

Steroid-induced diabetes in rheumatologic patients

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ABSTRACT

Glucocorticoids are widely used to suppress inflammation – especially in the acute phase – in several inflammatory and autoimmune rheumatologic diseases. Despite their efficacy, their long-term use or at high doses is associated with numerous well-characterised side effects. Hyperglycaemia or frank diabetes is one of the most common, as its prevalence is estimated between 10–20%. Its pathophysiology is mainly due to increased insulin resistance. In this review, we provide a practical guide on how to monitor patients who are started on glucocorticoids, and how to detect and manage steroid-induced hyperglycaemia or diabetes.

Definitions

Diabetes is a metabolic disease characterised by hyperglycaemia, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced, or both. It is classified into four broad categories:

1. Type 1, where autoimmune destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas leads to insulin deficiency.
2. Type 2, where there is a defective response of body tissues to insulin, leading to insulin resistance. In most cases there is also reduced or inappropriate insulin secretion.
3. Other specific types of diabetes, including endocrinopathies, diseases of the exocrine pancreas like chronic pancreatitis, medications like steroids and many genetic defects and syndromes.
4. Gestational diabetes.

In order for a patient to be diagnosed as diabetic, at least one of the following four criteria has to be met (1):

1. Fasting plasma glucose level ≥ 126 mg/dl (7.0 mmol/l) on at least two occasions.

2. Plasma glucose ≥ 200 mg/dL (11.1 mmol/l) two hours after a 75 g oral glucose tolerance test.
3. Symptoms of hyperglycaemia and random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).
4. Glycated haemoglobin (HbA1c) $\geq 6.5\%$.

Impaired glucose tolerance (IGT) is a pre-diabetic state of hyperglycaemia that is associated with insulin resistance and increased risk of cardiovascular disease, defined as two-hour glucose levels of 140 to 199 mg/dl (7.8 to 11.0 mmol/l) on the 75-g oral glucose tolerance test. On the other hand, impaired fasting glucose (IFG), refers to a condition in which the fasting blood glucose level is consistently elevated above normal, but it is not high enough to be diagnosed as diabetes mellitus and ranges from 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l). Both, IFG and IGT are referred also as prediabetes; patients with prediabetes have HbA1c values between 5.7–6.4% (2).

Steroid-induced hyperglycaemia and diabetes belongs to the third category of diabetes' classification and include patients with new onset steroid-induced diabetes. Patients who have been diagnosed as diabetics in the past belong to one of the first two categories of diabetes' classification and may require alterations to their medication because of steroid administration.

Prevalence

While there is universal agreement that glucocorticoids (GCs) exacerbate hyperglycaemia, the prevalence of new onset steroid-induced diabetes (NOSID) has been debatable. In many small or larger studies it ranges 5–45% with odds ratio between 1.3 and 2.7. Nevertheless, most studies agree that the prevalence of NOSID is approximately 10–20%, depending mainly on dose and duration of steroid administration. In a

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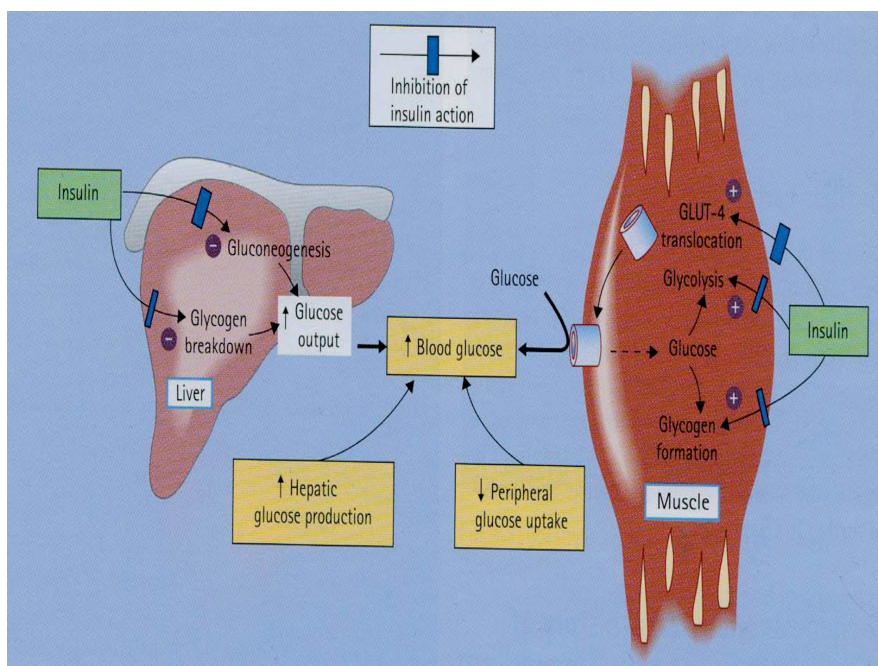


Fig. 1.* Pathophysiology of NOSID – inhibition of insulin action by glucocorticosteroids.
*Modified from reference 11.

small study with patients with rheumatoid arthritis (mean age 62 years), nearly 9% developed diabetes within two years after starting GCs treatment (3). In a prospective study of non-diabetic patients with primary renal disease treated with moderate-to-high dose GCs (prednisolone, 0.75 mg/kg daily), 42% were found to have 2-hour post-lunch plasma glucose values exceeding 200 mg/dl (11.1 mmol/l), although fasting glucose values were normal (4). In a cohort of patients receiving prednisolone (approximately 42 mg/day) for treatment of a variety of neurologic diseases, corticosteroid-induced diabetes mellitus developed in 50%, as determined by 2-hour postprandial glucose values >200 mg/dl (11.1 mmol/l) (5). In a case-control analysis of registry data from the United Kingdom, oral GCs therapy was associated with an odds ratio of 1.36 for development of NOSID, whereas data from a New Jersey Medicaid program demonstrated an odds ratio of 2.23 for occurrence of NOSID (6-7). In a retrospective analysis of elderly persons (mean age, 74.9 years), the odds ratio for NOSID was 2.31 in conjunction with an incidence rate of 12% (8). Of interest, one large meta-analysis of 93 publications involving 6,602 patients that examined the risk of

peptic ulcer disease in patients treated with GCs reported an odds ratio of 1.7 for NOSID (9).

In summary, both the dose and duration of GC treatment are strong predictors for development of NOSID. Age and increased body mass index have been identified as additional risk factors. Surprisingly, family history of diabetes has not clearly been related to an increased ratio of NOSID, nor sex or ethnicity (10).

Pathophysiology

The mechanism of glucocorticoid-induced diabetes mellitus is multifactorial, as illustrated in Figure 1 (11). GCs treatment impairs both glucose transport in fat and muscle cells and the ability of glucose to stimulate its own utilisation (glucose effectiveness), leading to reduced insulin sensitivity. Rizza *et al.* demonstrated this effect in 1982, as an intravenous infusion of hydrocortisone in healthy males was associated with a 50% reduction in insulin sensitivity, as determined by the insulin clamp technique (12). Apart from enhancing insulin resistance, GCs also increase hepatic gluconeogenesis and glycogenolysis, thus they increase glucose production from the liver (13). In addition, high doses of GCs are associ-

ated with reduced GLUT-2 expression and a decrease in glucose transport into the beta cells. They also seem to have direct harmful effects on insulin-secreting beta cells of the pancreatic islets by inducing apoptosis (14).

Nevertheless, the impairment in insulin function at the level of the liver, as well as the skeletal muscle and fat, is by far the main factor that predisposes to NOSID. Unfortunately, GCs can also increase appetite and weight, thus exacerbating insulin resistance.

Recognition and management of steroid-induced hyperglycaemia

All patients started on GCs should have their blood glucose levels checked before and after steroid initiation. The projected exposure can be classified as short-term, if less than a month of treatment is estimated to be sufficient, or long-term. Even short-term postprandial hyperglycaemia is associated with endothelial dysfunction in patients with or without diabetes (15). Thus, all patients with NOSID should receive diabetes treatment, aiming at fasting glucose levels 70–130 mg/dl (3.9–7.2 mmol/l) and 2 hours after meals <180 mg/dl (10 mmol/l).

Patients who already have diabetes or IGT before GCs are initiated (whether they were aware of it or not), should be expected to show an increased demand for diabetes' drugs dosages and should have more regular measurements of their glucose levels. They should also be referred to their diabetes specialist. Patients who were euglycaemic before GCs' administration should have intense glucose monitoring during the first 2–3 days (Fig. 2). Fasting as well as 2 hour postprandial glucose levels (especially after breakfast and lunch) measured by test strips and verified by serum levels if high, should take place. In the presence of diabetes, IGT or IFG the patient should be referred to a diabetes specialist.

To better understand the optimal time for checking plasma glucose and to apply appropriate treatment, the pharmacokinetic profile of the most commonly used formulations of GCs should be considered. Prednisone, methylprednisone and dexamethasone have a sim-

ilar profile; their plasma concentrations peak at approximately 1 hour and their half life is about 2.5 hours (16-17). In contrast, the pharmacodynamic profiles with respect to glucose tolerance are more prolonged and are consistent with the genomic effects of the drugs mediating gluconeogenesis and peripheral insulin sensitivity. Prednisone and methylprednisone demonstrate their peak effect at 4 to 8 hours with a duration of action of approximately 12 to 16 hours. Dexamethasone seems to have an even more extended effect, with a duration that might reach 20 hours (18). These properties of GCs explain why patients with NOSID might have normal fasting glucose levels, especially in the morning, but high fasting or postprandial levels throughout the rest of the day, that return closer to normal by bedtime. Furthermore, the circadian rhythm of internal steroid production and the fact that physicians try to resemble it by giving most of the daily dose of steroids in the morning, keep up with these glucose levels' variations.

Diet and exercise are the initial measures that every patient started on GCs should adopt. Unfortunately, some rheumatologic patients may have reduced capacity to exercise and diet measures alone often do not suffice. The next step would be to start an oral hypoglycaemic agent. Their pros and cons are summarised in Table I.

Metformin and thiazolidinediones would seem to be a reasonable initial agent, due to their salutary effects on insulin resistance (19). Metformin has precedence, since it is cheaper, there is a wide experience for its use and it does not seem to cause oedema or worsen osteoporosis like pioglitazone. Metformin is contraindicated if estimated glomerular filtration rate is <30 ml/min and in severe liver disease. Pioglitazone is contraindicated in the presence of heart failure of any degree and in liver diseases.

Sulfonylureas and glinides provide therapeutic alternatives by promoting pancreatic insulin secretion. Glinides have the advantage that are given preprandially and reduce postprandial hyperglycaemia, which seems to be

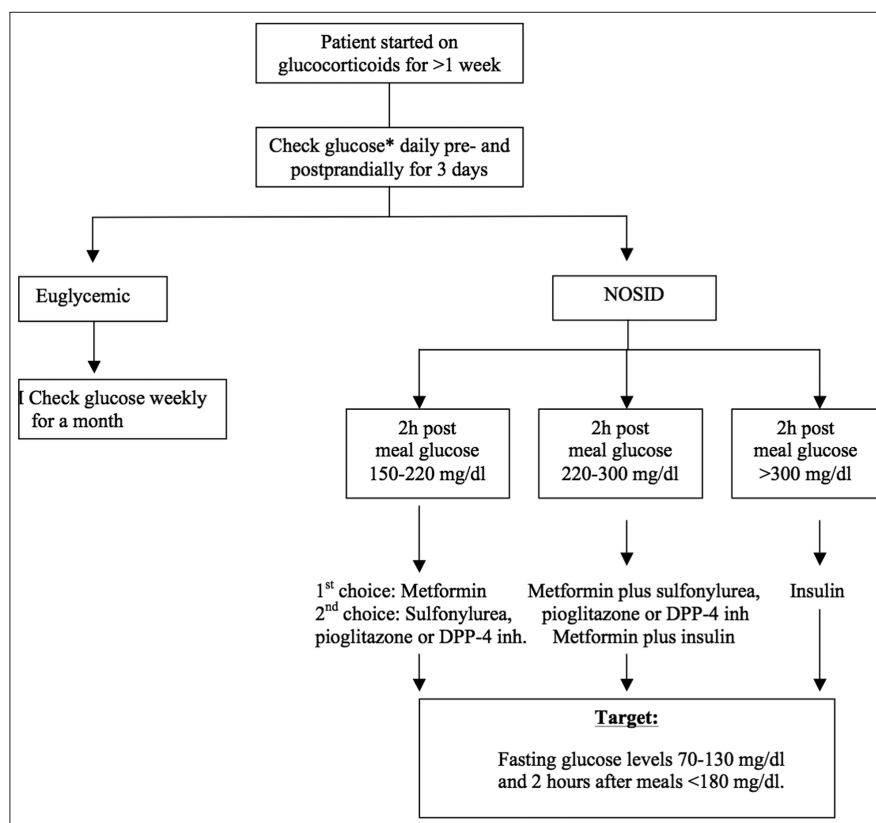


Fig. 2. Algorithm for new onset steroid-induced diabetes (NOSID) management.
*glucose levels measured by test strips and verified by serum levels if abnormal.

Table I. Advantages and disadvantages of oral hypoglycaemic agents

	Pros	Cons
Metformin	Reduced insulin resistance Reduced gluconeogenesis Low cost	Contraindicated in severe lung, kidney, liver disease Gastrointestinal disturbance
Sulfonylureas	Rapid onset of action Enhanced insulin secretion Low cost	High risk of hypoglycaemia Poor response rate (25%)
Thiazolidinediones	Reduced insulin resistance	Oedema-worsened heart failure Long-term fracture risk Cardiovascular risk
DPP-4 inhibitors	Very well tolerated Incretin effect	Expensive New and less studied Upper respiratory infections

the main issue in NOSID. Nevertheless, they are weak drugs and are rarely used. Sulfonylureas are more effective and have been long used, but their narrow therapeutic window as far as hypoglycaemia is concerned makes them unpopular, especially in elderly persons or those with lower GFR. Dipeptidyl peptidase-4 (DPP-4) inhibitors take advantage of the incretin effect and reduce plasma glucose levels by prolonging the action of endog-

enously released glucagon-like peptide-1 (GLP-1). They can be used in NOSID with or without metformin, but they have more or less the same limitations with metformin and are more expensive and less well-studied. Injectable options include GLP-1 analogues and insulin. GLP-1 agonists have only recently been introduced; their effects on NOSID have not been studied and their potential long-term side effects are not yet well known. In

addition they are very expensive and not significantly more potent than oral hypoglycemic agents. As a result, they are rarely used, even though their effects on reducing appetite and increasing insulin levels postprandially are attractive.

Insulin has many advantages and seems a reasonable option, especially when fasting or postprandial blood glucose levels are very high (>300 mg/dl, 16.6 mmol/l). Of all the available drugs, insulin is the only one that can be used, even in the context of multiple comorbidities. It does not cause significant drug interactions, and the dose can be adjusted upwards and downwards in increments to fit the patient's needs, especially when a larger GCs load is given up front and then is tapered either slowly or rapidly.

A direct comparison of prandial insulin, basal insulin, and premixed insulins in patients with type 2 diabetes mellitus has recently taken place, demonstrating that each is equally effective when used in comparable doses; this seems to be the case in NOSID too (20). Taking into account the pharmacokinetic profile of the GCs that are mostly used, the intermediate acting insulin NPH seems the best option when prednisone is started and long acting analogues like insulin detemir and glargine when dexamethasone is initiated. This is because intermediate acting insulin has its peak effect 6-8 hours after administration and its action lasts around 12-15 hours, whereas long acting insulins show no important peaks and last throughout the day (insulin glargine has actually a longer action than detemir). Unfortunately, both these two strategies of insulin administration do not fully cover the patient, as they fail to mimic the postprandial peak of endogenous insulin that starts when food reaches the small intestine and peaks during the first hours after a meal.

Alternative therapeutic schemes have been proposed. The first one would be the combination of one of these two insulin regimens with oral hypoglycemic drugs. The second one would be administration of a fast acting prandial insulin, initially just before the main meal and then maybe twice daily. The

last therapeutic option would be to initiate a premixed combination of an intermediate-acting plus a short-acting insulin before breakfast or lunch, depending on the fasting and postprandial glucose levels, that can then be titrated upwards once, twice (two thirds of the dose given before breakfast and one third before lunch or the evening meal) or three times daily. This regimen, with or without metformin, seems to achieve the best therapeutic effect and has gained popularity between diabetes specialists and diabetic patients. However, there are limitations from the use of premixed insulins regarding the tight schedule of the meals and the need for snack consumption 2-3 hours after administration to avoid hypoglycaemia.

Effects of steroids on cardiovascular risk

Many articles have recently tried to elucidate whether long term low-dose GCs increase cardiovascular risk or not (21-23). Patients that suffer from rheumatoid arthritis that take a daily dose of <10 mg/day of prednisone have been most extensively studied. The main questions are: Do GCs increase cardiovascular risk as a result of postprandial hyperglycaemia, obesity and higher cholesterol and blood pressure levels that they cause? Is this effect alleviated or even reversed due to the potent effect that GCs have on chronic inflammation in rheumatologic patients? Most of the relevant studies claim that low-dose steroid use (especially when used on a long-term basis), result in more or less increased cardiovascular events, even though no certain association has been identified (24-26). In a series of patients with rheumatoid arthritis without traditional cardiovascular factors and without cardiovascular disease who were treated long term, no association between left ventricular diastolic dysfunction, endothelial dysfunction, or subclinical atherosclerotic findings and the cumulative prednisone dose (mean cumulative prednisone dose of almost 16 grams) was found (27-29). In keeping with that, in a large and homogenous cohort of patients diagnosed with polymyalgia rheumatica (PMR), long-term steroid

therapy required for the treatment of PMR was not associated with a higher risk of heart failure, myocardial infarction, or cerebrovascular disease (30). In contrast, a trend for a protective effect of long-term steroid therapy used for the treatment of this inflammatory disease was found. Therefore, in some cases, the potential steroid-related improvement in the inflammatory burden observed in patients with different inflammatory rheumatic diseases might have a paradoxical protective effect on accelerated atherogenesis.

In a recent meta-analysis of 37 studies, the association between cardiovascular risk and low-dose GCs in rheumatoid arthritis patients was assessed, regarding both cardiovascular risk and "hard" outcomes (heart failure, stroke, myocardial infarction, mortality). This intriguing study showed a protective effect on serum lipid profile, an increase of NOSID, no significant effect on blood pressure and atherosclerosis, discrepancies regarding arterial stiffness and no effect on ventricular function or heart rate variability. On the other hand, there was an association with major cardiovascular events like stroke and myocardial infarction in most of the studies, as well as an increased mortality rate, especially in rheumatoid factor positive patients. The authors concluded that, even though the literature review showed poor association between low-dose GCs exposure and cardiovascular risk factors, a trend of increasing them was identified (31).

Key points

- The odds ratio of new onset steroid-induced diabetes is 1.3–2.7.
- Its pathophysiology is multifactorial, but insulin resistance is the main mechanism.
- Plasma glucose levels should be measured two hours postprandially to screen for NOSID, as fasting levels (especially in the morning) might be normal.
- Aims should be for fasting glucose levels 70–130 mg/dl and 2 hours after meals <180 mg/dl.
- Management options include mainly oral antidiabetics and insulin (see Fig. 2).

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