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REVIEW ARTICLE

Drug-Induced Hyperglycaemia and Diabetes

Neila Fathallah[1,3] · Raoudha Slim[1] · Sofien Larif[1] · Houssem Hmouda[2] · Chaker Ben Salem[1]

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Abstract Drug-induced hyperglycaemia and diabetes is a global issue. It may be a serious problem, as it increases the risk of microvascular and macrovascular complications, infections, metabolic coma and even death. Drugs may induce hyperglycaemia through a variety of mechanisms, including alterations in insulin secretion and sensitivity, direct cytotoxic effects on pancreatic cells and increases in glucose production. Antihypertensive drugs are not equally implicated in increasing serum glucose levels. Glycaemic adverse events occur more frequently with thiazide diuretics and with certain beta-blocking agents than with calcium-channel blockers and inhibitors of the renin–angiotensin system. Lipid-modifying agents may also induce hyperglycaemia, and the diabetogenic effect seems to differ between the different types and daily doses of statins. Nicotinic acid may also alter glycaemic control. Among the anti-infectives, severe life-threatening events have been reported with fluoroquinolones, especially when high doses are used. Protease inhibitors and, to a lesser extent, nucleoside reverse transcriptase inhibitors have been reported to induce alterations in glucose metabolism. Pentamidine-induced hyperglycaemia seems to be related to direct dysfunction in pancreatic cells. Phenytoin and valproic acid may also induce hyperglycaemia. The mechanisms of second-generation antipsychotic-associated hyperglycaemia, diabetes mellitus and ketoacidosis are complex and are mainly due to insulin resistance. Antidepressant agents with high daily doses seem to be more frequently associated with an increased risk of diabetes. Ketoacidosis may occur in patients receiving beta-adrenergic stimulants, and theophylline may also induce hyperglycaemia. Steroid diabetes is more frequently associated with high doses of glucocorticoids. Some chemotherapeutic agents carry a higher risk of hyperglycaemia, and calcineurin inhibitor-induced hyperglycaemia is mainly due to a decrease in insulin secretion. Hyperglycaemia has been associated with oral contraceptives containing high doses of oestrogen. Growth hormone therapy and somatostatin analogues may also induce hyperglycaemia. Clinicians should be aware of medications that may alter glycaemia. Efforts should be made to identify and closely monitor patients receiving drugs that are known to induce hyperglycaemia.

Key Points

Hyperglycaemia and diabetes may develop secondarily to use of drugs used in everyday clinical practice.

Increased awareness of drugs that alter glycaemic control, monitoring and prevention, whenever possible, are key elements for reducing complications related to drug-induced hyperglycaemia and diabetes.

✉ Neila Fathallah
neilafathallah@gmail.com

[1] Department of Pharmacovigilance, Faculty of Medicine of Sousse, Sousse, Tunisia

[2] Department of Medical Intensive Care Unit, Sahloul University Hospital, Sousse, Tunisia

[3] Department of Clinical Pharmacology, Faculty of Medicine of Sousse, Avenue Mohamed Karoui, 4002 Sousse, Tunisia

1 Introduction

Diabetes mellitus is defined as new development of a hyperglycaemic state that meets any of the following criteria: a fasting plasma glucose level ≥126 mg/dL on two separate occasions, a random plasma glucose concentration ≥200 mg/dL, a plasma glucose concentration ≥200 mg/dL 2 h after a 75 g oral glucose load or a glycated haemoglobin (HbA_{1C}) level ≥6.5 % [1]. The imputability of drugs in hyperglycaemic states is sometimes difficult, as this scenario has no distinguishing clinical features in comparison with the naturally occurring disease. Other possible diagnoses, including drug-induced pancreatitis, cirrhosis, kidney failure, stress hyperglycaemia and Cushing's syndrome, should be ruled out. The delay of occurrence of drug-induced hyperglycaemia is variable. It depends on the causative drug and can appear within hours or several weeks to months and even years after drug initiation.

Although the exact incidence of drug-induced hyperglycaemia in general is unknown, some controlled clinical trials have estimated the incidence of hyperglycaemia induced by several drugs such as glucocorticoids (GCs) and immunosuppressive agents [2, 3].

Drug-induced hyperglycaemia is often benign and may be clinically asymptomatic; however, development of severe hyperglycaemia manifesting as diabetic ketoacidosis and hyperglycaemic coma may occur.

Drug-induced hyperglycaemia can also be a serious problem, as it increases the risk of microvascular and macrovascular complications, infections, metabolic coma and even death.

Patients with predisposing factors for diabetes mellitus—such as sedentarity, body mass index ≥27 kg/m^2, impaired fasting glucose or glucose intolerance, family history of diabetes, history of vascular disease, history of gestational diabetes mellitus or at least one risk factor for metabolic syndrome—are particularly at risk of drug-induced hyperglycaemia, as some drugs can worsen pre-existing insulin resistance or pancreatic dysfunction.

Thus, these risk factors should be considered before initiation of drugs that are susceptible to disturbance of glycaemic control, and efforts should be made to identify and closely monitor patients receiving drugs that are known to induce hyperglycaemia.

In general, lifestyle choices are important when patients are taking any of the drugs implicated in increasing the risk of hyperglycaemia. If possible, discontinuation of the incriminated drug is the best option to reverse drug-induced hyperglycaemia. Reducing doses may minimize hyperglycaemia, especially with agents that exhibit a dose-dependent effect on glycaemia. The time needed to improve or return to baseline glycaemia generally depends on the offending drug. Hyperglycaemia is reversible within days with some drugs but may take longer if it is secondary to weight gain or peripheral insulin resistance.

This paper reviews the latest data concerning hyperglycaemia and diabetes secondary to drugs. A description of the main mechanisms, where available, is presented.

2 Methodology

All data were obtained from a Medline search from January 1960 to May 2015 and from *Reactions Weekly* from 1992 to May 2015, regardless of the language.

The keywords used in the Medline search were 'hyperglycaemia', 'hyperglycemia', 'glucose metabolism disorders' and 'diabetes', with the subheading 'drug-induced'. Some drugs were directly used as keywords, such as corticoids, diuretics and tacrolimus. Information from reviews focusing on this topic was also considered [4–8].

As for *Reactions Weekly*, the names of drugs identified by our Medline search were directly inserted into the search function on the journal website, with the subheadings 'hyperglycaemia', 'hyperglycemia' and 'diabetes' [9].

3 Pathophysiology of Drug-Induced Hyperglycaemia

Glycaemic control is maintained by a complex interplay of insulin, hepatic glucose production, peripheral glucose utilization and counterregulatory mechanisms, including mainly glucagon, catecholamines, growth hormone (GH) and cortisol [7].

Drugs may induce hyperglycaemia through a variety of mechanisms, including alterations of insulin secretion and sensitivity, direct cytotoxic effects on pancreatic cells and increases in glucose production. The main mechanisms and drugs implicated in drug-induced hyperglycaemia are summarized in Table 1.

4 Causative Drugs

4.1 Cardiovascular System

4.1.1 Antihypertensives

Despite their cardiovascular benefits in reducing blood pressure and cardiovascular risks, antihypertensive drugs, including diuretics, beta-blocking agents and calcium-channel blockers (CCBs), may adversely affect glucose homeostasis. Moreover, reports have suggested that

Table 1 Mechanisms of drug-induced hyperglycaemia

Mechanisms and drugs implicated
Diminution of insulin secretion and/or insulin production
Beta antagonists[a] (effects are attenuated but not abolished with cardioselective drugs)
Calcium-channel antagonists (related to calcium-channel blockade)
Phenytoin
Pentamidine[a]
L-asparaginase
Immunosuppressive drugs (tacrolimus, cyclosporine)
Diazoxide (direct effect on potassium channels)
Diuretics (related to hypokalaemia)
Antiarrythmics[a]
Diminution of peripheral insulin sensitivity and/or promotion of weight gain
Atypical antipsychotics
Antidepressant drugs
Glucocorticoids[a]
Beta agonists[a]
Oral contraceptives
Protease inhibitors
Growth hormone
Nicotinic acid[a]
Nucleoside reverse transcriptase inhibitors (except for didanosine)
Diuretics[a]
Statins[a]
Interferons[a]
Increase in glucose production through promotion of hepatic gluconeogenesis and/or glycogenolysis
Glucocorticoids[a]
Nicotinic acid[a]
Beta agonists[a]
Diuretics[a]
Beta antagonists[a]
Destruction of pancreatic cells, leading to beta-cell injury
Didanosine
Interferons[a]
Pentamidine[a]
Statins[a]
Glucocorticoids[a]

[a] More than one mechanism is proposed

hyperglycaemia occurring during antihypertensive therapy is a major cardiovascular risk factor [10, 11].

However, antihypertensive drugs are not equally implicated in increasing serum glucose levels. Glycaemic adverse events occur more frequently with thiazide diuretics and with certain beta-blocking agents than with CCBs [12], whereas inhibitors of the renin–angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, have been reported to be associated with a reduced risk of type 2 diabetes and metabolic risk in comparison with placebo and other antihypertensive treatments [13].

4.1.1.1 Thiazide Diuretics Thiazide diuretics are among the most commonly used antihypertensives. Significant adverse glycaemic events related to thiazide diuretics have been reported for more than 50 years [14]. Side effects on glucose homeostasis have been described even at low doses of thiazides [15–17]. Indeed, new-onset diabetes in hypertensive patients was more frequent in those receiving low-dose diuretic therapy than in those receiving long-acting nifedipine, with frequencies of 5.6 versus 4.3 % [16]. In a recent meta-analysis of antihypertensive trials, thiazides were associated with a higher risk of diabetes than placebo and, along with beta-blocking agents, they carried the highest risk among all major classes of antihypertensives [18].

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [17], a comparison between groups of patients receiving chlorthalidone, amlodipine and lisinopril was conducted. The incidence of diabetes was significantly higher in the chlorthalidone group (11.6 %) than in the other groups. However, and in spite of the risk of incident diabetes, thiazide diuretics do not seem to increase the risk of cardiovascular disease secondary to hyperglycaemia. This may be due, at least in part, to the effective reduction in blood pressure achieved by diuretic therapy [19].

Mechanisms of diuretic-induced hyperglycaemia seem to be related to a reduction in insulin secretion, secondary to diuretic-induced hypokalaemia [17, 20]. In fact, hypokalaemia is among the most important adverse effects of thiazide diuretics, and serum potassium levels decrease in a dose-dependent manner following thiazide treatment [21, 22], so hyperglycaemia secondary to thiazide diuretics may be due, in part, to decreased insulin secretion secondary to potassium loss. Substitution with potassium salts can prevent deterioration in glucose tolerance and may restore insulin sensitivity, similarly to drug withdrawal [23]. Other possible mechanisms that may result in thiazide-induced hyperglycaemia are elevated free fatty acid levels, which are known to decrease insulin secretion in response to glucose [24], significant reductions in insulin sensitivity and enhanced hepatic glucose production and/or catecholamine secretion and action [25].

The most practical approach for preventing thiazide-induced hyperglycaemia is to start with the lowest thiazide dosage and optimize serum potassium concentrations. Sometimes, thiazides should be used in combination with potassium supplements or potassium-sparing drugs, such as

amiloride. If ineffective, diuretics should be combined with another first-line antihypertensive drug rather than being given at an increased dosage [26].

4.1.1.2 Beta-Blocking Agents As with thiazide diuretics, clinical trials have reported that beta-blocking agents increase the risk of hyperglycaemia and new-onset diabetes [27]. However, in spite of this risk, both beta-blocking agents and diuretics have been associated with decreases in morbidity and mortality from cardiovascular events [28].

In the Atherosclerosis Risk In Communities (ARIC) study, over 12,000 nondiabetic subjects were identified and followed prospectively. Among hypertensive subjects, beta-blocking agents were associated with an increased risk of diabetes [29]. Moreover, in a post hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP) clinical trial (which evaluated chlorthalidone versus placebo), the addition of atenolol to a thiazide diuretic (chlorthalidone) increased the rate of new-onset diabetes by 40 % (16.4 % in chlorthalidone-treated patients versus 11.8 % in placebo-treated patients) [30].

The mechanisms of beta-blocker-induced hyperglycaemia are complex and include weight gain, direct action on inhibition of beta-2-adrenergic-mediated insulin release and decreased insulin sensitivity [31]. Blockade of other beta-receptor-mediated effects, such as glycogenolysis in muscle and disturbances in serum lipid levels, including elevated triglyceride levels and lowered levels of high-density lipoprotein cholesterol (HDL-C), may also contribute to impaired glycaemic control [31].

The differences between cardioselective and non-selective beta-blocking agents in terms of glycaemic effects have not been fully elucidated. A greater inhibitory effect on insulin secretion seems to be associated most frequently with non-selective beta-blocking agents, as reported with propranolol [32]. In addition, a meta-analysis including 94,492 patients reported an increase of 22 % in the risk of new-onset diabetes in patients treated with non-cardioselective beta-blocking agents [33].

However, beta-blocking agents with intrinsic sympathomimetic activity (betalol and pindolol) or alpha-blocking effects (carvedilol) have been reported to have a reduced impact on insulin sensitivity, with neutral or slightly favourable effects on glycaemic control [34, 35]. Interestingly, nebivolol does not seem to be associated with hyperglycaemia or new-onset diabetes [36].

Some precautions may contribute to prevention of glycaemic side effects secondary to beta-blocking agents. Use of low dosages combined with other agents, particularly CCBs, is highly recommended. Limiting weight gain and improving physical activity may also reduce the risk of hyperglycaemia induced by beta-blocking agents [31].

4.1.1.3 Calcium-Channel Blockers Although it is well known that intracellular calcium metabolism is involved in the regulation of insulin secretion [37] and that, theoretically, CCBs may reduce insulin secretion and induce hyperglycaemia in humans, it appears that clinical use is generally not accompanied by severe hyperglycaemia, and CCBs are generally considered as having an overall neutral metabolic profile [38].

In many meta-analyses [31, 39], the overall risk of diabetes secondary to CCB therapy was not significant. However, not all members of the CCB class have the same effect on glucose homeostasis [38]. Nicardipine [40], nifedipine [41] (when high doses are used), verapamil and diltiazem in cases of intoxication are the CCBs most frequently implicated in carbohydrate metabolism disturbances [42].

4.1.2 Antiarrhythmics

Hyperglycaemia has been reported with some antiarrythmic drugs. Encainide, a class Ic antiarrhythmic drug, has been associated with hyperglycaemia and even diabetes [43]. The proposed mechanism of this disorder is an increase in the plasma glucagon level (nearly 100 % over baseline in comparison with a mean glucagon rise in controls of only 8 %) [43]. Persistent hyperglycaemia may be related to delayed insulinopenia and insulin resistance [44].

Hyperglycaemia has also been reported to be a possible adverse effect of amiodarone, a class III antiarrhythmic used in ventricular and supraventricular tachycardia. However, the mechanisms of amiodarone-induced hyperglycaemia remain undetermined. Hyperglycaemia generally occurs after long-term use of amiodarone in adults [45] but has also been reported to be an early complication of amiodarone infusion in infants [46].

4.1.3 Lipid-Modifying Agents

4.1.3.1 HMG-CoA Reductase Inhibitors 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are among the most effective therapies in reducing cardiovascular risk in both primary and secondary prevention studies. However, hyperglycaemia and incident diabetes are actually well recognized side effect of statins [47].

Several meta-analyses have addressed the association between statin therapy and impaired glucose tolerance. In a meta-analysis of six trials, with a total of 57,593 patients, the incidence of diabetes was 13 % higher in patients receiving statin therapy than in those not receiving a statin [48].

In another meta-analysis of 13 major statin trials, including 91,140 participants, the risk of developing

diabetes over a 4-year period was 9 % higher in patients receiving statins than in patients randomized to placebo or standard care [49].

Diabetogenic effects seem to differ between the different types of statins. In the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial, there was a 32 % higher incidence of diabetes with pravastatin therapy in elderly patients (aged between 70 and 82 years) [50]. This risk was not reported with the same drug in younger patients (aged 31–75 years) in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial [51]. In that trial, age-dependent loss of beta-cell function was the suggested mechanism of the increased incidence of new-onset diabetes in elderly patients.

In addition, in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trials, although low-dose atorvastatin was not associated with a higher incidence of new-onset diabetes [52], high-dose atorvastatin (40 mg) was associated with a significant increase in glycaemic levels, and the incidence of diabetes was 34 % [53].

In addition, in both the West of Scotland Coronary Prevention Study (WOSCOPS) [54] and the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [55], an increasing risk of new-onset diabetes in patients with pre-existing major diabetes risk factors was reported. There is growing evidence that people with pre-existing risk factors for diabetes mellitus are more likely to develop diabetes with statin therapy. However, the absolute benefit of treatment with statins outweighs the increased risk of incident diabetes [56].

Several mechanisms have been suggested for statin-induced impairment of glucose metabolism. Processes altering pancreatic beta-cell function and a statin-induced decrease in circulating adiponectin levels are the main mechanisms explaining the development of drug-induced diabetes mellitus with statin therapy [57].

In individuals at higher risk of diabetes and at lower cardiovascular risk, the potential risk of incident diabetes secondary to statin intake should be considered before initiation of therapy. If possible, use of low statin doses and more careful monitoring for glycaemia are recommended. Moreover, lifestyle interventions should be implemented in individuals with a high risk of incident diabetes undergoing statin therapy [57].

4.1.3.2 Nicotinic Acid Nicotinic acid, also called niacin, is a B vitamin recommended for treatment of dyslipidaemia [58]. Although it has significant beneficial effects in increasing HDL-C levels and decreasing triglyceride and low-density lipoprotein cholesterol (LDL-C) levels, severe hyperglycaemia secondary to niacin therapy has been reported in many cases [59, 60].

In a recent research study examining the effects of niacin and a single bout of aerobic exercise on plasma glucose, insulin and C-peptide levels in sedentary nondiabetic postmenopausal women, there was a significant increase in mean glucose values following niacin therapy [61]. Niacin-induced hyperglycaemia is most frequently associated with high doses, pre-diabetes or diabetes. Moreover, aging (which is often associated with insulin resistance) is among the risk factors for hyperglycaemia during niacin therapy [62]. In addition, even short-term therapy has been reported to increase fasting glucose levels [60]. The mechanism of niacin-induced hyperglycaemia is complex. An increase in hepatic gluconeogenesis as a result of smaller amounts of fatty acids in the liver and impairment of beta-cell compensation, leading to insulin resistance (especially in elderly patients), are the most frequently suggested mechanisms of niacin-induced hyperglycaemia [62].

4.1.4 Diazoxide

Diazoxide is a non-diuretic benzothiadiazine derivative, which increases the plasma concentration of glucose by decreasing insulin secretion through opening of potassium/adenosine triphosphate channels in the membranes of pancreatic beta cells and increasing the hepatic output of glucose [63]. Many cases of hyperglycaemia including ketoacidosis and hyperosmolar nonketotic coma have been reported with diazoxide. Therefore, the use of diazoxide as an antihypertensive has been restricted because of severe cases of hyperglycaemia and, nowadays, diazoxide is used to control hypoglycaemia in patients with insulinoma rather than in hypertension [64].

4.2 Anti-infectives

4.2.1 Antibacterials

Hyperglycaemia appears to be more common with fluoroquinolones than with the other classes of antibiotics [65]. In fact, in a study comparing fluoroquinolones with macrolide antibiotics such as azithromycin and clarithromycin, gatifloxacin was associated with an increased risk of hyperglycaemia [66, 67]. Many reports have suggested that fluoroquinolones increase the risk of hyperglycaemia more frequently in diabetics and in the elderly population [68–70].

Indeed, in a retrospective inception cohort study of outpatients with a new prescription for fluoroquinolones, the odds ratios for hyperglycaemia were 4.5 (95 % confidence interval [CI] 3.0–6.9) for gatifloxacin, 1.8 (95 % CI 1.2–2.7) for levofloxacin and 1.0 (95 % CI 0.6–1.8) for ciprofloxacin [71], so the risk of hyperglycaemia seems to

be more important with gatifloxacin than with other fluoroquinolones [72].

Severe life-threatening events, including hyperosmolar nonketotic hyperglycaemic coma and diabetes ketoacidosis, have been reported more frequently with high doses of gatifloxacin with concomitant use of corticosteroids and in patients with renal impairment [70].

A fluoroquinolone-associated disorder in glucose metabolism is likely to be mediated by the action of the drugs on glucose transporter type (GLUT) 1, a protein responsible for transport of glucose into the central nervous system, as well as the peripheral tissues [73].

Infection may lead to alterations in carbohydrate metabolism, which is characterized by marked acceleration of glucose and lipid flux, so infection may disturb glycaemia. It is recommended that patients with diabetes should be carefully monitored. If signs or symptoms of glucose disturbances develop, fluoroquinolones should be stopped. Some guidelines have even suggested avoiding gatifloxacin in patients with diabetes [73].

4.2.2 Antimycobacterials

Isoniazid seems to be the most frequently implicated antimycobacterial in drug-induced hyperglycaemia and diabetes. It may cause hyperglycaemia by stimulating glucagon secretion and also by blocking specific steps of the Krebs cycle. Glycaemic control may therefore be affected by isoniazid, and the insulin requirements of diabetic patients may increase while they are on an isoniazid regimen [74].

Rifampicin-induced hyperglycaemia has also been reported and seems to be mainly due to an increase in intestinal absorption of glucose, secondary to rifampicin ingestion [75].

Therefore, an oral glucose tolerance test is indicated in both diabetic and nondiabetic patients receiving isoniazid and rifampicin.

4.2.3 Antivirals

Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) are included in current anti-HIV combination therapy. However, such treatments may have deleterious effects on glucose control, lipid metabolism, and body fat distribution. PIs (ritonavir, indinavir and amprenavir)—and, to a lesser extent, NRTIs—have been reported to induce alterations in glucose metabolism [76]. Didanosine, an NRTI, is known to induce hyperglycaemia, diabetes mellitus and even hyperosmolar nonketotic hyperglycaemia. Pancreatitis is a serious adverse effect of didanosine, and hyperglycaemia has been thought to be related in part to drug-induced pancreatic toxicity [77]. Abacavir is another NRTI that has been reported to induce diabetes [78].

PI-induced hyperglycaemia may occur in both diabetics and non-diabetics [79, 80]. In a cohort study including 113 patients receiving a PI and 45 HIV-infected patients never treated with a PI, impaired glucose tolerance occurred in 16 % of PI recipients, and diabetes mellitus occurred in 7 % [81].

A suggested mechanism of PI-induced hyperglycaemia has been proposed for indinavir. Increases in fasting glucose levels may be explained by a combination of insulin resistance without a compensatory increase in insulin release by pancreatic beta cells [82].

Moreover, ritonavir has been shown in vitro to be a potent, selective inhibitor of GLUT4, contributing to hyperglycaemia and insulin resistance [83]. Atazanavir is the first PI approved by the US Food and Drug Administration (FDA) with the property of not inhibiting GLUT4. So, atazanavir is thought to not disturb glycaemic and lipid levels as do the other PIs. In fact, a recent retrospective study, comparing darunavir and atazanavir, reported a multivariable-adjusted hazard ratio of 0.84 for diabetes and hyperglycaemia, and in comparison with darunavir-treated patients, atazanavir-treated patients had significantly lesser metabolic side effects [84].

In addition, oseltamivir, an antiviral medication used to treat influenza A and influenza B, has been reported to induce hyperglycaemia [85].

Baseline glucose levels should be determined prior to PI therapy, and follow-up tests should be performed every 3–4 months during the first year of therapy. If glucose levels remain within the normal range, monitoring may be performed less frequently [82].

4.2.4 Antiprotozoals

Pentamidine is an antiprotozoal agent known to cause severe disturbances in blood glucose homeostasis, such as hypoglyceamia and hyperglycaemia [69]. A number of cases of insulin-dependent diabetes mellitus following pentamidine therapy have been reported [86–88]. The exact mechanism of hyperglycaemia remains unclear, but it seems to be related to direct drug-induced dysfunction in pancreatic beta cells [87].

4.3 Drugs Affecting the Nervous System

4.3.1 Antiepileptics

Phenytoin and valproic acid are widely used in the treatment of epilepsy. Phenytoin is known to induce hyperglycaemia, which has been further associated with toxic concentrations [89, 90]. Phenytoin may therefore cause

reversible hyperglycaemia at toxic doses, but it does not appear to produce long-term effects on glucose tolerance when used in therapeutic doses [91]. The proposed mechanism is primarily inhibition of insulin release. Moreover, insulin resistance secondary to a post-binding defect in insulin action has been proposed [91].

Valproic acid is known to cause overweight and hyperglycaemia in both adults and children. Impaired glucose homeostasis was identified in 45 % of 114 epileptic patients treated with valproic acid [92].

4.3.2 Second-Generation Antipsychotics

Second-generation antipsychotics (SGAs), also known as atypical antipsychotics, have been used since 1990 in the management of psychosis. In comparison with typical antipsychotic agents, more reported disturbances in carbohydrate metabolism and weight gain have been reported with the SGA class.

Recent retrospective studies and isolated case reports suggest that SGAs are linked to the occurrence of hyperglycaemia, new-onset diabetes mellitus and cases of severe ketoacidosis. The majority of reported cases have involved either clozapine or olanzapine as the offending agent. Hyperglycaemia and diabetes mellitus have been described in 0.1–1 % of patients receiving olanzapine therapy [93]. More recently, observational studies have reported a much higher incidence (30 %) of hyperglycaemia and diabetes mellitus secondary to SGAs [94]. Olanzapine has been associated with a higher risk of incident diabetes than risperidone [95]. Even severe hyperglycaemia or exacerbation of pre-existing diabetes, sometimes leading to ketoacidosis, coma or death, has occurred with olanzapine [96].

Olanzapine and clozapine have been associated with hyperglycaemia, either secondary to weight gain and dyslipidaemia or independent of any weight disturbances [97–99]. In a review by Koller and Doraiswamy, 237 patients were identified with olanzapine-induced hyperglycaemia, and 188 involved new-onset diabetes mellitus, among whom 80 patients presented with metabolic acidosis [100].

Ziprasidone is another SGA that has been associated with severe hyperosmolar hyperglycaemia [101].

The mechanisms of antipsychotic-associated hyperglycaemia, diabetes mellitus and ketoacidosis are complex. Significant weight gain is observed in patients receiving SGAs, and it has been suggested that an increase in adipose tissue may contribute to insulin resistance [102]. However, cases of new-onset diabetes mellitus in the absence of weight gain have also been reported [103]. In fact, although weight gain with an increased body mass index is a common problem with antipsychotics, some reports have suggested that SGA-induced hyperglycaemia and diabetes mellitus without significant weight gain may be present at the time of presentation, supporting the hypothesis of a more direct antipsychotic-mediated effect on glucose metabolism and homeostasis independent of adiposity [104]. Moreover, depression and antidepressant drug use, cholinesterase inhibitor use and valproate use were found to increase fasting glucose levels in elderly psychiatric patients [105].

For patients receiving SGA therapy, some researchers have recommended regular screening for diabetes mellitus every 6 months [106]. In fact, patients with diabetes mellitus receiving SGAs should be monitored regularly for worsening glucose control. Those with risk factors for diabetes mellitus should undergo fasting blood glucose testing at the start of, and during, treatment with SGAs [106].

4.3.3 Antidepressant Drugs

Antidepressant drugs may cause both hyperglycaemia and hypoglycaemia [69]. Results concerning the link between antidepressant use and diabetes are conflicting. Many studies have reported that hyperglycaemia and diabetes mellitus might be induced by antidepressant drugs and that the incidence of diagnosed diabetes was higher among antidepressant users [107–109]. However, other studies have suggested that the association between antidepressant agents and diabetes may not be causal in nature and does not indicate an excess short-term risk of diabetes mellitus [110]. In fact, it is not clear if changes in glucose regulation following antidepressant therapy initiation are due to antidepressant drugs or to changes in mood and lifestyle [111].

In the Diabetes Prevention Program, the use of antidepressants at baseline was associated with an increased risk of type 2 diabetes at follow-up [107]. Hyperglycaemia was reported following treatment with clomipramine, fluvoxamine, imipramine, mianserin, mirtazapine, paroxetine and and sertraline, and the time to the onset of glucose dysregulation ranged from 4 days to 5 months after initiation of antidepressant therapy [111].

While long-term use of antidepressants with high or moderate daily doses has been associated with an increased risk of diabetes, low doses have not been found to increase the risk of glycaemic disturbances [108].

Moreover, the effect of antidepressants on glycaemic control seems to differ according to the antidepressant class. Treatment with tricyclic antidepressants (TCAs) has been associated with hyperglycaemia and worsening of glycaemic control by inducing weight gain and insulin resistance [112], while in short-term therapy, selective serotonin reuptake inhibitors (SSRIs) and bupropion have resulted in a decrease in plasma glucose levels, leading to

an improvement in glycaemia [113–115], but hyperglycaemia may adversely occur with SSRIs in long-term use [116].

Analyses of data drawn from a cohort of 150,000 adults revealed that antidepressant agents—especially when exceeding defined daily doses—are associated with an increase in the risk of diabetes mellitus. Moreover, the 5-year risk of diagnosed diabetes increases in a dose–response way. In this analysis, weight gain was more rapid among long-term antidepressant users than in non-users matched for depression-related characteristics [111]. Moreover, women appear to be more likely to be at risk of glucose dysregulation when taking antidepressants [117]. Reversible nonketotic hyperglycaemia induced by amoxapine developed in a woman with a history of nonketotic hyperglycaemic coma under preloxapine treatment [118].

4.4 Respiratory System

4.4.1 Adrenergics

Beta-adrenergic stimulants can produce hyperglycaemia in nondiabetic patients, particularly in those with severe asthma requiring high doses, in cases of intoxication or in cases of prolonged treatment [119, 120]. Complications of hyperglycaemia, such as ketoacidosis and lactic acidosis, may occur in patients treated with beta-adrenergic stimulants even with inhaled use [121], particularly during pregnancy [122] and even in children receiving nebulized salbutamol [123].

Hyperglycaemia is attributed to muscle and hepatic gluconeogenesis resulting from stimulation of beta2 adrenoreceptors.

4.4.2 Other Systemic Drugs for Obstructive Airway Disease

Theophylline is a phosphodiesterase inhibitor with beta-sympathomimetic activity related to an increase in theophylline-induced cyclic adenosine monophosphate (AMPc) levels. Theophylline overdose is known to be associated with hyperglycaemia [124]. In fact, a high dose of theophylline may induce elevated blood levels of catecholamines, epinephrine and norepinephrine. Thus, enhanced adrenergic activity may lead to metabolic disturbances, including hyperglycaemia [125].

However, even at therapeutic doses of theophylline, changes in plasma glucose, free fatty acids and insulin have been reported [126]. Both extremes of age appeared to be the primary risk factor for theophylline intoxication and hyperglycaemia [127].

4.5 Glucocorticoids

GCs are frequently used for treatment of inflammatory conditions and autoimmune diseases. Hyperglycaemia and diabetes are common adverse effects of GCs. Diabetes induced by GCs is also known as steroid diabetes, and even hyperglycaemic hyperosmolar nonketotic coma secondary to GC use has been reported [128, 129].

A recent meta-analysis indicated that the rates of GC-induced hyperglycaemia or diabetes were 32.3 and 18.6 %, respectively [2].

GC-induced hyperglycaemia may occur in non-diabetics or in diabetic patients, aggravating diabetes and worsening glycaemic control, leading in both cases to atherosclerosis and its complications [130].

The main risk factors for impaired carbohydrate metabolism induced by GCs are the dose and duration of therapy. All high-dose GC preparations (oral, inhalational, topical) are associated with hyperglycaemia and steroid-induced diabetes [131]. Intra-articular injection and intralesional administration of GCs in diabetics may also affect glycaemic control [132, 133]. Moreover, the risk of hyperglycaemia seems to increase with an increasing average daily steroid dose [134].

The main mechanism of GC-induced hyperglycaemia is reduced insulin sensitivity. In fact, steroids stimulate hepatic glucose production and inhibit peripheral glucose uptake in muscle and fatty tissue, resulting in insulin resistance. More recent studies have suggested deleterious effects of GCs on pancreatic beta cells, leading to decreased insulin production [135].

Early recognition and proper proactive management of GC-induced hyperglycemia are highly recommended. Patients on long-term GC treatment and even patients on transient GC treatment should be monitored at regular intervals [134].

Together with, or after, lifestyle measures, hypoglycaemic drugs with important insulin sensitizer effects are indicated. Other oral hypoglycaemic drugs or insulin therapy can be considered as the second drugs of choice.

4.6 Antineoplastic and Immunomodulating Agents

4.6.1 Antineoplastic Agents

Hyperglycaemia is a well-known side effect in patients receiving chemotherapy. In a report considering hyperglycaemia induced by neoadjuvant agents used in the treatment of solid tumour cancers, the findings suggested that some chemotherapeutic agents carry a higher risk of hyperglycaemia [136]. Docetaxel, alone or in combination with other agents, can promote hyperglycaemia. Also,

androgen-deprivation therapy increases the risks of hyperglycaemia and diabetes [137].

Decitabine, bortezomib, temzolomibe and vorinostat are antineoplastic drugs known to induce hyperglycaemia too [138–141].

Cyclophosphamide has been reported to induce hyperglycaemia and type 1 diabetes secondary to the presence of antibodies to pancreatic islet cells [142].

Hyperglycaemia has been described as a common event occurring during acute lymphocytic leukaemia chemotherapy [143]. It may occur in about 10 % of patients receiving L-asparaginase, which may present as mild glucose intolerance or severe hyperglycaemia, including metabolic complications [144, 145]. Diabetic ketoacidosis is a rare but severe complication of L-asparaginase therapy and is more likely to be reported in children with acute leukaemia [145]. Even death from ketoacidosis has occurred following asparaginase therapy [146].

Asparaginase-induced hyperglycaemia is likely due to a decreased serum concentration of insulin, secondary to defects in pancreatic beta-cell secretion [145].

In patients receiving chemotherapy, early diagnosis and proper treatment of hyperglycaemia (withdrawal of the culprit drug if possible, and diet and insulin therapy) may lead to significant regression of the clinical and biochemical abnormalities and, essentially, enable continuation of chemotherapy [136].

4.6.2 Immunosuppressive Agents

Calcineurin inhibitors (CNIs), including cyclosporine, sirolimus and tacrolimus, are widely used immunosuppressives in transplantation therapy. The risk of diabetes is actually well established with CNIs, and the suggested mechanism is a decrease in insulin secretion promoted by calcineurin [147].

Although concomitant use of GCs may be an explanation for hyperglycaemia, the effect of CNIs is well established in glucose homeostasis and should not be ignored.

Clinical studies have reported the effects of tacrolimus on insulin secretion in both transplanted and non-transplanted subjects. The findings suggested that tacrolimus decreases insulin secretion, regardless of initial glucose tolerance, without changes in insulin sensitivity [148].

Among all CNIs, tacrolimus is associated with a higher incidence of post-transplantation diabetes [149]. The incidence was 16.6 % with tacrolimus versus 9.8 % with cyclosporine, without any difference according to the transplanted organ [3]. Risk factors for hyperglycaemia include high blood levels of tacrolimus, age and concomitant use of high doses of GCs [150].

The effect of other immunosuppressive drugs on glucose homeostasis, such as mycophenolate mofetil (MMF), is less well documented, and the results are conflicting. In a recent study, the effects of withdrawal of a CNI and a switch to sirolimus on peripheral insulin resistance and the pancreatic beta-cell response was investigated in 41 kidney transplanted patients. The switch to sirolimus was associated with a 30 % increase in the incidence of impaired glucose tolerance and the occurrence of diabetes [151]. In another study, there was no difference in the incidence of diabetes in steroid- and tacrolimus-treated kidney recipients whether they received sirolimus or MMF [152].

Interferon (IFN) is a cytokine with various biological actions, such as antiviral and antitumoral activity; it regulates immune responses and cell differentiation.

Side effects of IFN therapy may include impaired glucose tolerance. The frequency of glucose intolerance and its progress is about 0.1–0.6 % [153, 154]. Diabetes mellitus and insulin-dependent diabetes mellitus have both been reported during IFN therapy [155, 156].

Insulin-dependent diabetes mellitus is relatively rare and is generally caused by destruction of pancreatic islet beta cells by the autoimmune system [157]. IFN-gamma-induced hyperglycaemia has also been related to insulin resistance [158].

Other immunosuppressive therapies, such as adalimumab, have also been reported to induce hyperglycaemia [159].

4.7 Genitourinary System and Sex Hormones

4.7.1 Oral Contraceptives

Marked hyperglycaemia has been associated with oral contraceptives (OCs) containing high doses of oestrogen but is not seen with the combined OCs used currently, which contain lower doses of oestrogen [160].

OCs may alter glucose homeostasis in a dose-dependent way. These alterations result in decreased glucose tolerance and increased insulin resistance, which are risk factors for type 2 diabetes mellitus and cardiovascular disease [161].

Although the use of low-dose combination OCs results in lesser effects on glucose homeostasis, oestrogen and high doses of combined estrogen–progestin have often had the greatest effect on carbohydrate metabolism. While oestrogen increases serum triglyceride, the androgenic progestins in OCs usually increase serum LDL-C and decrease HDL-C. This leads to major effects on plasma lipoprotein metabolism, as well as glycaemic homeostasis [161].

However, in a recent interventional review evaluating the effect of hormonal contraceptives on carbohydrate metabolism in healthy women and those at risk of diabetes due to overweight, no major differences in carbohydrate metabolism were found between different hormonal contraceptives in women without diabetes [162]. Overweight,

Table 2 Miscellaneous drugs inducing hyperglycaemia, and their suggested mechanisms (if available)

Drug	Clinical setting	Suggested mechanism	References
Acitretin	A 46-year-old male treated for extensive psoriasis	Unknown	[169]
Thalidomide	A 70-year-old patient with renal failure and colon cancer, treated with thalidomide for refractory multiple myeloma	Hyperglycaemia may be related to increased insulin resistance in peripheral tissues	[170]
Endosulfan	6 patients with acute endosulfan intoxication, all of whom had severe metabolic acidosis with a high anion gap and hyperglycaemia	Unknown	[171]
Thiopental and propofol	A comparison of the effects of thiopental and propofol on the haemodynamic and metabolic endocrine response to laryngoscopy and intubation in 14 healthy patients showed increases in plasma glucose levels following these therapies	Unknown	[172]
Ritodrine	Glycaemic effects following ritodrine or ritodrine and glucocorticoid reported in pregnant women	Unknown	[173]
Megestrol acetate	HIV-infected patients treated with megestrol acetate for progressive anorexia and weight loss, who developed hyperglycaemia	Hyperglycaemia is related to insulin resistance	[174]
Indomethacin	A 30-year-old man with no past history or family history of diabetes, who had an 8-year history of psoriasis and psoriatic arthritis; he developed an elevated blood sugar level during indomethacin therapy for his arthritis	There is a possible role of endogenous prostaglandins in glucose-induced insulin release	[175]
Calcitonin	Plasma glucose levels were investigated in 8 patients with Paget's disease of bone, receiving synthetic salmon calcitonin and human calcitonin	Calcitonin seems to have contra-insular effects on glucose metabolism: a decreased glycogen amount in the liver, inhibited insulin-induced glucose consumption by muscular and adipose tissues in vivo and in vitro, slowed-down insulin secretion during glucose loading and impaired glucose tolerance	[176]
Clonidine	A 9-year-old child with Tourette's syndrome treated with clonidine	It may be related either to a central site of clonidine hyperglycaemic action or to stimulation of growth hormone release	[177]
Furosemide	4 patients (3 with hypertension and 1 with congestive heart failure) receiving treatment with diuretics developed hyperglycaemia	In adipose tissue, furosemide inhibits the rate of glucose transport; in skeletal muscle, furosemide decreases the rate of glucose phosphorylation and glycolysis	[178]
Alprostadil	This case report described the postoperative course of an infant who, while under treatment with PGE-1, became severely hyperglycaemic with apparent ketoacidosis	In addition to its vasoactive properties, PGE-1 has many metabolic properties	[179]

HIV human immunodeficiency virus, *PGE-1* prostaglandin E1

as a sign of insulin resistance, seems to be the most important risk factor for OC-induced metabolic disorders.

In woman receiving OC treatment, regular monitoring of serum lipid levels and glycaemia should be maintained, especially in those who have other risk factors for metabolic syndrome [162].

4.7.2 Growth Hormone

Long-term GH therapy has been shown to induce hyperglycaemia by inducing insulin resistance and, in particular, by inhibition of insulin-stimulated glucose uptake in skeletal muscle [163]. Thus, GH counteracts the effects of insulin on lipid and glucose metabolism [164]. Many studies in healthy subjects have suggested that elevated free fatty acid levels are involved in the pathogenesis of insulin resistance, strongly suggesting a causal link between the lipolytic and insulin-antagonistic effects of GH [165].

Older and obese patients are more at risk of GH-induced hyperglycaemia. In addition, more frequent metabolic adverse outcomes have been reported with higher than recommended doses of GH [166, 167]. GH may also induce insulin resistance and hyperglycaemia in children,

but it is generally mild and transient [168]. However, severe nonketotic hyperglycaemia leading to death has also been reported [165].

4.7.3 Somatostatin Analogues

Octreotide is an octapeptide, which mimics natural somatostatin. Severe paradoxical hyperglycemia and bradycardia has been reported with use of preoperative subcutaneous octreotide in an infant undergoing subtotal pancreatectomy for congenital hyperinsulinism [169].

Pasireotide is a somatostatin analogue approved for the treatment of acromegaly. In clinical trials, most patients have experienced new or worsening hyperglycemia with pasireotide treatment, and the risk seems to be greater in diabetic and prediabetic patients [170].

Careful monitoring of glycaemic status is required prior to and during pasireotide treatment, and antidiabetic therapy should be indicated whenever possible.

4.8 Miscellaneous Drugs

Some drugs have been reported in isolated cases as potential causes of drug-induced hyperglycaemia (Table 2) [171–179]. Other responsible drugs, such as glucosamine, acetazolamide, morphine, chlorpromazine, adrenaline, phentolamine, prazocin and etacrynic acid, have also been reported [180–186].

In almost all cases, the mechanisms have not been formally tested. However, even in single cases, caution is greatly needed, and early detection and management of drug-induced hyperglycaemia are required.

5 Conclusion

Clinicians should be aware of medications that may alter glycaemia, and should initiate close follow-up of their patients. Moreover, patients receiving medications that may be implicated in hyperglycaemia should be educated about the importance of follow-up tests.

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Compliance with Ethical Standards

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