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Steroid therapy in patients with inflammatory bowel disease complicating diabetes diagnosis

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Abstract

Inflammatory bowel diseases (IBDs), such as Crohn's disease (CD), ulcerative colitis (UC) or type 1 diabetes (T1D) are autoimmune diseases that may have common susceptibility pathways. In the etiology of these diseases, scientists are seeking not only genetic, but also environmental factors, infections, nutritional deficiencies, and iatrogenic causes, especially in T1D. The relationship between T1D and steroid therapy, used in the treatment of the inflammatory bowel disease, has been well established for years. Steroids are most commonly known for causing drug-induced diabetes. We present a 35-year-old man, in whom a drug-induced diabetes was suggested due to a 4-week steroid therapy used as a treatment for his newly diagnosed ulcerative colitis and a literature review describing a similar problem.

To confirm the association between diabetes and steroid therapy, it was necessary to rule out an autoimmune background of the disease. However, the presence of autoantibodies to GAD and anti- α tyrosine phosphatase (IA-2) confirmed the diagnosis of T1D.

Aim of the study

This review aims to present the issue of type 1 diabetes in patients treated with steroid therapy for inflammatory bowel disease, and to summarize the current state of knowledge, so that in the future it will result in an accurate diagnosis and implementation of appropriate treatment.

Methods and materials

A literature review was conducted based on the PubMed database, using keywords: "diabetes mellitus", "inflammatory bowel diseases", "ulcerative colitis", „steroids", "insulin".

Conclusion

We should suspect T1D in patients, especially in the young population suffering from autoimmune diseases in order to prevent serious complications including dysfunction and failure of various organs, such as eyes, kidneys, nerves, heart and blood vessels.

Key words: diabetes mellitus; inflammatory bowel diseases; ulcerative colitis; steroids; insulin

Introduction

A direct link between some autoimmune diseases, including inflammatory bowel diseases (IBD) and type 1 diabetes (T1D), and their coexistence have not yet been established. More and more research points to a common genetic and molecular pathway. [1]Currently, there is an increase in the incidence of the abovementioned autoimmune diseases. Globally, both incidence and prevalence of T1D is increasing, with an overall annual increase in incidence of about 2-3% per year [2-4].

Currently, the average prevalence of IBD in the general population of Western countries is estimated at 1 in 1000 people. Although little epidemiological data are available for developing countries, the incidence and prevalence of IBD appear to have increased in virtually all regions of the world over the past 50 years, indicating its emergence as a global disease [5-9].

IBD may be treated with a variety of topical and systemic treatments, including aminosalicylates, steroids, and biological drugs.[10,11] IBD medications have been shown to affect diabetes mellitus (DM), and this fact should be considered in the management of patients with dual pathology. The effect of steroids on blood sugar management is well-documented, but it is essential to consider other medications as well. [12,13]

We present a case report of a patient treated with steroids for ulcerative colitis (UC), who developed significant hyperglycemia and was subsequently diagnosed with T1D. Deserving of interest here are the clinical situation when the patient developed DM, the autoimmune factors, and the impact of medications used as a treatment for UC.

Case report

In April, 2022, a 35-year-old male patient was urgently admitted to the endocrinology clinic for treatment of newly diagnosed diabetes mellitus and to determine the etiology of the disease. His medical history included typical symptoms – polydipsia, polyuria (5-6 L of fluids per day), and deterioration of visual acuity for the past 4 days. Prior to hospitalization, ambulatory fasting venous blood glucose level was at 417 mg/dl. His height (182 cm), body weight (68,5 kg), and body mass index (20,8 kg/m²) were within normal limits. On admission: heart rate steady, BP 133/85 mmHg, HR 72/min, saturation 97%, temperature, 36.5°C.

In medical history: bloody diarrhea and weight loss (13kg) since January 2022. These symptoms were the reason for hospitalization in February in the gastroenterology clinic, where ulcerative colitis was diagnosed. The patient was treated with: methylprednisolone 28 mg orally 2x per day, mesalazine 500 mg three tablets twice a day. After 3 weeks the methylprednisolone dose was reduced to 2x 24 mg. The patient was not instructed by his gastrologist to monitor his blood sugar levels while being treated with steroids. From the patient's medical files, it was also gathered that he was not monitoring his blood sugar levels prior to the implementation of steroids. After 4 weeks, the gastrointestinal symptoms resolved, but at the same time diabetic symptoms appeared.

On admission, venous blood glucose measurement was at 373 mg/dl (Normal range (N): 70-99mg/dl). The HbA1c level of 8.7% (N:4-6%) was found, which indicates long-term metabolic imbalance. Urinalysis showed elevated specific gravity of 1.030 (N: 1.012-1.026), glycosuria (≥ 1000 mg/dl) and ketonuria (15 mg/dl).

Acid-base imbalance was confirmed in the form of compensated metabolic acidosis. Venous blood PH was normal - 7.35 (N: 7.35-7.45) with decreased level of HCO_3^- 21.7 mmol/l (N:24-27 mmol/l) and compensatory decrease of pCO_2 - 39 mmHg (N: 41-51mmHg). Anti-glutamic acid decarboxylase (anti-GAD) was at > 2000 IU/ml (≥ 10 IU/ml - positive test), anti- α tyrosine phosphatase (IA2) < 0.10 IU/ml (< 10 IU/ml – negative test), anti-insulin (IAA) 7.7 uIU/ml (< 25 uIU/ml – negative test). No anti-pancreatic islet antibodies were detected. The level of anti-GAD antibodies was greater than 200 times the normal value, which led to the diagnosis of T1D. Despite numerous abnormalities indicating impaired glucose metabolism, pancreatic reserve was still preserved. The glucose level of 373 mg/dL, C-peptide level of 1.14 ng/ml (N: 0.81-3.85 ng/ml) and insulin level of 23.13 mU/l (N: 3-25 mU/l) were within normal limits. All the tests were performed on an empty stomach.

Laboratory tests revealed CRP of 11.423 mg/dl (N: 0-5 mg/dl), indicating an ongoing inflammation, possibly correlating with recently diagnosed UC. Its association with autoimmune diabetes also cannot be ruled out. Lipid profile revealed the following abnormalities: elevated total cholesterol at 195 mg/dl (N: 115-190 mg/dl) and triglycerides at 200 mg/dl (N: < 115 mg/dl), decreased HDL cholesterol at 36 mg/dl (N: > 40 mg/dl).

Due to high blood glucose levels and the development of acidosis, an intensive insulin therapy model was implemented while awaiting autoantibody results. Fast-acting human insulin analogue - lispro was used subcutaneously 3 times a day before main meals (6-8 units for breakfast, 6-8 units for lunch, 6-8 units for dinner), and long-acting human insulin analogue - glargine (12-14 units) around 10 p.m. Doses of insulin were adjusted (+/- 2 units) depending on glycaemia. After the diagnosis T1D, it was recommended to continue the insulin therapy. Due to a reduced inflammation in the course of UC, the patient required lower doses of insulin: lispro (4-5 units for breakfast, 5-6 units for lunch, 5-6 units for dinner), and long-acting human insulin analogue - glargine (10-12 units) around 10 p.m.

The diabetic diet with its modification due to accompanying UC, and regular physical activity were recommended. The patient was required to measure blood glucose levels daily - in the morning at fasting, before each insulin administration and 2 hours after the main meal, and in case of any deterioration. Due to the reduction of steroid doses, the patient was advised about the possible reduction in insulin requirements and the possibility of hypoglycemia. In case of blood glucose <70 mg/dl, an intake of 15 g of simple carbohydrates and another measurement of blood glucose after 15 minutes was recommended. The patient was offered Continuous Glucose Monitor (CGM), but due to its cost, the patient did not accept it. Additionally, the patient underwent an abdominal CT in an outpatient clinic, which ruled out a non-alcoholic steatohepatitis. The first visit to the outpatient clinic was recommended 2 weeks after hospitalization.

Discussion and state of knowledge

Much information regarding the genetics of IBD has been obtained through genome-wide association studies (GWAS) using single nucleotide polymorphism chips, based on the assumption that the disease is inherited polygenically. GWAS studies have identified more than 200 loci associated with IBD. Among these loci, 41 are specific to Crohn's disease (CD), 30 to UC, and 137 are common for both diseases. Several studies have reported a strong association between IBD and T1D. [14-17]. It has been suggested that the two diseases share a similar immunologically based pathogenesis. In addition to individual studies, recent meta-analyses on GWAS have also enabled the identification of dozens of susceptibility loci for T1D and CD, as single studies typically do not have sufficient computational capacity. Furthermore, comparison of susceptibility loci among different autoimmune diseases has revealed important insights into

their shared genetic architecture. These studies suggest that the study of related autoimmune diseases may help reveal common genetic pathways, and evaluation of known susceptibility loci for one disease in GWAS may reveal novel disease-loci for another disease. The study led by Kai Wang lists known susceptibility loci in a cohort of 1689 CD cases, 777 UC cases, 989 T1D cases, and 6197 control subjects of European descent. They identified multiple previously undescribed or unconfirmed disease associations, including known CD loci (ICOSLG and TNFSF15) and T1D loci (TNFAIP3) that increase UC risk, known UC loci (HERC2 and IL26) that increase T1D risk, and known UC loci (IL10 and CCNY) that increase CD risk. Furthermore, T1D risk alleles present at the PTPN22, IL27, IL18RAP, and IL10 loci have been shown to protect against CD [18].

In addition to the genetic connection between inflammatory bowel disease and diabetes, the influence of medications used in UC on the development of potential hyperglycemia must also be considered. According to the British Society of Gastroenterology (BSG), the European Crohn's and Colitis Organization (ECCO), and the American Gastroenterological Association (AGA), 5-aminosalicylate (5-ASA) medications such as mesalazine are recommended as a first-line treatment and for maintenance of remission in mild to moderate CU.

JAJ Bower showed that treatment with sulfasalazine in diabetic patients, decreased HbA1c levels, demonstrating a potential hypoglycemic effect of this drug group. [10] At the same time, sulfasalazine induces hemolysis, which may falsely lower HbA1c values.[19,20] Oral steroid therapy is used as a second-line treatment in mild to moderate relapses of UC in patients unresponsive to 5-ASA therapy. Intravenous forms are administered in severe relapses of the disease. These medical interventions have the potential to generate drug-induced hyperglycemia.[21] A meta-analysis of 12 studies assessing the prevalence of diabetes in steroid-treated patients without previously diagnosed diabetes found it in 18.6% patients.[22] In addition, up to 50% of patients with inflammatory bowel disease and treated with prednisolone have glucose intolerance.[23] Studies also show that steroid therapy can reveal previously unrecognized autoimmune diabetes. Considering these two mechanisms of hyperglycemia induction after steroid therapy, the cumulative risk of diabetes increases. It is particularly significant in patients with autoimmune diseases, including IBD, and is directly proportional to the steroid dose.

In addition, patients with T1D and UC, who receive corticosteroids as a first-line therapy have an increased risk of developing ketoacidosis, hyperosmolar hyperglycemia, and multiple organ complications (neurologic, hepato-biliary, osteoarticular, and vascular). [24-28] If steroid therapy significantly impairs glycemic control, the AGA guidelines recommend considering the inclusion of biological agents (anti-TNF alpha monoclonal antibodies) or immunosuppressants (thiopurines) with a potential to reduce insulin resistance. However, as there are not enough studies and no clear recommendations, the decision to implement this therapy requires individual consideration [24].

Conclusions

This case shows that various causes may influence the occurrence of diabetes in patients with inflammatory bowel disease. Monitoring the patient's blood glucose levels prior to and during the treatment is essential. Both the genetic background correlating with the development of autoimmune diabetes and the influence of treatment of gastroenterological disease, especially steroid therapy, should be considered. These factors may coexist and exacerbate the symptoms of hyperglycemia. The treatment of inflammatory bowel disease in patients with diabetes remains a clinical challenge, and requires further research to develop clear recommendations [29-30].

Key findings of the review:

- Type 1 diabetes mellitus should be taken into consideration in patients with previously diagnosed autoimmune diseases, such as ulcerative colitis presented in our patient.
- In steroid-treated patients with hyperglycemia, without previously diagnosed diabetes, autoimmune background of diabetes should be excluded.
- Drugs used to treat inflammatory bowel diseases affect carbohydrate metabolism, steroid therapy causes hyperglycemia, and biological therapy has the potential to cause hypoglycemia.
- Several genetic and pathophysiological links between T1D and IBD have been recognized, but further research is needed in order to relate them to the underlying common background of autoimmune diseases.
- Monitoring of the blood glucose levels both prior to and during the steroid treatment is of critical importance.

Disclosure

Authors contribution:

Conceptualization: Kinga Knop-Chodyła, Zuzanna Piasecka, Grzegorz Rudzki; **Methodology:** Ewelina Wesolek, Anna Kochanowska-Mazurek; **Software:** Anna Kochanowska-Mazurek; **Check:** Anna Kochanowska-Mazurek, Aneta Głaz; **Formal Analysis:** Grzegorz Rudzki, Ewelina Wesolek, Maria Kowalczyk; **Investigation:** Aneta Głaz, Ewelina Wesolek, Zuzanna Piasecka; **Resources:** Zuzanna Piasecka; **Data storage:** Kinga Knop-Chodyła, Maria Kowalczyk, Grzegorz Rudzki; **Writing – Rough Preparation:** Kinga Knop-Chodyła, Maria Kowalczyk, Zuzanna Piasecka, Aneta Głaz, Grzegorz Rudzki, Ewelina Wesolek; **Writing – Review and Editing:** Maria Kowalczyk, Kinga Knop-Chodyła, Aneta Głaz; **Visualization:** Kinga Knop-Chodyła, Zuzanna Piasecka, Aneta Głaz; **Supervision:** Kinga Knop-Chodyła; **Project administration:** Kinga Knop-Chodyła; All authors have read and agreed with the published version of the manuscript.

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