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Glucose intolerance and diabetes mellitus in ulcerative colitis: Pathogenetic and therapeutic implications

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Abstract

Diabetes mellitus is one of the most frequent co-morbidities of ulcerative colitis patients. The epidemiological association of these diseases suggested a genetic sharing and has challenged gene identification. Diabetes co-morbidity in ulcerative colitis has also relevant clinical and therapeutic implications, with potential clinical impact on the follow up and outcome of patients. These diseases share specific complications, such as neuropathy, hepatic steatosis, osteoporosis and venous thrombosis. It is still unknown whether the coexistence of these diseases may increase their occurrence. Diabetes and hyperglycaemia represent relevant risk factors for postoperative complications and pouch failure in ulcerative colitis. Medical treatment of ulcerative colitis in patients with diabetes mellitus may be particularly challenging. Corticosteroids are the treatment of choice of active ulcerative colitis. Their use may be associated with the onset of glucose intolerance and diabetes, with difficult control of glucose levels and

with complications in diabetic patients. Epidemiologic and genetic evidences about diabetes co-morbidity in ulcerative colitis patients and shared complications and treatment of patients with these diseases have been discussed in the present review.

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Key words: Diabetes mellitus; Ulcerative colitis; Diabetes complications; Inflammatory bowel diseases; Glucose intolerance; Medical therapy; Corticosteroids

Core tip: The relationship between ulcerative colitis and diabetes mellitus is intriguing, full of practical and speculative information, useful for clinical practice and basic research. Diabetes mellitus is one of the most frequent co-morbidities of ulcerative colitis and their epidemiological association suggests genetic sharing and stimulates studies for gene identification. Diabetes also shares specific complications with ulcerative colitis and represents a challenging condition in ulcerative colitis patients for the treatment of the disease, due to difficult control of glucose levels and for high risk of postoperative complications and pouch failure. All these issues have been discussed in the present review.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterised by mucosal inflammation, limited to the colon. Its inci-

dence and prevalence are increasing with time in different regions around the world, with the highest annual incidence of 24.3 per 100000 persons-year, and prevalence of 505 per 100000 persons in Europe^[1].

The disease is associated with high costs, disease-specific morbidity and decreased quality of life, mostly related to complications, surgery and co-morbid diseases.

Co-morbid diseases in UC include several immune mediated diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, psoriasis, hypothyroidism and diabetes mellitus^[2-7].

Among these diseases, diabetes mellitus is the most frequent condition and its association with UC has epidemiological, pathogenetic, clinical and therapeutic implications.

All these points represent the objects of the present review.

An electronic literature search was conducted using PubMed and Medline as primary sources. No time limits were specified up to the date of the search (September 2013). A comprehensive search was performed using the following search terms: “ulcerative colitis” or “inflammatory bowel diseases” and “diabetes mellitus” or “glucose intolerance”. The search was restricted to articles involving humans and those in the English language (or with an English abstract) and following identification of relevant titles, the abstracts of these articles were read to decide if the study was eligible.

The full text article was retrieved when the title and/or abstract seemed to meet the pre-defined eligibility criteria. A manual cross-reference search of bibliographies was carried out to identify articles missed in the computerised search.

DIABETES CO-MORBIDITY IN UC

Diabetes mellitus, like other autoimmune disorders, is significantly associated with UC, both in children and in adult patients. A recent large case-control study, which included more than 1200 children with inflammatory bowel disease (IBD), 488 of whom with UC, showed that UC is associated with a higher prevalence of diabetes than in controls (OR = 2.7, 95%CI: 1.1-6.6) with an overall prevalence of 2049 cases per 100000 children. Noteworthy, this association was confirmed excluding patient on treatment with anti-TNF alpha, and was the strongest among the other autoimmune conditions. It was also specific for UC, the association with Crohn's disease not being significant (OR = 1.4, 95%CI: 0.5-4)^[7]. Regarding the association between UC and diabetes, the estimates in this paediatric study were only slightly higher than those in adult studies. Indeed, few other studies examined the concomitance of autoimmune diseases among adult IBD patients without showing a significant increased risk for type 1 diabetes mellitus^[3,4] although this endocrine disorder represented the third most common co-morbid disease in UC patients (0.8%) after psoriasis (1.8%) and rheumatoid arthritis (1.1%). No study

has assessed the prevalence of type 2 diabetes mellitus in IBD, so far.

Interestingly, patients with both psoriasis and IBD showed significantly higher rates of diabetes (26.7% *vs* 11.0%) and autoimmune thyroiditis (2.1% *vs* 6.8%) and hepatitis (0.7% *vs* 6.2%) compared to individuals with psoriasis only^[8].

On the other hand, a large study made possible by the availability of the Multigeneration Register in Sweden, estimated the associations between type 1 diabetes mellitus and 33 autoimmune and related diseases in parents, offspring, siblings and twins. This study showed that type 1 diabetes in offspring was associated with 13 diseases in parents, including UC (standardised incidence ratio 1.23) and few other gastrointestinal diseases such as primary biliary cirrhosis (3.63) and celiac disease (2.73)^[9].

All these epidemiological findings suggest potential shared aetiological mechanisms for UC and type 1 diabetes mellitus. Although the aetiology for both diseases remains unclear, a large body of evidence supports the hypothesis that in genetically predisposed individuals, both host factors and environmental factors contribute to an uncontrolled immune function.

Co-morbidity among these autoimmune disorders and familial associations with several autoimmune and related diseases suggest genetic sharing and represent a challenge for gene identification.

On this regard, a recent genome-wide association study examined known susceptibility loci for IBD and type-1 diabetes mellitus in a cohort of 1689 Crohn's disease patients, 777 UC patients, 989 type-1 diabetes patients and 6197 control subjects, and identified multiple shared loci with opposite effects. In particular the study identified 1 diabetes mellitus locus (TNFAIP3) that confers UC risk and 2 UC loci (HERC2 and IL26) that confer type-1 diabetes mellitus risk^[10].

The genetic association between UC and type-1 diabetes mellitus has been also suggested by the description of a monogenic form of diabetes with the typical features of type 1 diabetes (autoantibodies to β cells, lean and young at onset of hyperglycemia, rapid disappearance of C-peptide production and insulin dependence) together with insulin resistance, which appears as a consequence of an autosomal-dominant mutation in the *SIRT1* gene. A recent case-report describes a family carrying a mutation in the *SIRT1* gene, in which all five affected members developed an autoimmune disorder: four members developed type 1 diabetes and one developed UC^[11]. It is particularly interesting to know that SIRT1 suppresses TNF α expression^[12]. Importantly, both type-1 diabetes and UC are strongly associated with this cytokine, and TNF antagonism improves both conditions^[13].

COMMON SHARED COMPLICATIONS IN DIABETES AND UC

Diabetes mellitus and UC share a number of complications, namely neurological, hepatobiliary, osteoarticular,

Table 1 Common shared complications in diabetes mellitus and ulcerative colitis

Neurological
Distal symmetric polyneuropathy (50% in DM and 0%-39% in UC)
Hepatobiliary
Cholelithiasis (20%-30% in DM, only after colectomy in UC)
Hepatic steatosis
Non alcoholic fatty liver disease
Osteo-articular complications
Osteoporosis
Vascular complications
Venous thrombosis (with ketoacidosis in DM, with active disease or surgery in UC)
Post-operative complications
Anastomotic dehiscence
Infections
Non-infectious complications

DM: Diabetes mellitus; UC: Ulcerative colitis.

vascular and post-operative. It is unknown whether concomitance of both diseases for a long time increases the risk of such complications.

Although diabetic patients with mild or quiescent UC are likely to have a favourable outcome, UC patients with recurrent or steroid-refractory active disease, with consequent long term steroid treatment, could present hyperglycaemia and hyperinsulinemia and an increased risk of complications. Unfortunately, the outcome of UC in diabetic patients has not been investigated so far and no data are reported in the large therapeutic trials.

Examples of the more frequently shared complications of diabetes mellitus and UC are presented hereafter (Table 1).

Neurological complications

Neuropathy is a well known complication of diabetes mellitus. In particular, distal symmetric polyneuropathy is the most frequent form of neurological involvement, occurring in up to 50% of diabetic patients^[14]. Peripheral neuropathy is also a neurological complication of inflammatory bowel diseases^[15,16] with an incidence ranging from 0% to 39%, depending on the features of the study populations and on the criteria adopted to define the neuropathy. A population-based study showed that incident at peripheral neuropathy in IBD patients occurs late in the course of the disease^[17] and is likely due to nutritional (*e.g.*, B₁₂ deficiency), iatrogenic (*e.g.*, metronidazole neurotoxicity) and immune-mediated causes.

Hepatobiliary complications

Cholelithiasis, a well known complication of 20%-30% of patients with diabetes mellitus probably due to impaired gallbladder contraction, obesity and hyperlipidemia^[18], is also reported as a complication in UC patients, but only after colectomy, likely due to changes in bile composition and increase in cholesterol concentration in bile^[19].

Hepatic steatosis is a frequent feature of both diabetes mellitus and UC. Nonalcoholic fatty liver disease

(NAFLD) is characterized by insulin resistance and it is often associated with type 2 diabetes mellitus^[20,21]. Up to 50% of these patients may have nonalcoholic steatohepatitis^[22]. NAFLD is also frequently reported in UC patients, apart from classical risk factors such as obesity or insulin resistance^[23].

Osteo-articular complications

Diabetes mellitus-induced osteoporosis is often present in diabetic patients, probably due to changes in osteoblast function and bone formation, sustained by hyperglycemia^[24].

A high prevalence of reduced bone density is also frequently reported in UC patients due to increased bone reabsorption, not balanced by an appropriate bone formation. Long duration of disease, low body mass index, colectomy and in particular high doses and prolonged treatment with corticosteroids (cumulative use of steroids) have been recognised as risk factors for this complication and fractures^[25-27].

Vascular complications

Diabetes mellitus and UC share vascular complications, such as venous thrombosis. UC is characterised by a potential hypercoagulable state and an incidence of systemic thromboembolic events higher than in the general population, usually correlated with active disease and surgery^[28-30]. Diabetes, although most commonly complicated by arterial thrombosis, may also be complicated by venous thromboembolism, in presence of ketoacidosis^[31-33].

Post-operative complications

Diabetes mellitus is a well known risk factor of poor outcome in colorectal surgery, mainly due to the occurrence of anastomotic dehiscence^[34], infectious and non-infectious complications.

Recently, it has been found that perioperative hyperglycemia, in diabetic patients and even in patients without a preoperative diagnosis of diabetes undergoing colorectal surgery, is associated with a high rate of infectious and noninfectious complications, reintervention and mortality^[34].

Adverse outcomes may be associated with a single postoperative elevated glucose value and the risk of morbidity and mortality is related to the degree of hyperglycemia^[35,36].

Therefore, it is not surprising that the post surgical period is one of the most important time frames for morbidity and mortality in UC patients with co-morbid diabetes mellitus.

Surgical-site infections is a major source of morbidity after colectomy for fulminant UC. A retrospective study including 59 patients operated for fulminant UC, showed that diabetes is one of the most frequent independent risk factors for surgical-site infections, along with white blood cell count, intraoperative blood loss and blood transfusion^[37]. The poor outcome of the postopera-

Table 2 Predictive risk factors for the development of diabetes mellitus and hyperglycemia in ulcerative colitis patients treated with corticosteroids

High dose of corticosteroids
Long duration of corticosteroids therapy
Advanced age
High body mass index
Family history of diabetes
Previous gestational diabetes

tive course in diabetic patients with UC has been also found in another large retrospective study that included 3754 patients undergoing ileoanal pouch, which showed that diabetes mellitus was an independent factor associated with the risk of pouch failure (HR = 2.31; 95%CI: 1.25-4.24)^[38].

CORTICOSTEROID-INDUCED DIABETES IN UC

IBD are immune-mediated disorders which appear in genetically predisposed subjects.

Corticosteroids are the main therapeutic agents in UC, because of multiple effects on the cellular and humoral immune system, including an inhibitory action on several pro-inflammatory cytokines and metabolites of arachidonic acid.

For more than 50 years corticosteroids, such as prednisone and methyl-prednisolone, have been used to treat IBD during the acute phase. However, more than 50% of patients do not respond to the therapy (steroid-resistance) or have a relapse after treatment discontinuation (steroid-dependence) and about half of them show side effects of variable severity^[39,40]. In most cases, the appearance and the seriousness of side effects (except from osteonecrosis and idiosyncratic reactions) are related to duration and dose of therapy.

Hyperglycemia and corticosteroid-induced diabetes are the most common systemic manifestations in IBD under steroid treatment and represent a real problem in the handling of UC patients with diabetes mellitus when relapses of the intestinal disease occur.

To date, there are few data on the incidence of corticosteroid-induced hyperglycemia or diabetes in IBD and also about the onset of acute diabetic complications, such as ketoacidosis and hyperosmolar hyperglycemic state, in diabetic patient affected by IBD, under steroid treatment. Most of our knowledge is derived from non-gastroenterological studies.

A case-control study, conducted on 55 elderly patients with active Crohn's disease compared to 66 control subjects not treated with steroids, showed that treatment with high doses of corticosteroids may increase the risk of hyperglycemia, even if the difference was not statistically significant (RR = 1.53; 95%CI: 0.54 - 4.32)^[41].

However, another case-control study that included a large number of patients (11855 cases and 11855 controls) showed that corticosteroids (prednisone or ana-

logues at a dose of 30 mg a day or more) confer a RR = 10 of hyperglycemia, compared to non treated patients^[42].

A retrospective study, including 25 patients affected by neuropathy (median age: 50 years) showed that treatment with prednisolone at a dose of 30-60 mg a day for at least 2 wk may result in a postprandial hyperglycemia, compatible with diabetes mellitus in 13 of 25 patients and demonstrated that advanced age is a risk factor for this complication^[43].

The importance of age in the onset of corticosteroid-induced diabetes is confirmed also by a cohort study conducted on a large geriatric population (median age: 75 years) that shows an increased risk of diabetes induced by oral corticosteroids (RR = 2.31; 95%CI: 2.11-2.54), compared to treatment with proton-pumps inhibitors (PPIs)^[44].

Finally, a recent literature review has confirmed that corticosteroid-induced hyperglycemia is common both in patients with and without diabetes and it has estimated an OR = 1.5-2.5 for the onset of diabetes mellitus in treated patients^[45].

Overall, the available studies, mostly conducted on patients not affected by IBD, confirm that the total dose of corticosteroids and the long duration therapy are important predictive risk factors for the development of diabetes mellitus. In addition, these studies underline that other factors, such as advanced age, high BMI, family history of diabetes or previous gestational diabetes should be considered and recommend monitoring the blood glucose level during steroid therapy (Table 2).

The possible underestimation of this condition in the handling of patient with IBD in clinical practice could be attributed to the short duration of steroids treatment and to the importance given to the fasting blood glucose only. High blood glucose levels in the short-term and in the postprandial period, should be considered for their prognostic value.

Concerning the role of the corticosteroids dose on the onset of diabetes, high doses of steroids are associated with high values of blood glucose levels and can induce diabetic ketoacidosis in patients with type 1 diabetes mellitus or hyperosmolar hyperglycemic state^[46,47].

The risk of these complications is particularly significant in diabetic patients with UC, in whom the first-line treatment is represented by corticosteroids.

TREATMENT OF UC IN DIABETIC PATIENTS

Treatment of patient with UC depends mainly on the activity and location of disease^[48,49].

Severe UC

Severe UC is characterized by bloody diarrhoea > 6 bowel movements/d and many signs of systemic toxicity (tachycardia > 90 bpm, fever > 37.8 °C, Hb < 10.5 G/dL or ESR > 30 mm/h)^[50].

Patients with severe UC should be admitted to hospi-

Table 3 Management of active severe ulcerative colitis in diabetic patients treated with corticosteroids

Disease monitoring	Disease treatment
Regular monitoring of blood glucose level	Rehydration with saline solution
Regular monitoring of disease activity (e.g., Disease Activity Index)	Correction of blood glucose levels
Plain abdominal X-ray	Treatment of hypokaliemia
Dosage of:	Treatment of hypomagnesaemia
C-reactive protein	Consider alternative treatments
Blood cell count	<i>Iv</i> cyclosporine A (4 mg/d)
Electrolytes	Infliximab (5 mg/kg or 10 mg/kg)
Anion gap	Adalimumab (160 mg/80 mg/40 mg eow)
Osmolality	Tacrolimus
Serum creatinine levels	Leucocyapheresis
Ketones	Other therapies (vedolizumab, visilizumab, abatacept, tofacitinib)
Urinalysis	
Blood gas analysis	

tal for intensive treatment^[49].

Corticosteroids, administered parenterally (e.g., Methylprednisolone 60 mg daily or hydrocortisone 100 mg four times daily), represent the first-line treatment of severe UC. Higher doses are not more effective, but lower doses are less effective^[51]. Duration of treatment is 7-10 d, since further extension of therapy carries no additional benefit. Response to therapy reaches 67% and non-responders UC patients require a second-line treatment, represented by cyclosporine, tacrolimus, infliximab or colectomy^[52].

Steroid treatment of severe acute UC, in particular in diabetic patients, requires particular attention to hyperglycemia induced by therapy. The combination of dehydration, electrolyte imbalance (hypokalemia and hypomagnesemia), the possible presence of a septic condition and the need of total parenteral nutrition are important risk factors for hyperosmolar hyperglycemic state and diabetic ketoacidosis, the major complications of diabetes mellitus. Both these conditions are particularly dangerous and burdened by significant mortality, particularly in patient in which the state of diabetes was previously unknown.

For this reason, in patients with diabetes mellitus with severe UC, in addition to a close monitoring of bowel disease which requires clinical evaluation, dosage of C-reactive protein, blood counts and abdominal X-ray studies, a careful evaluation of the diabetes is also required, through the regular monitoring of blood sugar and various blood parameters (electrolytes with evaluation of the anion gap and osmolality, phosphorus, magnesium, creatinine, urinalysis to evaluate ketones, blood-gas analysis to evaluate arterial or venous pH), in particular in patients with basal glycaemia exceeding 180 mg/dL (Table 3).

Therapy of this condition is essentially based on rehydration with saline solution, correction of blood glucose by administering intravenous or subcutaneous insulin and treatment of hypokalemia by re-integration of potassium, bicarbonates, magnesium and phosphate

(in diabetic ketoacidosis), in close collaboration with endocrinologist. Hypokalemia and hypomagnesemia are important risk factors for toxic megacolon^[53], require a prompt correction and suggest careful radiographic and biochemical monitoring, particularly when a septic condition coexists (Table 3).

Therefore, in diabetic patients with acute severe UC, close monitoring of the patient's clinical and biochemical condition is essential, in order to timely identify the opportunity of a second line medical treatment or the possible need for surgical treatment (Table 3). However, the outcome of severe UC in diabetics is still unknown.

In diabetic patients with unstable blood glucose control, steroid treatment can be replaced by intravenous cyclosporine (4 mg/d), infliximab (5 mg/kg or 10 mg/kg at 0, 2, 6 wk and then every two months) or adalimumab 160 mg/80 mg/40 mg eow^[49]. Efficacy and safety of cyclosporine and infliximab are comparable and, in clinical practice, the treatment choice should be guided by physician and centre experience^[54]. A study by Moskovitz *et al*^[55] showed that cyclosporine is less effective in patients treated with azathioprine and should be avoided in patients with low cholesterol or magnesium in view of the increased incidence of neurological side effects in this patient group. Furthermore, there is no scientific evidence on the effectiveness of cyclosporine in preventing colectomy^[56], while other studies have shown that Infliximab can reduce the rate of colectomy compared with placebo^[57]. So the choice should be placed on individual circumstances and the availability of drugs.

The use of tacrolimus, as an alternative to steroid therapy in diabetic patients, is generally not recommended. The tacrolimus, in fact, besides being unable to induce significant mucosal healing compared with placebo^[58], can induce long-term hyperglycemia or even diabetes, as well as hypomagnesemia and it may promote the onset of opportunistic infections^[49].

In contrast, leucocyapheresis, whose principle is based on the extracorporeal removal of leukocytes through an adsorptive system of cellulose acetate beads (Adacolumn, Otsuka Pharmaceuticals) or a polyester fibre filter (Cell-sorba, Asahi Medical Company) represents a potential therapeutic remedy with a good safety profile, serious side effects being very rare. Leucocyapheresis can be associated with any medical treatment, but the real effectiveness of this device in acute severe UC remains to be determined^[59].

Leucocyapheresis has a wide-spread acceptance in Japan, but its cost may limit its use and its future role in Europe will depend on the outcome of controlled trials^[49]. On this regard, clinical efficacy outcomes are variable, being encouraging in some studies and disappointing in others, and the answer might ultimately lie in the patients' disease status at entry. Patients with the first UC episode and short duration of disease or a fair level of intact mucosal tissue, seem to respond and can be spared from multiple drug therapy. Patients with extensive loss of mucosal tissue and those with a long history of exposure to multiple drugs, like corticosteroids, are

unlikely to respond^[60].

Other therapies such as vedolizumab, visilizumab, abatacept, tofacitinib, which are characterised by different mechanisms of action are currently under investigation and have no role in clinical practice to date^[61].

Mild-moderate UC

Treatment of mild-moderate UC depends on the site of disease.

The first line therapy of mild-moderate distal colitis is topical mesalazine and/or oral mesalazine, in once daily administration, which is as effective as divided doses. Combining topical mesalazine and topical steroids, such as beclomethasone dipropionate, also helps. Patients who fail oral/topical mesalazine and topical steroids should be treated with the addition of oral prednisolone.

In proctitis, it has been shown that topical mesalamine has a higher efficacy on symptoms and endoscopic resolution of the damage compared to topical steroids, generally using suppositories that are more appropriate than enemas. However, topical steroids may be used in substitution of mesalazine, if it is poorly tolerated, or in association with the latter. Indeed, the combination of beclomethasone dipropionate (3 mg) and mesalazine (2 mg) is able to induce an improvement in clinical, endoscopic and histologic proctitis, significantly superior to treatment with mesalazine alone^[62].

In diabetic patients with mild-moderate distal UC, systemic steroid therapy should be avoided by resorting to rectal or oral administration of mesalazine and/or beclomethasone dipropionate or to new therapies such as budesonide Multi-Matrix System (MMX), fluticasone or prednisolone metasulphobenzoate.

In treatment of extensive or distal colitis it is generally recommended, as first choice, a combination of oral and topical mesalazine^[49,63,64]. In fact, the use of mesalazine alone, although at high doses or in controlled release formulation (MMX), gives a percentage of remission of at least 41% and a partial response, not exceeding 72%. Furthermore, in many patients the occurrence of relapse of intestinal disease is not uncommon, even during an appropriate maintenance therapy with mesalazine. In these circumstances the use of systemic steroid therapy is generally recommended, even in non severe forms of colitis. In the diabetic patient, this treatment requires the same level of attention already mentioned for patients with severe colitis.

Controlled colonic release formulations of steroids and steroids equipped with low bioavailability, such as beclomethasone dipropionate, budesonide MMX, fluticasone or prednisolone metasulphobenzoate represent a potential therapeutic resource with the advantage of the absence or the minimisation of the side effects of other steroids, with respect to the suppression of the hypothalamic-pituitary-adrenal axis^[65].

Although there are no specific studies on the undesirable effects of this kind of steroids in diabetic patients with UC, it should be noted that, in both normal sub-

jects and elderly diabetic patients under dietary control, treatment with topical inhaled beclomethasone in high doses for 2 wk, did not produce significant changes in blood glucose and lipid metabolism^[66].

In addition, in both adults and pediatric patients, for whom steroid treatment of UC is the remedy of choice, the oral administration of beclomethasone dipropionate is well tolerated and induces a rapid clinical and endoscopic remission in mild to moderate UC, comparable to mesalazine^[67-69].

Budesonide MMX, 9 mg daily, is effective for the induction of remission of mild-moderate active UC. It is a novel oral formulation of budesonide that uses MMX technology to extend release to the colon, without notable increases in glucocorticosteroid-related side effects, probably due to low bioavailability and to targeted delivery of drug^[70].

In patients with UC fluticasone has negative results, but prednisolone metasulphobenzoate, by oral or topical administration, appears to be effective in active distal UC and in mild-to-moderate UC with a lower incidence of systemic adverse effects in comparison with other glucocorticosteroids^[71].

If systemic steroid treatment is necessary, the occurrence of hyperglycemia (particularly in patients with known diabetes) can be corrected or controlled by rapid-acting insulin, usually administered in the preprandial period (generally at a dose of 0.1 U/kg) or by using biguanides, such as metformin, or thiazolidinediones (also known as glitazones), drugs just approved for the treatment of diabetes mellitus type 2.

Metformin, and in particular the increase in dosage of this drug, is often burdened with gastrointestinal side effects such as nausea, vomiting, anorexia, diarrhea, abdominal pain. These symptoms are usually dose-related and occur especially at the beginning of therapy. In 3%-5% of cases, diarrhea may be persistent and cause discontinuation of the drug.

In contrast, the thiazolidinediones are oral antidiabetics with anti-inflammatory properties, potentially useful in patient suffering from UC. In particular, these drugs work by binding to the gamma sub-unit of PPAR (peroxisome receptors that trigger proliferation), receptors located inside the cell nucleus, abundantly expressed in adipose tissue and in the colonic epithelium. Experimental evidence has shown that these molecules have anti-inflammatory activity, in particular in colon and that treatment with these drugs is able to attenuate the production of inflammatory cytokines and to reduce inflammation in animal models of colitis. One uncontrolled study showed that rosiglitazone (a drug used in the United States for treatment of diabetes mellitus type 2) is able to improve moderately active colitis, refractory to treatment with mesalazine. The same group later confirmed the efficacy of the drug, compared to placebo, in a double-blind controlled study^[72,73]. Unfortunately, rosiglitazone was recently withdrawn from the market in some countries for the high risk of ischemic heart

disease and myocardial infarction, but other thiazolidinediones are on the market (such as pioglitazone) or should soon enter in the pharmaceutical reference book and could be used in diabetic patients with UC, if their efficacy in UC will be confirmed.

CONCLUSION

Diabetes mellitus is a common disorder, significantly associated with UC. Co-morbidity among these autoimmune disorders and familial associations with several autoimmune and related diseases, suggest a genetic sharing but, although some shared loci at risk have been identified, the clinical implications of this findings are still unclear.

Likewise, diabetes mellitus and UC share neurological, hepatobiliary, osteoarticular, vascular and post-operative complications. Their onset may be increased by the long-standing concomitance of both diseases. Although specific studies on this aspect have not yet been carried out, this deserves attention in clinical practice. In particular, the role of hyperglycaemia and the poor control of blood glucose level in diabetics deserve particular attention for the risk of morbidity of patients undergoing ileoanal pouch after proctocolectomy.

One of the most common and challenging problems in diabetic patients with UC is the medical treatment. Corticosteroids, the treatment of choice of active UC, may be associated with the onset of glucose intolerance and diabetes, and with the difficult control of blood glucose levels and complications in diabetic patients. Advanced age, high body mass index, family history of diabetes or previous gestational diabetes should always suggest the need of monitoring blood glucose level during steroid therapy. Likewise, rehydration, correction of blood glucose and hypokalemia in close collaboration with endocrinologists, as well as the close monitoring of the patient's clinical and biochemical conditions are essential in diabetic patients with acute UC. Moreover, the potential negative effects of metformin and the beneficial effects of thiazolidinediones on symptoms of UC in remission, should be considered.

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