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Diabetes in Cushing Disease

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Abstract
Purpose of Review This review focuses on the pathophysiological and clinical aspects of diabetes mellitus occurring in patients with Cushing disease (CD).
Recent Findings Insulin resistance and impairment in insulin secretion are both involved in the pathogenesis of glucocorticoid-induced diabetes. Correction of glucocorticoid excess does not always resolve abnormalities of glucose homeostasis, and correction of hyperglycaemia is specifically required. In fact, insulin resistance may persist even after correction of glucocorticoid excess and diabetes needs to be treated for long term. On the other hand, emerging drugs used in the treatment of CD, such as the novel somatostatin analog pasireotide, may have direct effects on glucose homeostasis regardless of control of cortisol excess.
Summary Diabetes mellitus is a frequent and early complication of CD with important diagnostic, prognostic and therapeutic implications. Specifically, diagnosis of CD in patients with diabetes may be difficult due to potential misinterpretation of markers of cortisol hypersecretion. Moreover, diabetes mellitus is often difficult to be controlled in CD requiring a careful and dedicated therapeutic approach. Finally, the coexistence of diabetes may influence the therapeutic decision making in CD, since drugs used in this setting may variably influence glucose homeostasis regardless of control of hypercortisolism.

Keywords Diabetes: · Cushing disease · Somatostatin analogs · hypoglycemic drugs

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Introduction

Cushing disease (CD) is a rare disease caused by an adrenocorticotropin hormone (ACTH)-secreting pituitary adenoma which results in increased production of cortisol by adrenal glands [1]. The prevalence of CD is estimated to be nearly 40 cases per million, whereas the incidence of CD ranges from 1.2 to 2.4 per million per year. CD is at least three times more prevalent in women than in men and mainly occurs during the fourth to sixth decades of life [2]. Complications which characterize CD significantly impair quality of life and survival of affected patients [3].

Hypercortisolism predisposes to insulin resistance and impairs β-cell function [4, 5]. Consequently, in many patients with CD diabetes mellitus can be observed when disease is diagnosed [6] and several patients with previously unrecognized CD may be firstly seen in diabetes outpatient clinics [7]. Moreover, drugs used for treating CD may per se influence glucose homeostasis regardless of biochemical control of hypercortisolism [6]. Finally, diabetes was reported in association with cardiovascular morbidity and mortality of CD [3].

This review will discuss pathophysiology and clinical issues in the management of diabetes mellitus in patients with CD.

Pathophysiology of Diabetes in CD

Glucocorticoids are diabetogenic agents because they reduce insulin sensitivity and impair beta-cell function [6] (Fig. 1).

Glucocorticoids bind specific receptors in pancreatic beta-cells inducing impairment of uptake and metabolism of glucose with consequent beta-cell dysfunction [6, 8]. Moreover, short-term exposure to glucocorticoids reduces the insulinotropic effects of glucagon-like peptide-1 (GLP-1) [9]. Interestingly, impairment of insulin secretion was also shown to be associated with high-normal cortisol values in subjects not affected by CD [10]. The inhibition of insulin secretion by glucocorticoids may play a critical role in determining development of diabetes in CD, since it may prevent the compensatory increase of insulin secretion in response to insulin resistance induced by glucocorticoids [4].

Glucocorticoids exert anti-insulin effects in the liver, skeletal muscle and adipose tissue (Fig. 1), by inducing a post-

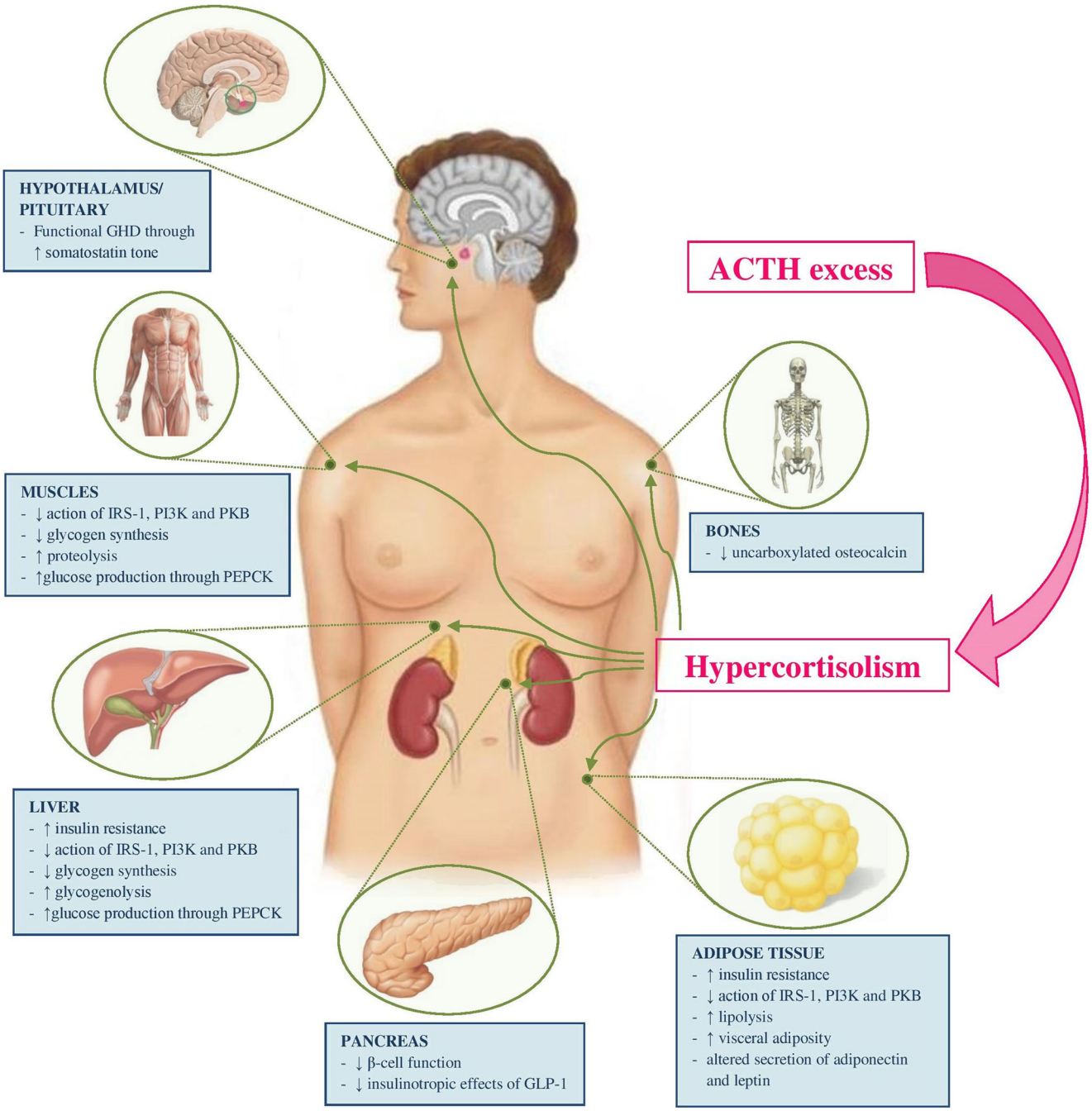

Fig. 1 Mechanisms and target tissues of the diabetogenic effect of hypercortisolism in Cushing disease. *ACTH*, adrenocorticotropin hormone; *GHD*, growth hormone deficiency; *IRS-1*, insulin receptor substrate-1; *PI3K*, phosphatidylinositol-3 kinase; *PKB*, protein kinase B; *PEPCK*, phosphoenolpyruvate carboxykinase; *GLP-1*, glucagon-like peptide-1

receptor defect of insulin receptor substrate-1 (IRS-1), phosphatidylinositol-3 kinase (PI3K) and protein kinase B (PKB) [6]. These actions cause a reduction of glucose uptake as an effect of impaired glucose transporter migration to the cell surface. Moreover, in skeletal muscle, glucocorticoids reduce the phosphorylation of insulin-stimulated glycogen synthase kinase-3, consequently impairing glycogen synthesis [11]. Insulin resistance is also indirectly favoured in CD by increased proteolysis and lipolysis resulting in elevation of amino acids and fatty acids which in turn may cause impairment in different steps of insulin signalling [12]. In CD, the distribution of body fat with increased visceral adiposity and consequent occurrence of metabolic syndrome predisposes to the development of insulin resistance [13]. Moreover, glucocorticoids may influence the secretion of adipokines, such as adiponectin and leptin, which may have a relevant impact on insulin sensitivity [14].

Glucocorticoids influence glucose metabolism also in the fasting state when an increase of glucose production from the liver (Fig. 1) may occur as an effect of induction of key enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) [15].

Over the last few years, there has been experimental evidence for the existence of crosstalk between bone remodelling and glucose metabolism with uncarboxylated osteocalcin postulated to play a central role in the control of fuel metabolism via improvement of insulin secretion and sensitivity (Fig. 1) [16]. In fact, osteocalcin knockout mice were shown to be glucose intolerant and insulin resistant, whereas injections of osteocalcin in these mice resulted in decreased weight gain, decreased insulin resistance, reduced hepatic steatosis and increased energy expenditure [17•]. Interestingly, patients with CD have generally low circulating osteocalcin levels [18], reflecting the inhibitory effects of hypercortisolism on osteoblast proliferation and function [19]. Indeed, glucocorticoid-induced osteoporosis is a unique clinical model to study such an interplay between bone remodelling and fuel metabolism since exposure to glucocorticoid excess is associated with both suppression of osteoblast function and impairment of insulin secretion and sensitivity. There are experimental data in animal models suggesting that suppression of osteoblast function induced by exposure to glucocorticoid excess may play a role in the pathogenesis of glucocorticoid-induced diabetes [20•]. In fact, targeted disruption of glucocorticoid signalling in osteoblasts partially prevented the impaired metabolic responses in experimental animals treated with glucocorticoids [20•]. Moreover, heterotopic expression of osteocalcin improved glucocorticoid-induced glucose intolerance [20•]. Whether this experimental evidence may be translated to humans exposed to glucocorticoid excess is still a matter of uncertainty [21•].

Glucocorticoids modulate growth hormone (GH) secretion by various and competing effects on the hypothalamus and pituitary gland, with final effects depending on hormone concentrations and time of exposure [22]. In patients exposed to glucocorticoid excess, GH deficiency (GHD) may develop as an effect on increased hypothalamic somatostatin tone (Fig. 1) [23]. The functional GHD may contribute to the development of metabolic complications of hypercortisolism, mainly mediated by alteration of body composition and consequent impairment of insulin action [24]. However, the real impact of GHD on diabetes in patients with CD is not yet fully elucidated.

Clinical Aspects

Patients with glucocorticoid-induced diabetes have generally a poorly controlled glucose homeostasis [25] and may harbour typical features of hypercortisolism, such as hypokalemia, facial plethora, easy bruising, reddish purple striae, proximal myopathy, dorso-cervical fat pad, sexual dysfunction in men and menstrual disorders, acne and hirsutism in women. Moreover, patients with glucocorticoid-induced diabetes may suffer from coexistent complications of hypercortisolism such as hypertension, recurrent infections, ischaemic cardiac disease, fragility fractures and neuropsychiatric disorders which may have a synergistic relevant impact in influencing quality of life and survival of patients with CD [26]. Noteworthy, in CD, risk of mortality is double than in the general population; diabetes, hypertension and uncontrolled hypercortisolism have been reported to predict risk of death in this setting [1].

Diagnosis of glucocorticoid-induced diabetes is based, as in the general population, on measurement of fasting plasma glucose, glycated haemoglobin (HbA_{1C}) and plasma glucose values under oral glucose tolerance test [27]. However, in patients exposed to glucocorticoid excess, the measurement of fasting glucose may underestimate the real prevalence of glucose disorders, as suggested by the observation that more than one half of patients with hypercortisolism and diabetes had normal fasting glucose [6]. Since the most important metabolic effects of glucocorticoid excess occur during the postprandial period, the diagnostic gold standard for identifying the impairment of glucose metabolism in CD is the oral glucose tolerance test [6].

Diagnosis of CD in patients with diabetes, even more than in the general population, may be a clinical challenge. Indeed, diabetes mellitus may induce per se a functional hypercortisolism and may influence the response to pharmacological tests used for diagnosis of CD, making difficult the interpretation of biochemical data in diabetic patients with suspected CD [28–30]. On the other hand, there is no single test that may be reliable alone to identify with certainty patients with hypercortisolism [31]. According to the current guidelines [32], screening for Cushing syndrome is

recommended only in those cases with clinical and biochemical features of cortisol excess. Screening for hypercortisolism is performed by measurements of urinary cortisol values, late night salivary cortisol and the 1-mg overnight dexamethasone suppression test. When these tests are abnormal and hypercortisolism is diagnosed, other tests are required to define the cause of cortisol excess. Endogenous hypercortisolism is classified in ACTH-dependent and ACTH-independent. This latter category includes tumours of adrenal glands autonomously secreting cortisol regardless of ACTH stimulation. The so-called ACTH-dependent hypercortisolism includes CD and ectopic Cushing syndrome caused by an extrapituitary tumour secreting ACTH. Measurement of serum ACTH, the corticotropin-releasing hormone (CRH) dexamethasone test, pituitary MRI and adrenal CT are required to define the cause of hypercortisolism [32]. Finally, it is noteworthy that the pituitary adenoma responsible for CD is a microadenoma in more than 90% of cases, which may be not visible during radiological examination.

Therapeutic Aspects

A correct management of diabetes in CD includes the correction of glucocorticoid excess and the control of hyperglycaemia.

Neurosurgical removal of pituitary adenoma performed by experienced neurosurgeon is considered the first-line therapy of CD [33]. Hypercortisolism undergoes remission in 65–90% of patients with microadenomas; 10-year recurrence rates range among 10 and 20% [34]. In macroadenomas, lower remission rates are reported and recurrences occur often earlier than for microadenomas. Therefore, nearly one third of patients experience in the long-term a failure of surgery and require an additional second-line treatment. Traditional radiotherapy or stereotactic radiosurgery has been proposed as second-line therapy, although the slow onset of potential beneficial effects and the high risk of hypopituitarism are critical drawbacks of these procedures [32–34]. Noteworthy, development of hypopituitarism may lead to a further impairment of cardiovascular risk in patients with diabetes and history of CD [35–37]. Furthermore, an increased mortality risk was shown to be associated with traditional radiotherapy in patients with ACTH-secreting adenomas, such as reported in patients with somatotropinomas and nonfunctioning pituitary adenomas [38].

Bilateral adrenalectomy is followed by a rapid and definitive treatment of hypercortisolism, but it induces permanent adrenal insufficiency with potential negative effects on quality of life and survival [39]. Indeed, an overtreatment of hypoadrenalism may occur in some patients, since replacement therapies do not completely mirror the endogenous hormonal production and their monitoring is also made difficult by the lack of reliable biomarkers of their action [40, 41]. It is noteworthy that over-replacement therapy with glucocorticoids may impair some persistent metabolic complications, as diabetes and osteoporosis, in patients with history of CD [42, 43].

Medical therapy of CD has recently become more important as compared to the past, due to the recent availability of novel compounds able to control cortisol secretion or action [32]. Several somatostatin receptors (SSTR), such as SSTR2 and SSTR5 which control ACTH secretion, are expressed by ACTH-secreting adenomas [44]. Conventional long-acting somatostatin analogs are not effective in CD probably because glucocorticoid-induced downregulation of SSTR2 attenuates the action of these drugs [45].

Pasireotide (SOM230) is a new somatostatin analog which binds with high affinity to four out of the five subtypes of the somatostatin receptors (SSTR1–3 and SSTR5) with much higher affinity for SSTR5 than conventional somatostatin analogs [44]. This is relevant for clinical use of pasireotide since SSTR5 is expressed on ACTH-secreting adenomas, without being downregulated by glucocorticoid excess and pasireotide was shown to effectively inhibit ACTH release both in vitro and in vivo, suggesting the potential for effective treatment of CD [46]. A multicenter, phase 2 study demonstrated that short-term therapy with pasireotide at two daily doses of 0.6 mg led to a significant decrease of urinary cortisol values in two third of patients and normalization of hormonal values in 17% of patients [47]. These beneficial effects were confirmed in a phase III clinical trial in which 20.4% of patients achieved normalization of urinary cortisol values after 6 months of treatment with 0.6–0.9 mg of pasireotide [48]. The safety profile of pasireotide was similar to that of conventional somatostatin analogs with respect to adverse events such as gastrointestinal disturbances and cholelithiasis, but with an increased frequency and degree of hyperglycaemia with pasireotide. This is due to the fact that pancreatic β-cells express the SSTR5, which in turn regulates insulin secretion. Therefore, in pasireotide-treated patients, an impaired insulin secretion is observed; the clinical relevance of this effect is increased by the insulin resistance state determined by hypercortisolism, persisting despite pasireotide treatment [48]. In fact, more than 70% of patients treated with pasireotide experienced hyperglycaemia or diabetes which induced treatment discontinuation in 5.6% of patients [48]. The mean HbA_{1C} increased from 5.8% in both the 0.6- and 0.9-mg groups at baseline to 7.2% and 7.4%, respectively, at month 6 [48]. Glucose and HbA_{1C} levels increased soon after the start of pasireotide treatment, necessitating the administration of glucose-lowering medications in almost half (45.6%) of the patients [48]. Based on these findings, a close monitoring of glucose homeostasis should be performed in CD patients undergoing pasireotide therapy at least every week for the first

2–3 months and periodically thereafter [49]. Moreover, patients should be trained in self-monitoring of glucose levels. Metformin is typically first-line treatment as in usual cases of diabetes mellitus [50]; however, new agents may be more effective in the management of pasireotide-associated hyperglycaemia. In fact, studies in healthy volunteers suggested that vildagliptin and liraglutide better perform than metformin in counteracting pasireotide-associated hyperglycaemia [51]. Additionally, pasireotide may suppress the GH/IGF-I axis, which is already under the inhibitory effects of glucocorticoids; this may worsen GHD and contribute to the development of abnormal glucose metabolism [52, 53].

Based on the results of the phase III trial, pasireotide became the first drug to gain approval for treatment of CD from the EMA in the EU in April 2012 and from the FDA in the USA in December 2012, being indicated for patients with persistent disease after pituitary surgery or for whom surgery is not considered an option.

ACTH-secreting adenomas express type 2 dopamine receptors [54], and dopaminergic drugs were shown to induce in vitro acute inhibition of ACTH secretion [45]. In patients with ACTH-secreting adenomas, long-term therapy with cabergoline at doses of 1 to 7 mg/week was shown to induce a sustained control of hypercortisolism in some cases [55, 56]. Indeed, most of biochemical effects occurred during the first 3 months of treatment; thereafter, an escape was observed. Moreover, prevalence of diabetes and glucose intolerance was reduced by cabergoline by 60% and 46%, respectively, and this did not depend on control of hypercortisolism [55]. Moreover, the other dopaminergic drug bromocriptine was able to normalize glucose homeostasis in patients with diabetes, likely by increasing insulin-mediated suppression of hepatic glucose production or enhancing splanchnic glucose uptake [57]. No significant side effects, except for hypotension in few patients, were observed during treatment of CD with cabergoline [55, 56].

Some drugs, such as ketoconazole, metyrapone and mitotane, act as adrenolytic agents inhibiting the biochemical synthesis of cortisol in adrenal glands [45]. These drugs are generally used in the short term due to important side effects (hepatic injury with ketoconazole, hyperandrogenism with metyrapone and gastrointestinal and neurological disturbances with mitotane). Interestingly, ketoconazole at doses ranging between 200 and 1000 mg daily was demonstrated to improve glucose metabolism either in patients with hypercortisolism or in those with type 2 diabetes [58, 59]. Ketoconazole is an imidazole derivative which is able to reduce cortisol levels by inhibition of a variety of cytochrome P450 enzymes [60]. In addition to its anti-steroidogenic effects, ketoconazole may also have extra-adrenal actions, such as its glucocorticoid receptor antagonism and inhibition of ACTH release [61].

Mifepristone is a high-affinity nonselective antagonist of the glucocorticoid receptor type II, with an affinity for the glucocorticoid receptor more than three times higher than that of dexamethasone and more than 10 times higher than that of cortisol [62]. The largest prospective multicenter trial of mifepristone was performed in 50 patients with endogenous hypercortisolism, including 43 patients with CD, who received mifepristone treatment for 24 weeks, with a starting dose of 300 mg/day, a maximum dose of 1200 mg/day and a final mean dose of 732 mg/day [63]. In 60% of patients who had diabetes or glucose intolerance, mifepristone induced an improvement of insulin sensitivity as suggested by a decrease of at least 25% of area under the curve for glucose after an oral glucose tolerance test [63]. In a post hoc analysis, insulin sensitivity was shown to improve early (few weeks) after mifepristone treatment as direct effect of glucocorticoid short-term blockade, whereas longer-term improvement in insulin sensitivity was shown to be more in relationship with the favourable changes in body composition which occurred not before 6 months of treatment [64]. Based on these results, mifepristone received FDA approval in the USA for the

Table 1 Newer anti-diabetic drugs, their mechanisms of action and their potential effects on clinical outcomes in Cushing disease (CD)

Drugs	Main mechanisms of action	Effects on CD outcomes
Peroxisome proliferator-activated receptor-γ agonists (pioglitazone, rosiglitazone)	Decrease in insulin resistance	Rosiglitazone could have anti-proliferative effects in ACTH-secreting pituitary adenomas [70] Rosiglitazone may increase the risk of fracture [72]
Incretins Dipeptidyl peptidase-4 inhibitors (vildagliptin) GLP-1 agonists (liraglutide, exenatide)	Stimulation of insulin secretion, decrease in glucagon secretion	Exenatide may specifically reverse the inhibitory effects of glucocorticoids on insulin secretion [76] Vildagliptin and liraglutide may specifically antagonize the inhibitory effects of pasireotide on insulin secretion [51] Liraglutide may protect from skeletal fragility [81]
Sodium-glucose co-transporter 2 inhibitors (canagliflozin, dapagliflozin and empagliflozin)	Increase in urinary glucose excretion	Potential increase in urinary and genital infections [75]

treatment of adult patients with endogenous CS who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Treatment of Diabetes

Although an improvement of glucose homeostasis generally occurs with normalization of cortisol levels, insulin resistance and cardiovascular risk may persist in several patients even after cure of hypercortisolism [1]. Therefore, an important therapeutic goal in patients with CD and diabetes is the control of hyperglycaemia independently of correction of hypercortisolism. Treatment of diabetes in patients with CD is not different with respect to the general population with type 2 diabetes [65]. However, several pathophysiological and clinical characteristics may change the therapeutic management of diabetes in patients with CD.

Physical activity can be recommended in CD patients. However, glucocorticoid-induced myopathy may greatly limit their physical activity [66].

As in type 2 diabetes [67], metformin can be used as first-line therapy of diabetes also in patients with CD, taking however into account that glucocorticoid-induced hyperglycaemia tends to be more pronounced in the evening than the morning. Metformin may have gastrointestinal undesired side effects, such as gut discomfort, flatulence or diarrhoea, which can be worsened by the concomitant use of pasireotide in CD patients. Risk of lactic acidosis particularly in the presence of advanced renal or hepatic insufficiency [68] should be considered in patients treated with metformin.

Peroxisome proliferator-activated receptor-γ agonists, as pioglitazone, may potentiate the effects of metformin on insulin resistance (Table 1) [69]. A potential advantage of this drug in CD may be the anti-proliferative effects on tumour cells already demonstrated in experimental models of ACTH-secreting pituitary adenomas (Table 1) [70]. On the other hand, such as in other clinical settings [71], pioglitazone is not usually recommended for the treatment of diabetes in CD due to its undesired effects, such as body weight gain, fluid retention with increased risk of oedema, heart failure and fractures [72, 73].

When diabetes is not controlled by insulin sensitizers, insulin secretagogues or insulin is used [65]. The doses of these drugs should be carefully personalized since patients with medically or surgically treated CD may develop hypoglycaemia due to variable control of hypercortisolism [6].

Sodium-glucose co-transporter 2 inhibitors have been recently introduced in the treatment of diabetes (Table 1) [74]. The increased risk of urinary and genital infections demonstrated in patients treated with canagliflozin, dapagliflozin and empagliflozin [75] may limit the use of these drugs in CD patients who are already exposed to an overall increase in recurrent infections.

Interesting results have been achieved using the incretins in glucocorticoid-induced diabetes (Table 1). In healthy volunteers treated with glucocorticoids, exenatide was shown to control diabetes by decreasing glucagon secretion and gastric emptying [76]. Studies in type 2 diabetes suggest that incretins may be used in glucocorticoid-induced diabetes [77] due to their beneficial effects on appetite, body fat secretory activity and distribution and postprandial dyslipidemia [78–80]. Interestingly, liraglutide and vildagliptin have been shown to significantly counteract the negative effects of pasireotide on glucose homeostasis (Table 1) [51]. Possibly, these drugs in CD may have additional benefits on skeletal health, as reported in the general population [81].

Conclusions

Diabetes mellitus is a frequent complication of CD. Diabetes mellitus develops early during the natural history of CD making frequently difficult the diagnosis of hypercortisolism in this clinical setting. Moreover, diabetes mellitus was shown to be an important determinant of mortality in patients with CD. Finally, coexistence of diabetes mellitus and CD may reciprocally complicate the therapeutic approach to the two diseases due to potential hyperglycemic effects of drugs used in the management of CD and to the severity of hyperglycemia in CD which often need multimodal and aggressive treatment.

Compliance with Ethical Standards

Conflict of Interest G. Mazziotti reports personal fees from Ipsen.
M. Doga, A.M. Formenti, S. Frara and F. Maffezzoni declare that they have no conflict of interest.
A. Giustina reports personal fees from Novartis, Ipsen and Pfizer.

Human and Animal Rights and Informed Consent This article reviews studies that involve human participants. The authors of cited articles are responsible for approval by the appropriate institutional and/or national research ethics committee and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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