that a well-designed, prospective, controlled study including younger patients is necessary to examine the protective effect of metformin against the development of IBD and that it is too early to consider metformin as a drug repositioning target for preventing IBD.

Recent advances in the development of antidiabetic drugs have been remarkable, and many drugs with new mechanisms of action are now under clinical application. In addition to metformin, dipeptidyl peptidase 4 (DPP-4) inhibitors, oral antidiabetic drugs that are now widely used in clinical practice, may have broad efficacy for diseases other than diabetes via increasing GLP-2 levels and are reported to improve gut barrier functions by a GLP-2-dependent mechanism in a murine obesity model [10]. The

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efficacy of a DPP-4 inhibitor for murine experimental colitis has also been reported [11]. GLP-2 analogs, which were recently applied clinically as a treatment for short bowel syndrome [12], also exhibit efficacy against experimental colitis in animal models [13]. In addition, GLP-1 receptor agonists, which can be used as oral antidiabetic agents for patients with type 2 diabetes, demonstrate potential efficacy against IBD. Villumsen et al. showed that the risk ratio for the adverse clinical events of IBD in patients treated with GLP-1 receptor agonists and/or DPP-4 inhibitors is lower than that in patients treated with other antidiabetic agents [14].

As the targets of therapeutic agents for diabetes recently shifted from the pancreas and insulin resistance to the gastrointestinal tract, it is expected that many future studies will evaluate the effects of antidiabetic drugs on intestinal inflammation, including IBD. Remarkable progress has also recently been made in the development of biomarkers for disease monitoring in IBD patients [15], and further research is expected to elucidate their mechanisms of action as well as the possibility of monitoring the onset and exacerbation of IBD when considering drug repositioning.

Declarations

Conflict of interest The author S.S. is an associate editor of the Journal of Gastroenterology. The remaining authors declare no conflict of interest for this article.

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