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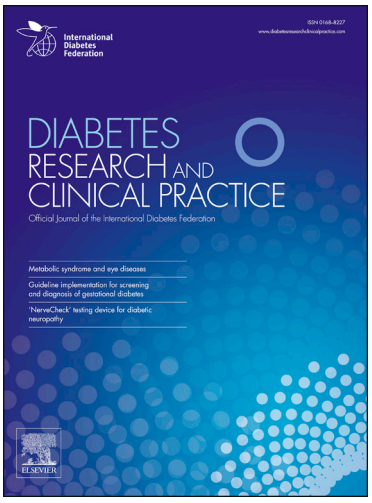

Review

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PII: S0168-8227(17)31936-8
DOI: https://doi.org/10.1016/j.diabres.2018.03.006
Reference: DIAB 7263

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 5 December 2017
Revised Date: 26 February 2018
Accepted Date: 2 March 2018

Please cite this article as: A. Bonaventura, F. Montecucco, Steroid-induced hyperglycemia: an underdiagnosed problem or clinical inertia? A narrative review, *Diabetes Research and Clinical Practice* (2018), doi: https://doi.org/10.1016/j.diabres.2018.03.006

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Steroid-induced hyperglycemia: an underdiagnosed problem or clinical inertia?

A narrative review

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Running title: steroid-induced hyperglycemia

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Abstract word count: 197 words

Manuscript word count (excluding title page, acknowledgments, conflict of interests, references, and figure legends): 6240 words

Reference number: 129

Number of Tables: 3

Number of Figures: 2

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Abstract

Corticosteroids are widely diffused drugs. An important side effect is the impairment of glycemic control both in patients with known diabetes and in normoglycemic ones potentially leading to steroid-induced diabetes mellitus (SIDM).

In this review based on papers released on PubMed, MEDLINE, and EMBASE from January 2015 to October 2017, we summarized and discussed main updates about the definition, the diagnosis, and the pathophysiology of steroid-induced hyperglycemia (SIH), with a look to new therapies. Main alterations responsible for the diabetogenic effect of corticosteroids are a negative impact on insulin sensitivity along with a derangement on insulin secretion, explaining the typical post-prandial hyperglycemia linked to the promotion of gluconeogenesis. An early and precise diagnosis of SIH and/or SIDM is necessary, but current criteria do not seem sensible enough. As an afterthought, the treatment should be reasoned and tailored according to proposed glycemic thresholds and patient comorbidities, choosing between antidiabetic oral drugs and insulin, the latter being preferable among hospitalized patients.

SIDM and SIH are frequent problems, but often underdiagnosed due to old diagnostic criteria. Dedicated guidelines universally shared are mandatory in order to harmonize the treatment of these conditions, thus overtaking single therapeutic strategies mostly arising from literature.

Keywords: corticosteroids; steroid-induced hyperglycemia; diabetes; complications; therapeutic strategy; glycemic variability.

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1. Introduction

Corticosteroids are widely used with different purposes in several diseases. Just to remember a few, they are acutely administered in exacerbations of chronic obstructive pulmonary disease (COPD), gout, and chemotherapy as well as chronically in sarcoidosis, autoimmune diseases, and inflammatory bowel diseases. Alongside with their anti-inflammatory and immunosuppressive properties, glucocorticoids are burdened by several side effects [1], among which metabolic impairments represent the most important, such as the development of central adiposity, increase in triglyceride rich lipoproteins and non-esterified fatty acids (NEFA), hepatic steatosis, and breakdown of skeletal muscle mass [2]. Steroids might exacerbate hyperglycemia in patients with diabetes or facilitate the development in apparently healthy subjects of the so-called steroid-induced diabetes mellitus (SIDM), which represents an independent risk factor for other steroid therapy complications [3]. A deep understanding of hyperglycemic steroid-induced disorders is of paramount importance for several reasons. Firstly, these derangements are very often underdiagnosed and problems arising from diabetes itself may cause frequent or prolonged hospitalizations or emergency room visits. Secondly, the combination of steroidal treatment and diabetes can greatly increase the risk of infections due to both immunosuppression and lasting hyperglycemia. Finally, the control of even transient hyperglycemia has demonstrated to decrease mortality and complication rates [4].

In this review based on papers released on PubMed, MEDLINE, and EMBASE from January 2015 to October 2017 (searched terms in combination: steroid-induced diabetes, steroid-induced hyperglycemia, glucocorticoid-induced hyperglycemia, hyperglycemia, corticosteroids; articles have been also retrieved through searches of reference lists and authors' files, while abstracts have not been considered), we aimed at discussing and summarizing the main updates about the definition, the diagnosis, and the pathophysiology of steroid-induced hyperglycemia (SIH) and SIDM, with a look at new therapies for their management. With respect to previous reviews in the field, we focused on understanding more recent pathophysiological mechanisms of SIDM and

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glucocorticoid-induced hyperglycemia (such as glycemic variability) and shedding some light on the therapeutic assessment, with a special interest to transient hyperglycemia and new drugs. We believe that this pathophysiological approach might be critical to improve clinical management of this frequent, but often underestimated condition.

2. Definition, diagnosis, and risk factors

The classical definition of SIDM refers to as an abnormal increase in blood glucose (BG) concentration during glucocorticoid use in patients with or without a previous history of diabetes [5]. Criteria for the diagnosis of diabetes by the American Diabetes Association, which have been accepted also by the Italian Society of Diabetology, rely on an 8-h fasting BG ≥126 mg/dL, 2-h post-75 g oral glucose tolerance test (OGTT) ≥200 mg/dL, a glycated hemoglobin value ≥6.5% or a random plasma BG value ≥200 mg/dL in patients with symptoms of hyperglycemia or hyperglycemic crisis [5, 6]. Anyway, two studies have underlined that patients with kidney and neurologic diseases under chronic steroidal agents showed post-prandial glucose values >200 mg/dL and fasting BG values <100 mg/dL [7, 8]. Hence, it is now clear that SIDM is underdiagnosed since classical criteria are not so sensitive. For this reason, the diagnosis of SIDM has been reliably suggested on the basis of the 2-h post-prandial glucose value >200 mg/dL at any time of the day. In particular, the post-prandial glycemia after lunch appeared very sensitive, especially for the administration of a single morning dose of intermediate-acting glucocorticoids [9]. Another proposal includes the measurement of fasting and post-prandial glycemia in three consecutive days among subjects without diabetes treated with corticosteroids with a diagnostic threshold of 150 mg/dL [10], but does not gain popularity.

As hyperglycemia is very common in the early posttransplant period due to immunosuppressive therapies, such as glucocorticoids, the definition of posttransplantation diabetes mellitus (PTDM) includes the presence of diabetes in the posttransplant period independently from the time of onset [11]. Glycated hemoglobin (HbA1c) has been considered for the diagnosis of PTDM with some

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caution and the OGTT is not suitable due to its difficulty and the risk to underestimate the typical glucose increase mainly occurring in the late afternoon and in the evening [12], as recently confirmed by Porrini *et al* [13]. Hence, OGTT should be restricted to selected patients, for whom other tests failed. Several risk factors for the development of SIDM have been reported and are depicted in Table 1 [7, 14-18]. Interestingly, gender does not seem to seriously impact on SIDM development [19], while early withdrawal of steroidal drugs has been described as a protective factor [20, 21].

3. Epidemiology

A real estimation of the risk of SIDM and SIH is very difficult due to different steroidal formulations, treatment duration, and dosing regimens. Moreover, in many studies only fasting glycemia is considered and this can lead to underestimate the real dimension of the disease.

A meta-analysis by Liu *et al* including 13 studies has shown that the overall event rate of hyperglycemia among patients using glucocorticoid-related treatments was 32.3%, whereas 18.6% of patients developed SIDM [22]. Other studies found a nearly doubled risk of developing SIDM, ranging from 1.36 (95% confidence interval [CI] 1.10-1.69) [23] to 2.31 (95% CI 2.11-2.54) [24]. Interestingly, Gulliford *et al* reported no association between diabetes and injected, inhaled, or topical glucocorticoids or glucocorticoid eye drops, while the adjusted odds ratio (OR) for diabetes among patients treated with three or more oral glucocorticoid prescriptions was 1.36 (95% CI 1.10-1.69), with an estimated population attributable risk of 2% [23]. Some years later, the use of inhaled corticosteroid (e.g. fluticasone) has been demonstrated to increase the rate of diabetes (rate ratio [RR] 1.34; 95% CI 1.29-1.39) and diabetes progression (RR 1.34; 95% CI 1.17-1.53) [25]. Besides, a direct correlation between the highest inhaled corticosteroid doses and increased incidence of SIDM has been described [25]. In the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) randomized trial, a short-term (5 days) vs. a conventional (14 days) systemic glucocorticoid treatment has been tested in patients with COPD exacerbation and the prevalence of

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new or worsening hyperglycemia at discharge across the whole cohort was nearly 60% (OR 0.98, 95% CI 0.58-1.66) [26]. In a meta-analysis by Breakey *et al*, both oral and intravenous glucocorticoid therapy has been demonstrated to increase the risk of hyperglycemia in all subjects with known respiratory diseases [27].

Among patients with hematologic malignancies treated with glucocorticoids, the incidence of fasting plasma hyperglycemia after 8 weeks was 68.7%, whereas the incidence of frank diabetes or prediabetes was estimated at 34.3%. Indeed, post-prandial capillary hyperglycemia had an incidence of 15.6%, which added to diabetes and prediabetes led the incidence of SIDM among hematologic patients to nearly 50% [28]. Recently, in a cohort of patients with hematologic malignancies requiring frequent, high-dose corticosteroids, hyperglycemia has been described with a prevalence of 39% [29].

With concern to PTD, the incidence of SIDM differs according to the transplanted organ and the time occurring from transplantation. Kidney-transplanted patients showed a variable incidence of SIDM ranging from 15-30% after 1 year [30] to nearly 25% after 3 years [31], with a bimodal trend, within and over 3 months from transplantation [13]. PTD incidence is of 24% after 6 months from liver transplantation [32], of 15.7% after 2 years from heart transplantation [33], and increases up to approximately 60% after lung transplantation [34].

Finally, SIH is a very common finding among hospitalized patients without diabetes treated with high-dose steroid therapy [16]. Fong *et al* found that 86% of hospitalized patients showed at least one BG value ≥144 mg/dL and 70% a glycemic value ≥180 mg/dL, while mean glycemic values ≥144 mg/dL have been found for 48% of subjects [35]. The study also confirmed data from Burt *et al* in prednisolone-treated COPD patients [36] indicating that hospital SIDM has a rapid onset within 2 days after the initiation of the therapy with a peak in the late afternoon [35]. Therefore, glucose monitoring across the first 48 hours is very important in order to identify the most patients developing hyperglycemia, stopping further testing in case of absence of hyperglycemia within the first 48 hours [37].

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Table 2 summarizes epidemiological data divided by different conditions according to main recent studies published within 2015 and 2018 [29, 38-54].

4. Pathophysiology of SIH

Precise mechanisms accounting for glucocorticoid effects on glucose homeostasis are still incompletely understood and the greatest part of the current knowledge dates back to studies in rats and humans appeared in '60s and '70s [55].

Glucocorticoids perturb glucose metabolism by decreasing the pancreatic production and release of insulin in a dose-dependent manner, by reducing insulin sensitivity, and by increasing glucose production. Moreover, glucocorticoid effects are present also in adipose and muscle tissues (Figure 1).

4.1 Steroidal-related pancreatic β cell dysfunction and insulin-resistance

Glucocorticoids have been demonstrated to impair β-cell function in healthy men, following both an acute and a 2-week exposure [56]. Steroid-induced pancreatic dysfunction in healthy men has been confirmed by van Raalte *et al* [57] and a pro-apoptotic effect of corticosteroids has also been postulated to contribute to β-cell failure [58]. Different studies in animal models have verified the impact of corticosteroids both intravenously and orally administered on insulin release, which is acutely abrogated in healthy subjects, showing stable levels of fasting insulin and high glucose levels [9]. *In vitro* studies using rodent islet cells have pointed out several mechanisms by which steroids can acutely alter insulin secretion: (i) reduced uptake and oxidation of various metabolites (including glucose); (ii) increased outward potassium currents limiting calcium influx; (iii) decreased efficacy of calcium ions on the insulin secretory process; (iv) alteration of the parasympathetic nervous system [2, 59]. In particular, prednisolone time-dependently inhibited glucose-stimulated insulin secretion in INS-1E cells and decreased both pancreatic-duodenal homeobox (PDX) 1 (a major regulator of the expression of a number of key β-cell genes [60]) and

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insulin expression leading to a great reduction in cellular insulin content [61]. The role of prednisolone in inducing β-cell dysfunction has been further confirmed and extended as glucocorticoid-induced increase in fasting and post-prandial glucagon levels showed that prednisolone can also alter islet-cell functional balance, with a possible role for the autonomic nervous system imbalance, as abovementioned [62]. In addition, prednisolone treatment in healthy individuals has been found to dose-dependently impair insulin-stimulated capillary recruitment, which is strongly related to adverse metabolic effects, such as post-prandial glycemic excursions and reduced insulin sensitivity as well as high systolic blood pressure [63]. Moreover, glucocorticoid receptor-mediated impairment of endoplasmic reticulum pathways occurred concurrently with the upregulation of calpain 10 and the increased cleavage of caspase 3, underscoring that a prolonged exposure to prednisolone actively promotes apoptosis [61]. However, considering the use of glucocorticoids among patients with systemic inflammation, e.g. rheumatoid arthritis, it is conceivable that β-cell effects induced by inflammation can impair β-cell function under glucocorticoid *stimuli* [64]. A prolonged glucocorticoid exposure can enhance the previous mentioned pro-apoptotic effect, leading to final β-cell failure [65]. Similarly, but indirectly, β-cell failure can derive from elevated levels of triglycerides and NEFA, e.g. the so-called lipotoxicity [66]. Therefore, also in long-term glucocorticoid treatment, glucocorticoids are likely to induce both *in vitro* and *in vivo* hyperinsulinemia and hyperglycemia, ultimately leading to β-cell failure [2]. Anyway, due to ethical issues, effects in humans after prolonged exposure to glucocorticoids cannot be tested and studies are limited to maximally 14 days. Very recently, Fine *et al* have investigated some pathways *via* which glucocorticoids could modify β-cell signaling in order to assure insulin secretion [67]. To make a long story short, glucocorticoids, such as corticosterone and cortisol, can block voltage-dependent calcium channel function and calcium fluxes both in rodent and human β-cells, but insulin secretion has been shown to remain unaffected by these alterations. Following this perturbation, a parallel upregulation of cyclic adenosine monophosphate (cAMP) as well as an increase in the amount of membrane-docked insulin secretory granules have been found, thus

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preserving insulin secretion. As a further proof of it, lipotoxicity has been proven to limit glucocorticoid effects and similarly the complete deletion of 11β-hydroxysteroid dehydrogenase type 1 – reducing cortisone to the active hormone cortisol – normalized calcium and cAMP signals. Hence, the study by Fine *et al* has identified an enzymatically amplified feedback loop by which glucocorticoids promote cAMP upregulation maintaining insulin secretion unaltered in spite of ionic impairment and whose failure can partly explain the diabetogenic effect of glucocorticoid excess, such as that of prolonged systemic administration of steroidal therapy, typically coupled with impaired lipid metabolism [67].

Among different steps in the insulin signaling within cells, the binding between insulin and its receptor (IR) is important because it promotes an increased kinase activity and tyrosine phosphorylation of many downstream signaling molecules, such as insulin receptor substrate 1 (IRS-1) through IRS-4. These molecules can trigger the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, leading to various downstream effects, all associated in particular with proliferative effects of insulin [68]. In skeletal muscle, glucocorticoids cause insulin resistance by a reduced transcription of IRS-1 and an increased transcription of the protein tyrosine phosphatase type 1B (PTP1B) and the p38MAPK [69], the latter being increased in liver, too [70]. Glucocorticoids can decrease IRS-1 and IRS-2 levels in fat [71], while a decreased phosphorylation of IR and IRS-1 have been demonstrated in the liver in response to glucocorticoids [72]. In 2007, the contribution of the bone to the insulin resistance induced by glucocorticoids has been firstly postulated. Lee *et al* demonstrated a role for osteocalcin in insulin resistance in knockout mice developing glucose intolerance and insulin resistance [73]. Proposed mechanisms for these alterations were: (i) a decreased pancreatic β-cell mass, responsible for hypoinsulinemia and (ii) a low adiponectin levels causing insulin resistance. Later, the disruption of the IR in osteoblasts was demonstrated to reduce osteocalcin levels and lead to similar metabolic changes [74]. As a confirmation, when osteocalcin was infused, a reduction in insulin resistance and an increase in glucose-driven insulin release were proven [75]. In 2012, Brennan-Speranza *et al*, by

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using transgenic mice (Col2.3-11β-hydroxysteroid dehydrogenase type 2), surprisingly revealed a protection from obesity, hyperlipidemia, and insulin resistance usually associated with steroid agents. These transgenic mice did not increase neither in body weight nor in triglyceride levels and did not develop abnormalities in glucose metabolism after 4 weeks of treatment with corticosterone. These results have been confirmed also after expressing osteocalcin in mice livers *in vivo* [76].

4.2 Steroid-induced gluconeogenesis, glycogenolysis, and fatty acid catabolism

Corticosteroids are strictly involved in the hepatic metabolism of glucose, thus increasing gluconeogenesis *via* the expression of different genes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (Figure 1) [77, 78]. Moreover, corticosteroids can indirectly increase glucose production by limiting the metabolic actions of insulin [79] as well as they increase the quantity of substrates for hepatic gluconeogenesis *via* their actions on muscles and adipose tissue. In skeletal muscles, corticosteroids stimulate protein degradation and reduce protein synthesis, resulting in high levels of amino acids and progressive muscle atrophy (the so-called steroid myopathy) (Figure 1) [80, 81] and contribute to the reduced glucose uptake and the increased glycogenolysis (Figure 2) [82]. With regard to reduced glucose uptake in muscle and adipose tissues, the main mechanism resides in the inhibition of the glucose transporter type 4 (Figure 2) [83]. In adipose tissue, steroids are responsible for increased lipolysis and subsequent accumulation of NEFA, which interfere with insulin-induced glucose uptake [84]. Following prednisolone treatment, an increase in plasma concentrations of resistin has been described and linked to impaired microvascular function (Figure 1) [63]. As the same, adiponectin, usually promoting insulin sensitivity in tissues, is suppressed by glucocorticoid treatment, appearing as another actor in the steroid-induced insulin resistance [85]. Apart from the ability of corticosteroids to increase counter regulatory hormone levels [62], an important role for the steroid-related increase in the endogenous production of glucose has been hypothesized for the nuclear receptor peroxisome proliferator-activated receptor α in knockout mice [86], with the autonomic nervous system

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accounting for a crucial role. Dexamethasone has been found to reduce the expression and phosphorylation of the IRS-1, PI3K, and protein kinase B (PKB)/Akt both in L6 skeletal muscle cells and in rat skeletal muscle (Figure 2) [87, 88]. A reduced insulin sensitivity can reside in corticosteroid-induced changes in protein and lipid metabolism, too [89].

The effects of corticosteroids are also linked to their pharmacodynamics, which actually has been evaluated only in healthy volunteers. Insulin resistance is mainly post-prandial developing within nearly 4 hours [90], but the variability of BG is strictly linked to dose, route of delivery, type of steroidal drug and its half-life, as illustrated in Table 3. For intermediate-acting steroids, such as prednisone, a single morning dose will cause hyperglycemia especially after lunch and in the late afternoon, with negligible effects on fasting glycemia. For long-acting corticosteroids, such as dexamethasone, the effect on glycemia will last for more than 24 hours and a slight decrease after an overnight fast might be present. Differently, for intra-articular steroidal drugs, such as triamcinolone, the peak of action can be from 2 to 24 hours after the administration and last until 5 days later.

In light of what described in the present chapter, new studies investigating metabolic effects of glucocorticoids are strongly needed. To date, the most knowledge relies on old data dating back to nearly fifty years, whilst in last decades many progresses have been done. Acquisitions concerning new mechanisms of actions of corticosteroids are now described in literature and pointed out as major contributors for the pathogenesis of diabetes and the development of its complications, such as epigenetics, just to cite one [91].

4.3 Glycemic variability during glucocorticoid therapy

Since glycemic variability is highly debated for its potential role in the development of diabetic complications, glucocorticoid therapy represents a powerful trigger for glycemic excursions. This aspect has been investigated by van Hooijdonk *et al* among critically-ill patients administered with hydrocortisone boluses in the setting of the intensive care unit [92]. Authors concluded that bolus

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infusion of hydrocortisone was associated with a higher glycemic and insulin rate variability across all Acute Physiology and Chronic Health Evaluation (APACHE) II score, irrespective of potential confounders, such as type of admission, body mass index, and age as well as a previous diagnosis of diabetes. Interestingly, glycemic variability was found to a lesser extent for more severely ill patients [92], thus confirming the pivotal role of the sympathetic nervous system in the glycemic homeostasis. Anyway, measures of glycemic variability have been made by two basic tools, such standard deviation and glycemic lability index, and results should be considered with some caution. Glycemic excursions during glucocorticoid therapy are typically influenced by pharmacodynamic and pharmacokinetic properties, with the typical peak of BG concentration in the later part of the day and a normalization of BG values in the morning for those taking short- or intermediate-acting glucocorticoids. Anyway, in contrast with type 2 diabetes, glycemic variability in patients with SIH or SIDM is likely to be affected by insulin resistance. The study by Weber-Carstens *et al* did demonstrate this aspect by showing that among patients administered with 50 mg of hydrocortisone, the ratio of caloric intake and insulin dosage did not change during the study period [93], so that BG increase reflected the reduced insulin sensitivity, which is a known pathophysiological mechanism of SIH and SIDM, as already discussed. Moreover, experimental and clinical data fret over high BG values suggesting a stringent control of SIH for hospitalized patients, as confirmed in critically ill patients, whose survival was linked to lower BG with respect to non-survivors [94]. Indeed, both mean and standard deviation of BG were significantly associated with intensive care unit mortality (OR 1.23 and 1.27, p <0.001, respectively) and in-hospital mortality (OR 1.21 and 1.18, p <0.001 and p=0.013, respectively) [94], thus corroborating the concept that a decrease in glycemic variability might represent a promising therapeutic target in order to ensure a better prognosis, especially among critically ill patients. Anyway, future studies are advised to include some more complex indicators of glycemic variability as the mere standard deviation may not encompass all glycemic variations around abnormal high BG values and especially between abnormal high and low BG values, which could be more harmful for critically ill patients. As well, further

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investigations evaluating new potential pathophysiological mechanisms and better therapeutic strategies (continuous vs. bolus insulin regimens) are warranted. In this view, even though not feasible for critically ill patients, dipeptidyl peptidase (DPP)-4 inhibitors could represent a promising therapeutic weapon when adopting a pathophysiological approach in non-critically ill patients [94].

5. Therapeutic management

As for diagnostic criteria, no clear therapeutic goals have been established. For this reason, current glycemic threshold for non-critically ill, hospitalized patients are commonly accepted [95]. In this view, the treatment for SIDM and SIH should be started for fasting BG levels >140 mg/dL and post-prandial BG levels >180 mg/dL. The target of glycemic values should remain within the 140-180 mg/dL range in the majority of patients, with levels <140 mg/dL only among selected patients, all this avoiding hypoglycemic crisis.

The need for a specific management of SIH relies on data indicating that clinical outcomes worsen when glycemia is not adequately controlled. Among patients undergoing non-cardiac surgery, perioperative hyperglycemia has been associated with increased duration of hospitalization, risk of intensive care unit admission, and in-hospital complications (such as pneumonia, wound and systemic infections) as well as a strong association between mortality and glucose levels both before surgery and after surgery has been demonstrated [96]. Early hyperglycemia after glucocorticoid initiation has been found as a prominent risk factor for adverse outcome in patients with acute graft-versus-host disease [47]. Among patients with hematologic malignancies under high-dose corticosteroids, maximum glucose values represented a predictor of length of in-hospital stay, in particular among those without prior diabetes [29].

Considering differences in steroid posology, the therapeutic approaches to SIH and SIDM must always be tailored on the single patient. As previously described, taking into consideration pharmacokinetics and pharmacodynamics of different compounds as well as the pre-existing

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glycemic profile and comorbidities is very important in order to start the best and less harmful hypoglycemic therapy. Accordingly, the choice among oral antidiabetic drugs or insulin is a critical step, which should consider also the duration of the corticosteroid therapy.

Temporary steroidal therapy is a frequent schedule, characterized by a high initial dose then tapered with the improvement of the disease, so that glycemic decompensation, even if at a high degree, is limited in time. For this purpose, a hypoglycemic drug being potent, immediately acting, and with a long duration of action would be the better choice. Unfortunately, oral hypoglycemic drugs do not own all of these features and less useful. Especially for patients without a history of diabetes or with adequately controlled diabetes (e.g. pre-prandial glycemia <200 mg/dL), diet and lifestyle may be sufficient to achieve therapeutic goals [17].

5.1 Insulin secretagogues

Some long-lasting sulfonylureas have been tested in kidney-transplanted patients giving partial results, as from one hand they induce insulin release contributing to glucose uptake by peripheral tissues, but on the other hand their narrow therapeutic window increase the risk for hypoglycemia [97]. Sulfonylureas could be better used for those patients administered with intermediate- or long-acting steroids, even with two or more daily doses [98]. Recently, in a pilot study including patients with lymphoproliferative disorders requiring short courses of high-dose steroids, the treatment protocol started with gliclazide 80 mg and recommended to start insulin directly for glycemic values >324 mg/dL, showing to be safe with no episodes of hypoglycemia and no hospital admissions [51]. On the contrary, glinides own an immediate onset of action and a short half-life, better adapting to the post-prandial increase of glycemia induced by corticosteroids and providing a negligible risk of hypoglycemia [9].

5.2 Insulin sensitizer agents

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Among insulin sensitizer agents, metformin can represent a good option because it directly counteracts glucocorticoid effects by enhancing insulin sensitivity and reducing gluconeogenesis. Its benefits include the low cost, its positive impact on weight, and a very low risk of hypoglycemia. Anyway, literature is scarce, including two studies [99, 100], as well as metformin can be contraindicated due to the underlying disease treated by steroids. Seelig *et al* recently displayed for the first time that preventive metformin treatment was effective in patients without diabetes under corticosteroid treatment with regard to glycemic control, also after adjustment for gender, total glucocorticoid dose, and HbA1c [100].

Thiazolidinediones enhance insulin action in skeletal muscle and adipose tissue, with scarce effect on insulin secretion. Even though used for long-time for SIDM [101, 102] due to their antagonistic effects on human metabolism in both adipose and muscle tissues compared to glucocorticoids [103], their side effects are not negligible, in particular water retention and the increased risk of bone fractures are shared with corticosteroids and can be therefore amplified.

5.3 Incretins and glifozins

DPP-4 inhibitors and glucagon-like peptide (GLP) 1 have been proven as effective in the control of hyperglycemia by enhancing the glucose-dependent release of insulin and peripheral glucose uptake, inhibiting glucagon secretion, and speeding gastric emptying [104, 105]. In particular, DPP-4 inhibitors should be considered as first-choice treatment in light of their quick onset of action, their crucial role on post-prandial glycemia, and their limited risk of hypoglycemia. About this, sitagliptin has been described to improve some aspects of islet-cell function (e.g. fasting C-peptide and post-prandial glucagon secretion.), but cannot prevent glucocorticoid-induced derangement of post-prandial insulin response [106]. An ongoing study is analyzing the ability of sitagliptin on glucose metabolism in men with metabolic syndrome concurrently treated with prednisolone 30 mg daily (ClinicalTrials.gov Identifier: NCT00721552). In humans, the incretin effect is known to be reduced by glucocorticoids despite normal concentrations of active GLP1, suggesting that steroids

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might alter GLP1-mediated activation of PKA [107]. Exenatide infusions have been described to prevent the acute diabetogenic effects of prednisolone in healthy volunteers [57]. Another mechanism by which GLP1 receptor agonist treatment can prevent glucocorticoid-induced hyperglycemia is the reduction of the gastric emptying rate, which is a typical pharmacological effect of this compound [108]. Exenatide administered subcutaneously has been reported to decrease BG levels in glucocorticoid-induced glucose intolerant mice, concurrently improving insulin resistance [109]. Therefore, suggested mechanisms for exenatide in SIDM may include restoration of the endogenous incretin effect and early insulin secretion, reduction in glucagon concentrations, and negligible risk of hypoglycemia [110].

To date, no studies are available for the new sodium-glucose cotransporter-2 inhibitors in the setting of SIDM.

5.4 Insulin

In all other situations, especially for glycemic values >200 mg/dL, insulin therapy is now considered the drug of choice [17]. Different schemes have been used, such as prandial insulin or schemes based on steroid dose and body mass index [111]. The prandial scheme is based on patient weight, total meal calories, and personal food pattern (e.g. snacks between meals or not). The initial dose is calculated at 0.1 U/kg *per* meal, then modified based on the glycemic response and the amount of supplementary insulin required to correct the pre-prandial hyperglycemia: 0.04 U/kg *per* meal when glycemia ranges between 200-300 mg/dL, 0.08 U/kg *per* meal for glycemia >300 mg/dL. It is advisable to increase the initial dosage in case of repeated pre-prandial corrections [112]. Basal insulin should be used with high doses of glucocorticoids, mainly among patients with a prior history of diabetes and those with persistent fasting glucose >200 mg/dL. The starting dose is 0.1 U/kg before bedtime, with corrections when glycemia is persistently >300 mg/dL despite pre-prandial corrections: 0.04 U/kg for glycemia between 300 and 400 mg/dL, 0.05 U/kg when glycemia is >400 mg/dL [112]. Another possibility, especially for those receiving a single daily

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steroid dose in the morning, is to administer basal insulin in the morning in order to blunt the late afternoon/evening peak of intermediate-acting corticosteroids (prednisone and prednisolone) avoiding the dose increase of prandial insulin [113]. In case of multiple steroid doses, basal insulin should be reduced to 30% of the entire quantity of daily insulin with the remaining 70% to be divided across meals [37].

5.5 Management of SIH/SIDM in hospitalized patients

With regard to the management of SIH in critically and non-critically ill patients, current guidelines give no precise indications, so that ongoing clinical practice is mainly driven by data coming from clinical studies and reappraisals made by reviews [37, 114, 115].

First of all, it is important to remember that the definition of hyperglycemia in hospitalized patients is based on BG levels >140 mg/dL and associated with poor outcomes (increased length of stay, infections) [37, 116]; accordingly, an admission HbA1c value ≥6.5% suggests that diabetes preceded hospitalization [117]. While not fully investigated in the setting of intensive care unit, SIH has been widely studied among hospitalized patients with cancer, who are typically treated in various settings, such as the internal medicine ward, the intensive care and palliative care units. Anyway, in a review by Brady *et al* investigating the management of SIH in cancer patients, all considered studies defined hyperglycemia for blood glycemic values >180 mg/dL, confirming that hyperglycemia, whatever the cause, is undertreated in hospitalized patients [118].

With concern to glucose monitoring, Pilkey *et al* [119] developed a guideline suggesting glucose monitoring twice a week before dinner, except for values between 180 and 360 mg/dl, for which the control is advised twice a day. In case of glucose values higher than 360 mg/dl, the start or the increase in insulin doses can be considered with a twice-a-day monitoring for two days. In patients without a history of diabetes, when hyperglycemia required treatment, the choice of drugs may range from oral antidiabetic agents, such as metformin, in combination with insulin until multiple daily doses of insulin [119]. For patients with known diabetes, the first step of the therapy included

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diet in nearly one third of patients in two studies, while oral antidiabetic oral agents shared similar percentages (52% vs. 43) [118]. On the contrary, insulin was differently used, mainly before steroid therapy administration [120, 121]. In this regard, sliding scale regimens showed increased rates of hypoglycemia, confirming that basal-bolus regimen warranted a greater safety and could be considered the best way to manage SIH, especially when insulin is administered before GC administration [111, 121, 122].

In 2012, Umpierrez *et al* published a clinical practice guideline for the management of hyperglycemia in hospitalized patients [37]. Bedside glucose testing should be initiated for all patients receiving glucocorticoid therapy and can be discontinued in normoglycemic patients when glucose values are <140 mg/dl without insulin therapy for at least 24-48 h. Previously normoglycemic patients receiving corticosteroids were advised to be monitored for at least 24-48 h after the beginning of the therapy and those with glycemic values persistently >140 mg/dL require ongoing glucose testing while starting an appropriate therapy. Discontinuation of oral antidiabetic drugs is advised in favor of subcutaneous basal-bolus insulin regimen. The starting insulin dose and its posology has to be tailored on the basis of severity of hyperglycemia, type of corticosteroid drug, and duration of the treatment, although the suggested starting dosage is between 0.3 and 0.5 U/kg [37]. For patients on high-dose glucocorticoid therapy and in those with severe hyperglycemia not controlled by basal-bolus regimen, continuous insulin infusion might be taken into account as an alternative [37]. Similarly to Umpierrez *et al*, in 2013 the Associazione Medici Diabetologi (AMD), Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI) and Società Italiana di Diabetologia (SID) published the Trialogue project aiming at helping internists in the management of hospitalised patients with hyperglycemia [115]. In acute patients with hyperglycemia under steroid treatment, insulin is the best therapy and should be administered according to the basal-bolus regimen. This regimen has been shown to better control fasting BG values as well as to easily modify insulin boluses on the basis of hyperglycemic peaks, which typically are found in the second part of the day [115].More recently, the Standards of Medical Care in Diabetes stated that

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glucocorticoid type and duration of treatment are pivotal elements to determine insulin regimens [117]. According to glucocorticoid half-life and peaks, intermediate-acting or long-acting insulin can be chosen. In accordance with other consensus statements, Standards conclude that generally adjustments based on anticipated changes in glucocorticoid dosages and glucose tests are critical to determine the insulin posology [117].

Actually, no indications are available for post-discharge management of patients with SIH/SIDM. In our opinion, current guidelines for post-discharge management of patients with diabetes can be considered [37, 115, 117]. In particular, a structured discharge plan should be organized for each patient, based on discharge setting (home with or without visiting nurse services, assisted living, rehabilitation, skilled nursing facilities, etc.) For self-sufficient patients discharged to home, the self-monitoring of BG and antidiabetic therapy will represent an important part of the management of SIH/SIDM with regard to type and duration of glucocorticoid therapy. An outpatient follow-up visit with a physician (primary care provider, endocrinologist, or diabetes educator) is advised for all patients within 1 month. In case of change in antidiabetic drugs or poor glycemic control after the discharge, an earlier appointment within 1-2 weeks represents to best strategy as well as frequent contact in order to avoid hyper- and hypoglycemia [117].

5.6 Transient hyperglycemia: what to do?

Apart from considering what just abovementioned on the need to treat early SIH, it is worth discussing whether it is strictly necessary to treat transient SIH, especially in the hospital setting. The study by Popovich *et al* [123] analyzed the results of a randomized controlled trial involving patients with community-acquired pneumonia admitted to hospital and treated with 50 mg prednisone or placebo for 7 days [38]. As expected, patients under prednisone treatment presented with higher mean glucose levels and BG variability compared to patients in the placebo group, both for those with and without diabetes. In spite of hyperglycemia, the primary outcome (e.g. time to clinical stability) was not inferior for patients with diabetes and this was confirmed by a regression

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analysis, supporting the concept that the presence of diabetes or SIH did not modify the benefit of prednisone therapy in this clinical situation [124]. Interestingly, the amount of insulin among patients with diabetes under prednisone was no greater than for those with diabetes on placebo; on the contrary, among patients without diabetes, those administered with prednisone received a larger amount of insulin compared to the placebo group [123]. Taking together all of these data, it seems that the question of hyperglycemia amongst the steroid-treated patients has not been completely solved. Although endocrinologists are correctly stressing on the glycemic control among hospitalized patients [125], it is widely known that this task is not always achieved due to the variable clinical status of patients, changing steroid doses, and especially the limited time of observation during the hospital stay. Actually, the evidence from literature about glycemic thresholds in hospitalized patients is controversial [126]. These aspects have been partially investigated [127, 128], mainly in the setting of the intensive care unit [129], but randomized clinical trials with a great number of patients coupling with a tight glycemic control are still lacking. Some information can be inferred from the Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery) showing how basal bolus insulin regimen in a surgical cohort of patients suffering from diabetes warranted a better glucose control and consequently a lower rate of complications than sliding scale insulin [4]. Accordingly to the analysis by Popovich *et al* [123], it is unlikely to apply the results from RABBIT 2 Surgery to medical patients under corticosteroid treatment as well as a reflection is necessary about the real need to treat tightly transient SIH. For this purpose, large randomized clinical trials are welcomed to hopefully put an end to this important issue.

6. Conclusions

SIH implicates both clinical and economic problems due to its high prevalence, particularly in long-term treated patients. The social impact of SIDM and SIH is linked to increased hospitalizations due to acute complications, whilst few data are available for chronic complications, which appear to be

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underdiagnosed. Corticosteroid therapy is known to favor macrovascular complications in patients with diabetes, but not mortality. This different incidence depends on many factors, first of all referring to dose, route of administration, and duration of treatment of corticosteroids. The main *caveat* lies on the early and precise diagnosis of SIDM and/or identification of SIH, which must rely on 2-h post-prandial glycemia. To date, the following treatment should be reasoned and individualized accordingly to above proposed glycemic thresholds, choosing between antidiabetic oral drugs and insulin, even though the latter would have always to be preferred, especially for hospitalized patients.

The diabetogenic effect of corticosteroids is referred to a negative impact on peripheral and central insulin sensitivity along with derangement on insulin secretion, causing most frequently post-prandial hyperglycemia, especially in the late afternoon and in the evening. Starting from here, the therapeutic approach is aimed at limiting these dysfunctions in order to progressively reduce complications. Recently, incretin-based therapies, such as DPP-4 inhibitors and GLP1 receptor agonists, have become a new weapon in the armory of diabetologists at first and of clinicians taking care of patients with diabetes and SIDM or SIH then. In light of the action on meal-related insulin secretion and reduction of glucagon secretion, this new class of drugs directly target two important pathophysiological features of SIDM and SIH with a very low risk of hypoglycemia due to their glucose-dependent mechanism of action.

SIDM and SIH are frequently encountered problems in the clinical practice, which need to be coped with on the basis of current indications. In this perspective, precise guidelines universally shared dealing with SIDM and SIH management would be welcomed in order to harmonize the treatment of these conditions overtaking single therapeutic strategies.

Acknowledgments

This study was supported by a grant from the European Commission (FP7-INNOVATION I HEALTH-F2-2013-602114; Athero-B-Cell: Targeting and exploiting B cell function for treatment

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in cardiovascular disease) and a grant from the Swiss National Science Foundation to Dr. F. Montecucco (#310030_152639/1).

We are grateful to Luca Liberale, MD for his precious comments and suggestions.

Conflict of interest: none.

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Figure 1. Mechanisms of glucocorticoid-induced hyperglycemia. Glucocorticoids own diabetogenic effects by impairing insulin sensitivity in liver, skeletal muscle, and adipose tissue as well as altering pancreatic β-cell function at different levels. Red arrows indicate negative effects, while green arrows stand for positive effects.

Abbreviations: G6P: glucose-6-phosphatase; PEPK: phosphoenolpyruvate carboxykinase.

Figure 2. Molecular pathways of glucocorticoid effects on glycemic and protein metabolism. Insulin can stimulate glucose uptake in cells *via* the translocation of glucose transporter (GLUT) 4 from the intracellular compartment to the cell surface. After binding to its receptor, insulin triggers GLUT4 migration by the activation of cytosolic proteins (insulin receptor substrate-1, phosphatidylinositol 3 kinase, and Akt/protein kinase B. Glucose can then be processed by non-oxidative pathways leading to glycogen synthesis, which is enhanced by insulin *via* the glycogen synthase kinase blocking glycogen synthase. Glucocorticoids are shown to impair insulin signaling cascade, resulting in reduced glucose uptake and glycogen synthesis. Moreover, the blunted insulin signaling is responsible for glucocorticoid-induced protein catabolism.

Red, rounded arrows indicate inhibitory pathways. Red crosses show inhibitory effects by glucocorticoids.

Abbreviations: GLUT4: glucose transporter 4; GS: glycogen synthase; GSK-3: glycogen synthase kinase-3; IGF-1: insulin-like growth factor 1; IRS-1: insulin receptor substrate-1; mTOR: mammalian target of rapamycin; MuRF-1: Muscle Ring Finger-1; P: phosphorylated; PI3K: phosphatidylinositol-3 kinase; PKB, protein kinase B; PP-1: protein phosphatase-1.

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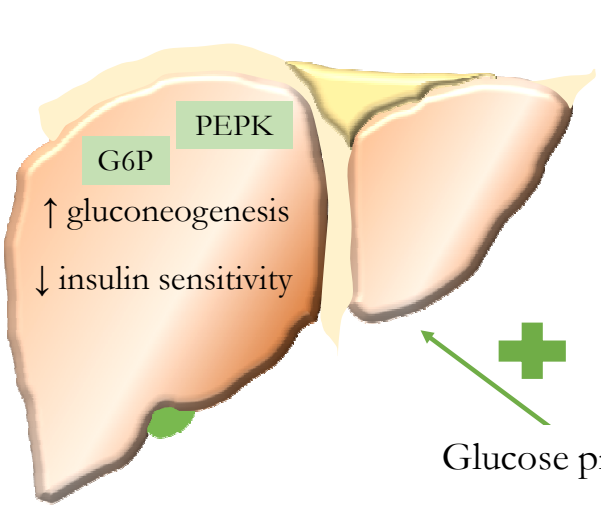
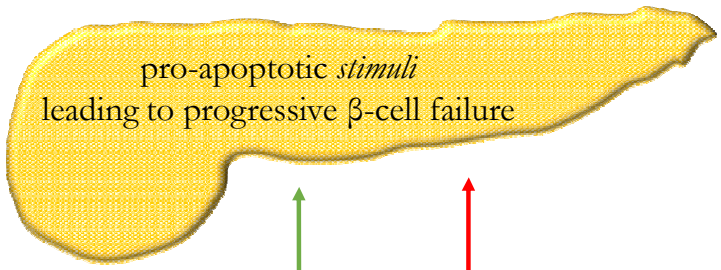




Glucose production

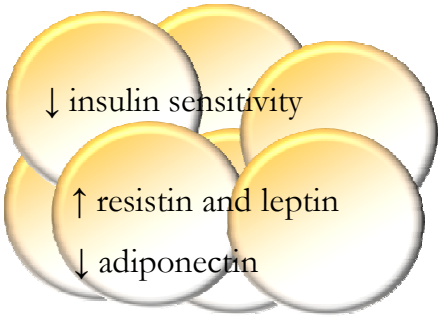
Glucagon

Insulin

Impaired incretin effect

Glucocorticoids

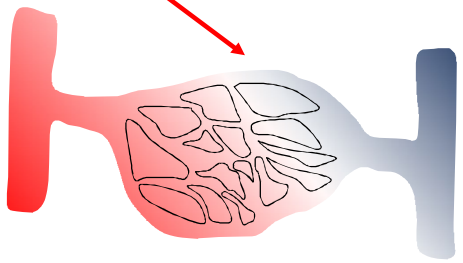
Lipolysis



Glucose uptake

Proteolysis

Capillary recruitment



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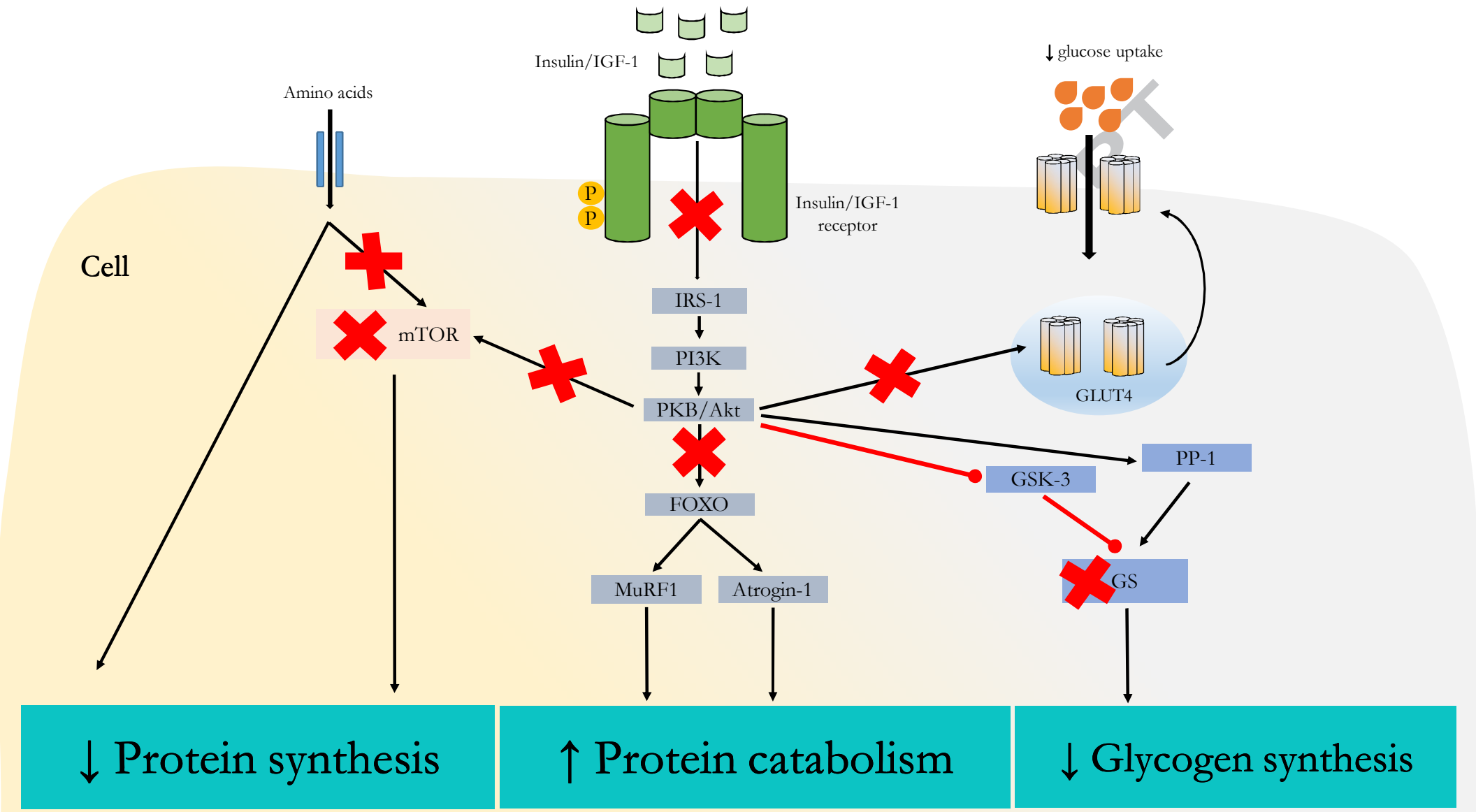

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Table 1. Risk factors for steroid-induced diabetes mellitus

Dosage and type of the drug
Duration of treatment
Posology (e.g. continuous vs. bolus treatment)
Age ≥65 years old
Male sex
BMI* >25 kg/m^2
African American ethnic group
eGFR° <40 mL/min/1,73 m^2
HbA1c$^{\$}$ ≥6.0%
History of gestational diabetes
Family history of diabetes mellitus
Concomitant use of mycophenolate mofetil and calcineurin inhibitors
Previous history of IFG§ and/or IGT¶

Legend

* BMI: body mass index

° eGFR: estimated glomerular filtration rate

$ HbA1c: glycated hemoglobin

§ IFG: impaired fasting glucose

¶ IGT: impaired glucose tolerance

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Table 2. Most recent studies investigating steroid-induced hyperglycemia and/or diabetes mellitus

Authors	Design	Diseases	Patients	Results
Hematological diseases and cancer				
Aberer *et al*, 2017 [52]	RCT	GvHD	10 patients under GC therapy assigned to either an automated decision support system (GlucoTab®) or conventional treatment followed-up for 6 months	67.2% and 65.4% of glycemic values were within the 70-180 mg/dL range for Glucotab® and conventional treatment, respectively. Hypoglycemic values were less frequent for Glucotab® group.
Stauber *et al*, 2017 [47]	Retrospective study	Acute GvHD	104 patients receiving systemic GC therapy with glucose parameters assessed soon after initiation of GC.	Early hypoglycemia was associated with shorter overall survival when considered across 3 different tertiles (p<0.0001). Patients under insulin treatment experienced an increased risk of death (HR 2.52, 95% CI 1.49-4.24; p=0.0005). A score based on early hyperglycemia and non-response to GC within 7 days identified 3 risk groups, with patients carrying both risk factors showing the worst overall survival at 5 years (4.1% vs. 75.4% in patients with none, p=0.0002).
Serrano *et al*, 2017 [53]	Prospective cohort study	Hematological malignancies	96 patients treated with high GC doses for at least 4 days. Patients diagnosed with GID were administered with NPH insulin, while those diagnosed with HGPD continued basal-bolus insulin regimen and were added NPH as GID protocol.	30 patients developed HGPD and 66 GID with no difference in glucose control. Hypoglycemia was more frequent in the HGPD group. Accordingly, when comparing GID and HGPD, the highest insulin dose was 30 IU (IQR:18-45 IU) and 79.5 IU (IQR 43.5-109.5), respectively (p<0.001).
Vidler *et al*, 2017 [51]	Prospective study	Lymphoproliferative malignancies	34 patients prescribed with high-dose GC checked capillary blood glucose before breakfast and dinner.	17 patients developed SIH/SDM, while those with T2D developed SIH and 3 required insulin. Among non-diabetic patients, 8 developed SDM. Pre-treatment HbA1c was higher among patients developing SDM (p=0.002).
Healy *et al*, 2017 [29]	Retrospective study	Hematologic malignancies	168 patients receiving systemic GC therapy for a 2-month period.	Patients without diabetes under a GC dose equivalent to >12 mg dexamethasone showed a greater increase in BG levels compared to a dose <12 mg (p=0.011). The maximum BG value predicted the length of hospital stay among patients

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				without diabetes (p=0.01) as well as with acute leukemia or stem cell transplantation (p=0.03 and 0.01, respectively).
Gerards *et al*, 2016 [39]	Randomized crossover study	Patients with SIH during antineoplastic chemotherapy	26 patients with T2D or random BG level >216 mg/dL randomized to first SSI or first IMI as add-on to their routine diabetes medication on the days they used GC medication.	By using CGM, patients in the IMI arm showed a higher proportion of BG values within the target range (70-180 mg/dL) than SSI (p<0.001), whereas no severe hypoglycemic events have been registered.
Lung diseases				
Torres *et al*, 2015 [50]	Multicenter, randomized, double-blind, placebo-controlled trial	Severe CAP	120 hospitalized patients were randomized to either an IV bolus of 0.5 mg/kg per 12 hours of methylprednisolone or placebo for 5 days within 36 hours from hospital admission.	Hyperglycemia occurred in 11 patients in the methylprednisolone group and in 7 patients in the placebo group (p=0.34).
Blum *et al*, 2015 [38]	Multicenter, randomized, double-blind, placebo-controlled trial	CAP	785 hospitalized patients were randomly assigned to either prednisone 50 mg/day or placebo for 7 days within 24 hours from presentation.	In the prednisone group, a higher rate of in-hospital hyperglycemia needing insulin treatment was registered when compared to the placebo group (19% vs. 11%, respectively). This association was then confirmed by the logistic regression analysis (OR 1·96, 95% 1·31-2·93; p=0·001).
Tagarro *et al*, 2017 [48]	Multicenter, double-blind, parallel-group, placebo-controlled clinical trial	Parapneumonic pleural effusion	57 hospitalized children aged 1 month to 14 years receiving either IV dexamethasone (0.25 mg/kg/dose) or placebo every 6 hours over a period of 48 hours along with antibiotic therapy.	Patients receiving dexamethasone experienced a shorter time to recovery (HR 1.95; 95% CI 1.10-3.45; p=0.021). The only difference between dexamethasone and placebo groups in terms of complications or adverse events was found for hyperglycemia (RR 2.5, 95% CI 1.2-5.5; p=0.02).
Gerards *et al*, 2018 [40]	Double-blind RCT	AECOPD	46 hospitalized patients with known T2D under prednisone (at least 30 mg) were randomly assigned to dapagliflozin 10 mg/day or placebo as add-on to their eventual routine diabetes medication.	No difference in the time spent within the target range (3.9-10 mmol/L), mean BG values, and incidence of hypoglycemic events between was found between groups.
Immune diseases				

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Lv *et al*, 2017 [54]	Multicenter, double-blind, RCT	IgA nephropathy	262 patients randomized to oral methylprednisolone (0.6-0.8mg/kg/day) or placebo for 2 months, followed by a progressive weaning over 4-6 months.	New-onset diabetes has been found in 2 patients in the GC group and in 3 patients in the placebo group, with no statistically significant difference.
Radhakutty *et al*, 2016 [45]	Open, interventional and cross-sectional study	Rheumatoid arthritis	36 subjects, of whom 18 subjects not administered any oral GC for at least 6 months and 18 subjects taking a stable oral prednisolone dose of 4-10 mg/day for at least 6 months. The first group was evaluated before and after prednisolone 6 mg/day for 7 days.	Fasting BG was higher after acute prednisolone (p=0.02), while there was no difference for chronic administration. With regard to insulin resistance, Matsuda index was lower both after acute and chronic prednisolone (p=0.01 and p=0.04, respectively). Postprandial Aix75 as well as noradrenaline excretion were lower only after acute prednisolone ($p\leq$0.001 and p=0.02, respectively).
Tanaka *et al*, 2018 [49]	Case report	Thyroid ophthalmopathy	5 patients administered methylprednisolone pulse therapy developing SDM were treated alternately with mitiglinide (30 mg/day) and repaglinide (1.5 mg/day) during the second or third pulse therapy. All patients were assessed by CGM.	BG levels before lunch and dinner showed a better glycemic control with repaglinide (p=0.043 for both vs. mitiglinide).
Orthopedic disorders				
Kim *et al*, 2015 [41]	Prospective trial	Disorders of the hand or wrist requiring an injection of corticosteroid	25 adult, diabetic patients administered with an injection of 1 mL with 10 mg of triamcinolone acetonide mixed with 1 mL of 1% lidocaine with no epinephrine.	20 patients showed an increase in their BG from baseline, which returned to normality after 5 days (p=0.005). Patients with HbA1c ≥7% were found with higher BG values (p=0.003) lasting for a longer time than those with HbA1c <7% (p=0.0004). A correlation between HbA1c and increased BG levels from day 1 to 4 was found (p=0.0003 for day 1, p<0.0001 for other days).
Posttransplantion complications				
Mourad *et al*, 2017 [43]	Multicenter, prospectively randomized, open-label study	PTDM	1166 patients undergoing kidney transplantation treated with prolonged-release tacrolimus, basiliximab, MM, and 1 bolus of intraoperative corticosteroids. Patients in arm 1 received tapered GC,	By a Kaplan-Meier analysis, the incidence of PTDM after 24 weeks was similar for both arms, with no statistically significant difference (p=0.579).

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			stopped after 10 days, while patients in arm 2 received no steroids after the intraoperative bolus.	
Pirsch *et al*, 2015 [44]	Prospective, double-blind RCT	PTDM	277 patients following kidney transplantation who early withdrew GC were investigated to evaluate whether GC avoidance could reduce PTDM risk.	By evaluating different PTDM definitions, only age, but not GC use, was a significant risk factor for PTDM for more than one definition (HR ranging from 1.02 to 1.03 and with *p* ranging from <0.001 up to 0.04).
Miscellaneous				
Radhakutty *et al*, 2017 [46]	Open-label stratified RCT	Acute medical condition not further specified	50 consecutive hospitalized patients treated under oral prednisolone ≥20 mg/day as a single morning dose received a total daily dose of insulin of 0.5 IU/kg (isophane plus aspart in one group and glargine plus aspart in the other group.	On day 1, no significant differences in percentage of time outside a target glucose range of 72-180 mg/dL, mean daily glucose, and glucose <72 mg/dL was registered in both groups.
Lakhani *et al*, 2017 [42]	Randomized, open-labeled, parallel arm trial	Any medical condition	67 patients randomized to control group (standard basal-bolus insulin) or the experimental one ("correctional insulin" matching the glycemic profile of the GC with or without background basal-bolus insulin).	Mean BG values were lower in the experimental group (p= 0.0001), as confirmed by all parameters of glycemic variability (p=0.0001). Hypoglycemia event rates was low in both groups, but statistically significant only for severe events in the experimental group (p=0.0001).

Legend

AECOPD: acute exacerbation of chronic obstructive pulmonary disease. AI: augmentation index. AIx75: augmentation index normalized for a heart rate of 75 beats per minute. AUC: area under the curve. BG: blood glucose. CAP: community-acquired pneumonia. CGM: continuous glucose monitoring. CI: confidence interval. GC: glucocorticoid. GID: glucocorticoid-induced diabetes. GvHD: graft-versus-host-disease. HbA1c: glycated hemoglobin. HGPD: hyperglycemia in a patient with previous diagnosed diabetes. HR: hazard ratio. IMI: intermediate-acting insulin. IQR: interquartile range. IU: international unit. IV: intravenous. MMF: mycophenolate mofetil. OR: odds ratio. PTDM: posttransplantation diabetes mellitus. RCT: randomized clinical trial. NPH: neutral protamine Hagedorn. RR: risk ratio. SDM: steroid-induced diabetes mellitus. SIH: steroid-induced hyperglycemia. SSI: sliding scale insulin. T2D: type 2 diabetes.

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Table 3. Half-life of different glucocorticoids

Drug	Half-life (h)
Short-acting	
Cortisone Hydrocortisone	8-12
Intermediate-acting	
Prednisolone Prednisone Methylprednisolone	12-16
Deflazacort Fludrocortisone Triamcinolone	12-24
Long-acting	
Betamethasone Dexamethasone	20-36

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