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MINIREVIEWS

Effect of inflammatory bowel disease treatments on patients with diabetes mellitus

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Abstract

As medical care progresses and the number of patients with chronic conditions increases there is the inevitable challenge of managing patients with multiple co-morbidities. Inflammatory bowel disease (IBD) is an umbrella term for are inflammatory conditions affecting the gastrointestinal tract, the two most common forms being Ulcerative Colitis and Crohn's disease. These diseases, usually diagnosed in young adults, exhibit a relapsing and remitting course and usually require long-term treatment. IBD can be treated with a number of topical and systemic treatments. We conducted a review of the current published evidence for the effects these medications can have on diabetes mellitus (DM) and glycaemic control. Searches were conducted on medline and embase with a timeframe from 1947 (the date from which studies on embase are recorded) to November 2020. Suitable publications were selected and reviewed. Current evidence of the impact of aminosalicylates, corticosteroids, thiopurines, and biologic agents was reviewed. Though there was limited evidence for certain agents, IBD medications have been shown to have an effect of DM and these effects should be considered in managing patients with dual pathologies. The effects of steroids on blood sugar control is well documented, but consideration of other agents is also important. In patients requiring steroids for Ulcerative Colitis, locally acting steroid agents delivered rectally may be preferred to minimise side effects in those with distal bowel Ulcerative Colitis. A switch to other agents should be considered as soon as possible in people with diabetes to limit the impact on glycaemic control. 5-aminosalicylates appear to play a role in the reduction of hemoglobin A1c (HbA1c), although the literature suggests these may be falsely low readings. Consequently, monitoring of people with diabetes on these agents may require daily monitoring of capillary blood sugars rather than relying simply on HbA1c; for example fructosamine performed 3-6 monthly, although this risks missing the rise in readings. There is only limited evidence of the effects of thiopurines on

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diabetes and further investigation is needed into the possible relationship between them. However, given the current available evidence it may be preferable to commence patients with diabetes on thiopurines as soon as possible, whilst also monitoring for side effects such as pancreatitis. There appears to be more evidence supporting a link between tumor necrosis factor-α inhibitors and DM. Both infliximab and adalimumab have evidence suggesting that both can cause reduced blood sugar levels. Further studies on the effects of the various biological agents mentioned are required alongside any novel biologic therapy and the impact of dual biologic therapy in the future.

Key Words: Inflammatory bowel disease; Diabetes mellitus; Crohn's disease; Ulcerative colitis; Anti-tumor necrosis factor-α; Corticosteroids

Core Tip: For patients with diabetes mellitus and inflammatory bowel disease, medication may influence glycaemic control. Furthermore, immunosuppressive therapy may modify the likelihood of other autoimmune conditions. Further studies on the effects of the various biological agents mentioned are required alongside any novel biologic therapy and the impact of dual biologic therapy in the future.

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INTRODUCTION

As medical care progresses and the number of patients with chronic conditions increases there is the inevitable challenge of managing patients with multiple co-morbidities. Inflammatory bowel disease (IBD) is an umbrella term for are inflammatory conditions affecting the gastrointestinal tract, the two most common forms being ulcerative colitis and Crohn's disease. These diseases, usually diagnosed in young adults, exhibit a relapsing and remitting course and usually require long-term treatment.

Almost 6.8 million people globally have been diagnosed with IBD[1]; approximately one quarter of these people live in the United States, with a prevalence ranging from 252 to 439 cases *per* 100000 population[2]. In the United Kingdom, the prevalence has been reported as high as 373 *per* 100000 people[3]. Australia had an estimated 89000 people living with IBD in 2018[4].

The global prevalence of diabetes mellitus (DM) has been estimated as 9.3% in 2019; approximately 463 million people[5]. Given these figures, it is inevitable that these conditions will co-exist and treatment of one may have unintended consequences on the other.

IBDs can be treated with a number of topical and systemic treatments, including aminosalicylates, steroids and biological agents[6]. We conducted a review of the current published evidence for the effects these medications can have on DM and glycaemic control.

METHODOLOGY

Using Medline and Embase, the search terms "Inflammatory Bowel Disease" and "Diabetes Mellitus", as well as specific medications "infliximab", "adalimumab", "vedolizumab", "ustekinumab", "thiopurine", "budesonide", "prednisolone" and "aminosalicylates" were utilised with a timeframe from 1947 (the date from which studies on Embase are recorded) to November 2020.

Publications were included if the medications used in IBD treatment, as listed above, were linked to glycaemic control. All English language publications were included. Our search identified a wide range of publications that included case studies, cohort studies and clinical trials. These were all reviewed with heavier weighting given to clinical trials over case studies. Furthermore relevant publications from the search papers references were also reviewed.

RESULTS

Aminosalicylates

The British Society of Gastroenterology (BSG), the European Crohn´s and Colitis Organisation (ECCO) and American Gastroenterological Association (AGA) consensus guidance recommends 5-aminosalicylates (5-ASAs), such as mesalazine, as the standard initial therapy for induction and maintenance of remission in mild to moderate ulcerative colitis[6-8]. However, the AGA does not recommend 5-ASAs in patients with moderate to severe ulcerative colitis[9]. 5-ASAs are not shown to be efficacious in the induction or maintenance of remission in Crohn's disease[6,10,11].

There is limited evidence of the effects of sulfasalazine on hemoglobin A1c (HbA1c) values. Sulfasalazine has been shown to cause haemolysis[12], which can cause falsely low HbA1c readings[13,14]. A case report of a patient with type 1 diabetes suggested sulfasalazine was associated with spuriously low HbA1c readings[15]. One study looking at people with diabetes concluded that sulfasalazine has glucose-lowering properties, after noting that patients on sulfasalazine had notably lower HbA1c values [16].

Corticosteroids

The BSG and ECCO consensus guidelines on the management of IBD both recommend oral corticosteroids (prednisolone, budesonide or beclomethasone dipropionate) as the first line treatment for induction of remission in Crohn's disease and for moderate to severe flares of ulcerative colitis[6,7] while AGA guidance recommends use of biologic treatments[9,11]. Corticosteroids are also recommended as second line treatment for mild to moderate flares of ulcerative colitis in patients who have failed to respond to aminosalicylate therapy by BSG, ECCO and AGA[2,7,8]. In patients with acute severe colitis, intravenous corticosteroids (hydrocortisone or methylprednisolone) are the recommended treatment to induce remission[6,7,9,10].

Drug-induced hyperglycaemia is most commonly the result of steroid therapy[17, 18] and undiagnosed diabetes can also be unmasked by steroid therapy[19]. A meta-analysis of 12 studies assessing the incidence of DM in patients receiving steroid treatment reported rates of 18.6%[20]. A recent cohort study demonstrated a significant dose-dependent rise in cumulative risk of diabetes in patients with immune-mediated diseases (including IBD) treated with steroids[21]. One case-control study reported a significant increase in relative risk of hyperglycaemia in patients treated with steroids compared to non-steroid treated patients[22].

Up to 50% of IBD patients treated with prednisolone suffer from adverse effects such as glucose intolerance[23]. However, with increasing use of controlled colonic release formulations of corticosteroids, such as Budesonide[24], there is the potential to reduce the rate of steroid-induced hyperglycaemia in the future.

In patients requiring recurrent or prolonged courses of corticosteroids, BSG guidelines recommend the baseline recording of fasting serum glucose or HbA1c and 3 moly monitoring thereafter[6].

Thiopurines

Thiopurines (azathioprine and its metabolite 6-mercaptopurine) are purine analogues that target the metabolism of nucleic acids[25]. They are used as steroid sparing agents in the management of IBD. Although they are not effective monotherapy in the induction of remission[6-11], the AGA recommends dual treatment with anti-tumor necrosis factor (TNF) therapy to induce remission in Crohn's disease[11]. Thiopurines are recommended as maintenance monotherapy for Crohn's disease and for the escalation of maintenance therapy in patients with ulcerative colitis requiring 2 or more courses of steroids in the past year on 5-ASAs by the BSG and ECCO guidance[6, 7,10]. The AGA guidance suggests early escalation to biologic therapy in cases of moderate to severe ulcerative colitis[9] and though thiopurine therapy is preferred to no treatment, biologic therapy is also preferred in Crohn's disease[11].

A double-blind randomised control trial comparing azathioprine to placebo demonstrated no effect on insulin dose or HbA1c at one year[26]. A prior unmasked randomised trial compared azathioprine with prednisolone to no treatment had reported lower insulin needs at one year[27].

Biologics

Escalation to treatment with a biological agent is internationally recommended in patients with acute severe colitis who fail to respond to intravenous corticosteroids by day 3 of treatment[6,7,9]. Additionally, according to BSG and ECCO use of biologics may be appropriate for patients who have persistent disease activity in ulcerative colitis and Crohn's disease that has failed to respond to oral therapies[6,7,10]. The AGA suggests that early use of biologic therapy is preferable to a "step up" approach for the management of moderate to severe ulcerative colitis[9] and anti-TNF therapy is recommended in combination with thiopurines for induction of remission in Crohn's disease[11]. However, for maintenance therapy no guidance is offered as to whether dual therapy is beneficial compared to monotherapy with anti-TNF due to insufficient evidence at time of review[11]. The AGA also recommends biologic monotherapy over thiopurine monotherapy for the maintenance of remission in moderate to severe ulcerative colitis[9]. Biological agents used in ulcerative colitis and Crohn's disease include infliximab, adalimumab, vedolizumab and ustekinumab.

Infliximab

Infliximab is a monoclonal antibody that inhibits the action of TNF-α[28]. Elevated levels of TNF-α have been linked to insulin resistance[29]. In a study using mice as an animal model, infliximab treatment was associated with improved signal transduction through the liver's insulin receptors in mice with high fat diet-induced obesity and diabetes[30].

Overexpression of TNF-α in adipose tissue and skeletal muscle has been documented in insulin-resistant patients[31,32]. Administration of TNF-α was shown to induce insulin resistance in a healthy subject group[33].

There is anecdotal evidence suggesting TNF inhibitors improve glycaemic control in individuals with Diabetes. One case report showed a 29-year-old man with Autoimmune Diabetes had improved glycaemic control, with reduced incidence of hypoglycaemic episodes, after initiating treatment with infliximab; remission of his Crohn's disease occurred alongside an immediate and sustained 2.4-fold increase in insulin secretion, and progressive 6.9-fold reduction in insulin resistance[34]. Another case report detailed a patient with type 2 DM who was able to cease insulin treatment altogether when on infliximab; once infliximab was withdrawn, insulin needed to be restarted[35]. A study involving 45 patients with either Rheumatoid Arthritis or Ankylosing Spondylitis found a significant decrease in insulin resistance with minimal confounding factors reported[36].

Of note, however, is that anti-TNF therapy has not been shown to prevent the development of type 1 diabetes in two separate case reports[37,38]. TNF-α may predispose to type 2 DM by inducing impaired glucose tolerance, but this is not conclusive.

Adalimumab

Adalimumab is also a monoclonal antibody to TNF-α[39], and can be used as an alternative to infliximab[6,10]. In a study using obese rats as test subjects, administration of adalimumab was shown to significantly reduce the fasting blood sugar levels of treated rats *vs* untreated[40]. A case report highlighted a previously well-controlled type 1 diabetic patient who reported erratic blood sugar control within 12 h of receiving adalimumab treatment, causing severe hypoglycaemic episodes[41]. Separate case reports have also shown that patients who received adalimumab experienced improvement in their glycaemic control, in some cases resulting in hypoglycaemic episodes[42,43].

A United States study with n = 67756 found a significantly increased risk of developing diabetes in patients commencing infliximab and adalimumab *vs* abatacept in patients with Rheumatoid Arthritis. Obesity was a confounding factor however, as the incidence of obesity was higher in patients on infliximab or adalimumab therapy [44]. No clinical trials have established a link between patients with IBD s commencing infliximab or adalimumab and the development of DM.

Vedolizumab and ustekinumab

Vedolizumab and ustekinumab have been recommended in patients whom anti-TNF

Table 1 Summary of medications and glycaemic effect

IBD medication	Glycaemic effect
Aminosalicylates	Potential hypoglycaemic effect
Corticosteroids	Significant cause of hyperglycaemia
Thiopurines	Possible reduced insulin resistance
Infliximab	Appears to reduce insulin resistance
Adalimumab	Potential hypoglycaemic effect

IBD: Inflammatory bowel disease.

therapy has failed for the induction and maintenance of remission of Crohn's disease [6,7,10].

No relevant papers were identified showing a link between these medications and diabetes (Table 1).

DISCUSSION

As our review of the literature demonstrates, some IBD medications have been shown to have an effect of DM. Though far from comprehensive in view of the paucity of evidence, these effects should be considered in managing patients with dual pathologies. The effects of steroids on blood sugar control is well documented, but consideration of other agents is also important. In patients requiring steroids for ulcerative colitis, locally acting steroid agents delivered rectally may be preferred to minimise side effects in those with distal bowel ulcerative colitis[6]. A switch to other agents should be considered as soon as possible in people with diabetes to limit the impact on glycaemic control.

Of 5-ASAs appear to play a role in the reduction of HbA1c, although the literature suggests these may be falsely low readings. Consequently, monitoring of people with diabetes on than relying simply on HbA1c; for example fructosamine performed 3-6 monthly, although this risks missing the rise in readings[45].

There is only limited evidence of the effects of thiopurines on diabetes. Although one randomized control trials was promising in showing lower insulin requirements after one year of treatment[18], further investigation is needed into the possible relationship between them. However, given the result of this trial it may be preferable to commence patients with diabetes on thiopurines as soon as possible, whilst also monitoring for side effects such as pancreatitis.

CONCLUSION

There appears to be more evidence supporting a link between TNF-α inhibitors and DM. Both infliximab and adalimumab have evidence suggesting that both can cause reduced blood sugar levels. Although evidence is largely anecdotal or animal studies, for physicians commencing patients on biologic therapy, the effect of on diabetes control may factor into the decision. Further studies on the effects of the various biological agents mentioned are required alongside any novel biologic therapy and the impact of dual biologic therapy in the future.

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