Effect of inflammatory bowel disease treatments on patients with diabetes mellitus

Joshua Ashley Jack Bower, Lauren O'Flynn, Rakhi Kakad, David Aldulaimi

Abstract
As medical care progresses and the number of patients with chronic conditions increases there is the inevitable challenge of managing patients with multiple comorbidities. 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 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 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 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 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 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 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 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 on diabetes mellitus (DM) and glycaemic control.
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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

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 sulfasalazin 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 of 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[12,43].

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 and commencing infliximab or adalimumab and the development of DM.

**Vedolizumab and ustekinumab**

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

## REFERENCES

1. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020; 5: 17-30 [PMID: 31648971] DOI: 10.1016/S2468-1253(19)30333-4
2. Loftus EV Jr. Update on the Incidence and Prevalence of Inflammatory Bowel Disease in the United States. Gastroenterol Hepatol (N Y) 2016; 12: 704-707 [PMID: 28035199]
3. Stone MA, Mayberry JF, Baker R. Prevalence and management of inflammatory bowel disease: a
cross-sectional study from central England. Eur J Gastroenterol Hepatol 2003; 15: 1275-1280 [PMID: 14624149 DOI: 10.1097/00042737-200312000-00004]

4 Liu J, Kariyawasam V, Borody T, Katekari P, Leong R. High age-specific prevalence of inflammatory bowel disease amongst the elderly in the city of Sydney, Australia: a metropolitan, population-based study. Gut 2018; 67: A35-A36

5 Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Monta A, Ogurtsova K, Shaw JE, Bright D, Williams R. IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019; 157: 1078-1083 [PMID: 3158657 DOI: 10.1016/j.diabres.2019.107843]

6 Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett JK, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IDF guidelines eDelphi consensus group, Gaya DR, Lgbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019; 68: s1-s106 [PMID: 31562236 DOI: 10.1136/gutjnl-2019-318484]

7 Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, Kucharz Z, Molnár T, Raine T, Sebastian S, de Sousa HT, Dignass A, Carbonnel F; European Crohn’s and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis 2017; 11: 769-784 [PMID: 28513805 DOI: 10.1093/eparcc/jlx009]

8 Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology 2019; 156: 587-604 [PMID: 30579664 DOI: 10.1053/j.gastro.2018.12.006]

9 Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology 2020; 158: 1450-1461 [PMID: 31945371 DOI: 10.1053/j.gastro.2020.01.006]

10 Torres J, Bonovas S, Doherty G, Kucharz Z, Gisbert JP, Raine T, Adatina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gangel G, Gionchetti P, Gomillon F, Gonzalez-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Ross A, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn’s Disease: Medical Treatment. J Crohns Colitis 2020; 14: 4-22 [PMID: 31711158 DOI: 10.1093/eparcc/jja180]

11 Terdiman JP, Gruss CB, Heidelberg JJ, Sultan S, Falck-Ytter YT; AGA Institute Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute Guideline on the Use of Thiopurines, Methotrexate, and Anti-TNF-α Biologic Drugs for the Induction 13 and Maintenance of Remission in Inflammatory Crohn’s Disease. Gastroenterology 2013; 145: 1459-1463 [DOI: 10.1053/j.gastro.2013.10.046]

12 Taffet SL, Das KM. Sulfasalazine. Adverse effects and desensitization. Dig Dis Sci 1983; 28: 833-842 [PMID: 6163906 DOI: 10.1007/BF01296907]

13 Radin MS. Pitfalls in hemoglobin A1c measurement: when results may be misleading. J Gen Intern Med 2014; 29: 388-394 [PMID: 24002631 DOI: 10.1007/s11606-013-2595-x]

14 Gallagher EJ, Le Roth D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes. J Diabetes 2009; 1: 9-17 [PMID: 19261515 DOI: 10.1111/j.1753-0440.2009.00009.x]

15 Tack CJ, Wetzelz JS. Decreased HbA1c levels due to sulfonylamine-induced hemolysis in two IDD patients. Diabetes Care 1996; 19: 775-776 [PMID: 8799639 DOI: 10.2337/diabetes.19.7.775]

16 Haas RM, Li P, Chu JW. Glucose-lowering effects of sulfasalazine in type 2 diabetes. Diabetes Care 2005; 28: 2238-2239 [PMID: 16123497 DOI: 10.2337/diabetes.28.9.2238]

17 Fathallah N, Slim R, Larif S, Hnouha H, Ben Salem C. Drug-Induced Hyperglycemia and Diabetes. Drug Saf 2015; 38: 1153-1168 [PMID: 26370106 DOI: 10.1007/s40264-015-0353-2]

18 Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogan H, Avorn J. Glucocorticoids and the risk for initiation of hyperglycemic therapy. Arch Intern Med 1994; 154: 97-101 [PMID: 8267494]

19 Perez A, Jansen-Chaparro S, Saiji I, Bernal-Lopez MR, Mihambres I, Gomez-Huelgas R. Glucocorticoid-induced hyperglycemia. J Diabetes 2014; 6: 9-20 [PMID: 24103089 DOI: 10.1111/1753-0407.12090]

20 Liu X, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. Ann Nutr Metab 2014; 65: 324-332 [PMID: 25402408 DOI: 10.1159/0003563892]

21 Wu J, Mackie SL, Pujades-Rodriguez M. Glucocorticoid dose-dependent risk of type 2 diabetes in six immune-mediated inflammatory diseases: a population-based cohort analysis. BMJ Open Diabetes Res Care 2020; 8 [PMID: 32719077 DOI: 10.1136/bmjdr-2020-001220]

22 Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hyperglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 1997; 157: 1681-1686 [PMID: 9250229]

23 Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, Moayyedi P.
Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; 106: 590-9 quiz 600 [PMID: 21407179 DOI: 10.1038/ajg.2011.70]

24 Campieri M, Adamo S, Valpiani D, D’Arienzo A, D’Albasio G, Pitizalis M, Cesari P, Casetti T, Castiglione GN, Rizzello F, Manguso F, Varoli G, Gionchetti P. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003; 17: 1471-1480 [PMID: 12823149 DOI: 10.1046/j.1365-2036.2003.01669.x]

25 Imboden JB, Hellmann DB, Stone JH. Current diagnosis and treatment rheumatology 3. New York: McGraw-Hill Medical, 2012

26 Cook JJ, Hudson I, Harrison LC, Dean B, Colman PG, Werther GA, Warne GL, Court JM. Double-blind controlled trial of azathioprine in children with newly diagnosed type I diabetes. *Diabetes* 1989; 38: 779-783 [PMID: 2656346 DOI: 10.2337/diab.38.6.779]

27 Silverstein J, Maclaren N, Riley W, Spiller R, Radjenovic D, Johnson S. Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. *N Engl J Med* 1988; 319: 599-604 [PMID: 3045545 DOI: 10.1056/NEJM198809083191002]

28 Jin J, Chang Y, Wei W. Clinical application and evaluation of anti-TNF-alpha agents for the treatment of rheumatoid arthritis. *Acta Pharmacol Sin* 2010; 31: 1133-1140 [PMID: 20711219 DOI: 10.1038/aps.2010.134]

29 Spranger J, Kroke A, Möhlig M, Hoffmann K, Bergmann RM, Ristow M, Boehig H, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 2003; 52: 812-817 [PMID: 12606524 DOI: 10.2337/diabetes.52.3.812]

30 Tajiri EP, De Souza CT, Ueno M, Cintra DE, Bertollo MB, Carvalheira JB, Saad MJ, Velloso LA. Infliximab restores glucose homeostasis in an animal model of diet-induced obesity and diabetes. *Endocrinology* 2007; 148: 5991-5997 [PMID: 17761768 DOI: 10.1210/en.2007-0132]

31 Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995; 95: 2409-2415 [PMID: 7738205 DOI: 10.1172/JCI117936]

32 Saghizadeh M, Ong JM, Garvey WT, Henry RR, Kern PA. The expression of TNF alpha by human muscle. Relationship to insulin resistance. *J Clin Invest* 1996; 97: 1111-1116 [PMID: 8613535 DOI: 10.1172/JCI118504]

33 Van der Poll T, Romijn JA, Enderdt E, Borm JJ, Bäumer HR, Sauerwein HP. Tumor necrosis factor mimics the metabolic response to acute infection in healthy humans. *Am J Physiol* 1991; 261: E457-E465 [PMID: 1928337 DOI: 10.1152/ajpendo.1991.261.4.E457]

34 Timper K, Hruz P, Beglinger C, Donath MY. Infliximab in the treatment of Crohn disease and type 1 diabetes. *Diabetes Care* 2013; 36: e90-e91 [PMID: 23801815 DOI: 10.2337/dc13-0199]

35 Yazdani-Biuki B, Stiel H, Brezinschek HP, Hermann J, Mueller T, Kripl P, Graninger W, Wascher TC. Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-alpha antibody infliximab. *Eur J Clin Invest* 2004; 34: 641-642 [PMID: 15379764 DOI: 10.1111/j.1365-2362.2004.01390.x]

36 Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 765-766 [PMID: 15458960 DOI: 10.1136/ard.2004.026534]

37 Tack CJ, Kleijwegt FS, Van Riel PL, Roep BO. Development of type 1 diabetes in a patient treated with anti-TNF-a therapy for active rheumatoid arthritis. *Diabetologia* 2009; 52: 1442-1444 [PMID: 19440690 DOI: 10.1007/s00125-009-1381-0]

38 Bloom BJ. Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 2606-2608 [PMID: 11083287 DOI: 10.1002/1529-0131(200011)43:11<2606::AID-ANR31>3.0.CO;2-X]

39 Wong M, Ziring D, Korin Y, Desai S, Kim S, Lin J, Gjertson D, Reed E, Singh RR. TNFalpha blockade in human diseases: mechanisms and future directions. *Clin Immunol* 2008; 126: 121-136 [PMID: 17916444 DOI: 10.1016/j.clim.2007.08.013]

40 Shuwa HA, Dallatu MK, Yeldeh MH, Ahmed HM, Nasir IA. Effects of Adalimumab, an Anti-tumour Necrosis Factor-Anti (TNF-a) Antibody, on Obese Diabetic Rats. *Malays J Med Sci* 2018; 25: 51-62 [PMID: 30914847 DOI: 10.21315/mjms2018.25.4.5]

41 Boulton JG, Bourne JT. Unstable diabetes in a patient receiving anti-TNF-alpha for rheumatoid arthritis. *Rheumatology (Oxford)* 2007; 46: 178-179 [PMID: 16998233 DOI: 10.1093/rheumatology/kel322]

42 Arif S, Cox P, Afzali B, Lombardi G, Lechler RI, Peakman M, Mirenda V. Anti-TNFalpha therapy--killing two birds with one stone? *Lancet* 2010; 375: 2278 [PMID: 20609973 DOI: 10.1016/S0140-6736(10)60394-7]

43 van Eijk IC, Peters MJ, Nurmoohamed MT, van Deutekom AW, Dijkmans BA, Simsek S. Decrease of fructosamine levels during treatment with adalimumab in patients with both diabetes and rheumatoid arthritis. *Eur J Endocrinol* 2007; 156: 291-293 [PMID: 17322487 DOI: 10.1530/EJE-06-0693]

44 Desai RJ, Dejeane S, Jin Y, Liu J, Kim SC. Comparative Risk of Diabetes Mellitus in Patients With Rheumatoid Arthritis Treated With Biologic or Targeted Synthetic Disease-Modifying Drugs: A Cohort Study. *ACR Open Rheumatol* 2020; 2: 222-231 [PMID: 32267094 DOI: 10.1002/acr2.11124]

45 Shepard JG, Airee A, Dake AW, McFarland MS, Vora A. Limitations of A1c Interpretation. *South Med J* 2015; 108: 724-729 [PMID: 26630892 DOI: 10.1044/smj.0000000000003381]
